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CONTENTS

EDITORIAL
THE TRIALS TO BE FACED
By Carla S. Garcia & Aaron M. Glickman ............................................................... 7

DEPARTMENTS

PROFILES
1. INTERVIEW WITH DR. V. M. VENKATESAN
   By Helen Lewandowski ............................................................................................. 8

ETHICS
1. GUT REACTIONS: AN ETHICAL ANALYSIS OF EMERGING BIOTECHNOLOGIES
   By David J. Satin ........................................................................................................ 11

MEDICINE ON THE INTERNET
1. ONCOLOGY ON THE INTERNET
   By Munsif Bhimani .................................................................................................... 13

MEDICINE AND THE LAW
1. ALTERNATIVE CANCER THERAPIES AND THE 714X STORY
   By Mahmoud Sharaf ..................................................................................................... 15

HISTORY OF MEDICINE
1. THE CAUSE AND THE CURE: Illness and Healing in Traditional Cultures
   By Sherry Rohekar ..................................................................................................... 17

PROMOTION AND PREVENTION
1. THE TESTICULAR SELF-EXAM: Should a Widespread Education Program be Implemented?
   By Asif Doja ................................................................................................................. 19

THINKING ON YOUR FEET
1. A CASE OF CEREBELLO-PONTINE TUMOUR
   By Allan Vescan .......................................................................................................... 21

HUMOUR
1. CLASSROOM MUSINGS
   By Benjamin Barankin ............................................................................................... 23
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FEATURE ARTICLES

1. THE MUTAGENICITY OF SURGICAL SMOKE IN ELECTROSURGICAL PROCEDURES
   By Sandy Widder ............................................................... 26

2. ANGIGENIC INHIBITORS: New Possibilities for Cancer Therapy
   By Tisha Toy ........................................................................ 28

3. SENTINEL NODE LYMPHOSCINTIGRAPHY: The Role of Nuclear Medicine in the Investigation and Treatment of Melanoma and Breast Cancer
   By Kent Dunn ........................................................................ 31

4. HEALTH AND HARMONY: Live Music at the London Regional Cancer Centre
   By Jennifer Wong and Michael Sanatani ................................. 34

5. FUNCTIONAL BRAIN MAPPING AND THE REMOVAL OF BRAIN TUMOURS
   By Peter Howard ................................................................. 37

6. THE ROLE OF PROSTATE-SPECIFIC ANTIGEN FOR SCREENING IN THE FAMILY PHYSICIAN’S OFFICE
   By Raj Waghmare and Mark Evans ......................................... 40

7. METASTASES TO BONE
   By Matthew R. G. Menon .................................................... 43

8. OVERVIEW OF THE PALLIATIVE ROLE OF RADIOTHERAPY
   By Erica Wong ......................................................................... 49

9. PALLIATION OF INOPERABLE CANCER OF THE ESOPHAGUS WITH STENTS: A Systematic Review
   By Gabriel Chan ........................................................................ 52

10. MALIGNANCY AND THE ANEMIA OF CHRONIC DISEASE
    By Gary Kay ........................................................................... 55

11. ONCOLOGIC EMERGENCIES: Febrile Neutropenia
    By Ian MacDonald ................................................................... 58

12. AT RISK FOR BREAST CANCER: The Ups and Downs of Genetic Breast Cancer Testing
    By Glenna Cuccarolo ............................................................. 61

13. THE FREE FIBULA FLAP FOR OROMANDIBULAR RECONSTRUCTION
    By Joe Mai, Dr. Jonathon Trites and Dr. John Yoo ....................... 63

14. WHILE MERLIN SLEEPS: A Review of the Biology of Neurofibromatosis Type 2 and the Role of merlin as a Tumour Suppressor
    By David Skidmore and Gregory M. Kelly, Assistant Professor, Department of Zoology; UWO ..................................... 66

15. ENDOCRINE THERAPIES OF ADVANCED BREAST CANCER IN POSTMENOPAUSAL WOMEN
    By Michelle Suga ................................................................. 70

16. DYSPLASTIC NEVI: A Clue to Increased Cutaneous Melanoma Risk
    By Noreen Galaria and George F. Murphy, M.D. ....................... 74

17. MEDICAL STUDENT STRESS, MISTREATMENT AND WELLNESS
    By Bindu Kumar ..................................................................... 76

U.W.O. Medical Journal 69 (2) 1999
EDITORIAL

THE TRIALS TO BE FACED

By Carla Garcia & Aaron M. Glickman, Editors-In-Chief

Of all the diagnoses that a person can be labeled with, cancer has always been one of the most feared, and certainly the most varied in what it means to both the patient and his health care providers. Some of the most aggressive, lethal disease processes fall under the heading of ‘cancer’—diagnoses that usually carry life expectancies of weeks or months. And yet, other neoplasms carry very little morbidity and mortality, and have cure rates of over 90%. One name, but thousands of diseases, each with its own treatment, prognosis, and high-risk population. In this sense, at least, not much has changed since the times in which people died inexplicably of illnesses vaguely referred to as ‘consumption’ or ‘wasting sickness’.

Despite this, the field of oncology itself—the treatment of the one disease that is really many different ones—has become one of the most dynamic and rapidly changing areas of medical research today. Over the last three decades, we have gone from a time in which the only treatment available was surgery to a situation in which a newly diagnosed patient and his physician are often faced with a menu of options in treatment protocols.1 The arrival of radiotherapy, followed by the still ever-growing pharmacopoeia of chemotherapy, have been followed more recently by immunological, histological, and molecular genetic discoveries into the treatment of cells which have lost the delicate and essential control required to function normally.2 Each new step in each field has repercussions that usually extend throughout all of oncology, and not just the specific cancer for which it was developed.

The social and public health aspects of cancer are as dramatic as the recent technological advances. It is the second most common killer in both men and women after heart disease in North America. More alarmingly, the world burden of cancer seems to be increasing at a considerable rate: in 1985, 7.6 million cancers were diagnosed world wide, and 5 million people died of their cancers. In 1990, the number of deaths rose to about 5.7 million, and the predicted number of deaths for the year 2000 is 7.1 million, and a projected 10.6 million new diagnoses will be made.3 Much research and speculation has revolved around these climbing numbers, and everything from the depleted ozone layer to extended lifespans have been implicated.3,4

The social repercussions of the demographics will hopefully be lessened by technological advances in oncology treatment. It is clear from the number of submissions for this volume of the University of Western Ontario Medical Journal that oncology is an area of active research and investigation in our medical community. It is, however, also clear from the number of submissions for this volume that oncology impacts significantly on most, if not all, branches of medicine. This makes it a problem that will require immense resources into and likely beyond the next millennium.

REFERENCES
Dr. Varagur M. Venkatesan is a Radiation Oncologist at the London Regional Cancer Centre (LRCC) who has a special interest in brachytherapy. Brachytherapy is a form of radiotherapy wherein the radioactive substance is placed near or in contact with the tumor. Treatment in this way is called brachytherapy which means "short distance therapy" as opposed to teletherapy or long distance therapy. Although brachytherapy has been available to cancer patients for a few decades, it is currently performed in only selected centres across Canada. One of these centres is the London Regional Cancer Centre.

Dr. Venkatesan received his under-graduate medical education in India, following which he moved to England to pursue training in Ear, Nose and Throat Surgery. He completed an ENT fellowship in Edinburgh, and received post-fellowship training at the University of Wales, Cardiff, U.K. He emigrated to Canada in 1983 and trained in radiation oncology at the London Regional Cancer Centre. Six years later, he joined the London Regional Cancer Centre as a staff radiation oncologist, a position he has held since that time. In 1993, Dr. Venkatesan had the opportunity to travel on sabbatical to Nancy, France where he received advanced training in head and neck brachytherapy. He also received training in prostate brachytherapy in Seattle, Washington. He is an Associate Professor in the Department of Oncology at the University of Western Ontario, and is involved in clinical research pertaining head and neck and prostate cancer. He is married and has a son who is at the University of Windsor doing a business degree. His favorite activities include cricket, golf and traveling with his family.

Could you talk about head and neck brachytherapy?

Head and neck brachytherapy is widely practiced in Europe, especially in France and Italy. However in Canada it is still in its infancy. The radioactive source that is used in head and neck brachytherapy is iridium 192 whose half-life is 74 days. It is a temporary implant (i.e. the radiation source is left in the area of interest for a few days and then removed). In some tumors of the head and neck, brachytherapy is used as the primary modality of treatment, however in others it is used as the final phase of treatment (boost), that is, after an initial course of external beam radiation. The obvious advantage of brachytherapy in treating any malignancy is that the radioactive source is placed either in the tumor or very close to the tumor and hence receives a relatively higher dose of radiation. However, as you move away from the source, the radioactivity falls precipitously, and the surrounding normal tissue receives a relatively less amount of radiation. Hence, if brachytherapy procedure is carried out properly, (i.e. the sources are placed in appropriate locations and at appropriate intervals) we are able to achieve very good tumor control with acceptable treatment complications. One of the major side effects of external beam radiotherapy in head and neck cancers is xerostomia (dry mouth) which occurs as a result of irradiation of salivary glands. In brachytherapy, since the major salivary glands do not receive significant amount of radiation, the incidence of xerostomia is minimal. This is a major advantage. Brachytherapy in general is not only a science but also an art. It is less forgiving compared to external beam radiotherapy, meaning that if the procedure is not carried out properly, and the implant is suboptimal, the outcome is bound to be poor. There is major emphasis in the quality control aspect of brachytherapy when you obtain training in brachytherapy. If the radioactive sources are too close or too far apart, you may end up with not enough radiation, which means tumor control is poor, or too much radiation in which case the complications are bound to be severe and unacceptable. Adequate training is essential before one contemplates carrying out brachytherapy.

Since I have had formal training in ear, nose and throat surgery, I felt I could use my expertise to treat patients with head and neck cancer. My previous surgical training has certainly helped me in learning the techniques of head and neck brachytherapy. I started the head and neck brachytherapy program at the London Regional Cancer Centre a few years ago. Since then I have been able to do "Ir implants in highly selected patients with tumor involving the tongue, floor of mouth and lips.

You are also using brachytherapy to treat patients with prostate cancer. Can you describe the principles of this treatment?

Dr. Glenn Bauman and I have started a prostate brachytherapy program at the London Regional Cancer Centre. It is done in a multidisciplinary setting in
conjunction with the urology department and the radiology department. Dr. Joe Chin is the urologist involved, and we are also collaborating with Dr. Downey, a radiologist at the University Hospital and Dr. A. Fenster, a scientist at the Robarts Research Institute who has a special interest in 3D transrectal ultrasound.

Prostate brachytherapy involves implantation of radioactive iodine seeds ($^{125}$I) into the prostate and seminal vesicles under transrectal ultrasound guidance (TRUS) utilizing a template to guide the needle. Radioactive $^{125}$I seeds are permanently implanted in the prostate and they release the radiation over a period of time. The largest experience of transrectal ultrasound guided prostate brachytherapy is from Seattle, Washington, where over 1500 patients have been treated over the last 10 to 12 years. In a selected group of prostate cancer patients, extremely good results have been reported by them. These include patients with small, low grade prostate cancers with PSA <10. The grade of the tumor is determined by the pathologist, who assigns a score to the tumor based on the histopathological features and this is referred to as the Gleason score. In the studies reported to date, they have found that the patients with a Gleason score of 6 or less tend to do very well. Serum prostate specific antigen (PSA) level is a very useful prognostic indicator in prostate cancer. PSA is a glycoprotein that can be measured in the serum of patients. Higher values indicate worse prognosis. The number of radioactive iodine seeds that are inserted under transrectal ultrasound guidance is determined by the size and shape of the prostate gland, which is again determined by the transrectal ultrasound. The procedure is carried out by a team consisting of the urologist, radiation oncologist, and the radiologist. The procedure can be done either under general anaesthesia or spinal anaesthesia and takes approximately an hour or two.

Currently, the modalities of treatment which are considered to be standard for organ confined prostate cancer are surgery and external beam radiotherapy. Prostate brachytherapy is still considered somewhat experimental. It has been around for approximately 10 to 15 years, and hence, long term results of this treatment modality are not available. It is hoped that in 5 to 10 years, it will be considered as one of the acceptable treatment options for organ confined prostate cancer. Brachytherapy is now offered to a highly selected group of patients who have small organ confined tumors with Gleason score 6 or less and a PSA less than 10. We feel that these patients benefit the most. We have already treated several patients using this modality and the program is expanding to the point that in the near future, we will be doing at least one or two implants per week. We are in the process of commencing a trans-Canada randomized trial which compares radical prostatectomy with brachytherapy for early stage low grade organ confined prostate cancer with PSA less than 10.

How does brachytherapy compare to more conventional treatment modalities for prostate cancer?

If the patients are selected properly for prostate brachytherapy using the criteria outlined above, the outcome is thought to be comparable to surgery and external beam radiotherapy. There are no prospective randomized trials which compare brachytherapy with other modalities. The results are mainly from retrospective series. One of the main advantages of brachytherapy is the convenience to the patient. The patient is discharged home on the day of the procedure or the very next day and the post-operative recovery is quick, he returns to his life routine within a short period of time after the $^{125}$I implant. Brachytherapy does have side effects, including urinary frequency, nocturia, dysuria and urgency. There is a small risk of perineal hematoma. A small proportion of patients, less than 3%, develop complete urinary retention for which an indwelling urinary catheter is required for a period of time. The incidence of impotence is thought to be relatively less compared to surgery and external beam radiotherapy. Most of the side effects from prostate brachytherapy are usually minimal and temporary. If properly selected, the incidence of incontinence with brachytherapy is very low compared to radical prostatectomy. The duration of hospitalization as stated above is less compared to surgery. One of the major advantages of brachytherapy over external beam radiation therapy is the duration of treatment is short and hence it is very convenient to the patient. As stated before, prostate brachytherapy is an art as well as a science and there is a learning curve for the team which carries out the implant.

It has been recently reported that it takes the team approximately 4 to 5 years to perfect this technique. The results of prostate implant is only as good as the geometry of the implant and there is less room for error compared to external beam radiotherapy. It is less forgiving compared to external beam radiation. If the radioactive seeds are not inserted in appropriate places, you may end up with the seeds too far apart resulting in under-dosage and hence poor tumor control or the seeds may be crowding in one area resulting in a hot spot and, hence, increased complication rate such as urinary incontinence due to urethral damage. This is very much a technique oriented modality and the expertise of people concerned is very important in terms of outcome.

Is there a difference in survival between prostate cancer patients treated with brachytherapy and those treated with surgery and external beam radiation?

Currently we have 8-year results on the tumor control and complication rates for prostate brachytherapy from the Seattle group. In patients who are carefully selected for brachytherapy the results are very comparable to surgery and external beam radiation therapy. However, since we do not have long term follow-up, (i.e. 10 to 15 years follow-up) we cannot claim that the results of brachytherapy are as good as those of surgery and radiotherapy. To some extent, brachytherapy has withstood the test of time. The Seattle group have demonstrated that the biochemical progression free and clinical disease free survival curves have reached a plateau at 8 years.

In your opinion, what are important issues in prostate cancer research at the present time?

i. **Conformal External Beam Radiotherapy using Computerized Tomography (CT)**
A practical issue in external beam radiotherapy is how best to deliver the radiation dose, to the prostate gland without giving excessive radiation to the surrounding normal tissue. We are now using a new technique called “conformal external beam radiation therapy” which refers to treating the prostate with a margin. Computerized tomography (CT) has improved our ability to localize and reconstruct the tumor and the anatomy of the surrounding structures in order to accurately design the radiotherapy treatment fields. Many studies are currently underway to assess the efficacy and toxicity of conformal external beam radiation therapy in prostate cancer. In simple terms, the patient is immobilized, the location and extent of the prostate gland is delineated using a CT scan and then with sophisticated computerized technology, the radiation dose is delivered to the prostate gland with a margin in an accurate manner. With this unique technique, we have now proved that it is possible to give a relatively higher dose of radiation to the prostate gland with acceptable side effects. In patients with somewhat bulky prostate cancers, we hope that by giving higher doses of radiation than before, we might be able to achieve better control of the tumor. We ultimately hope that this will translate to a better survival. There are many cancer centres wherein research pertaining to this area are being carried out including ours. Since we are only treating the prostate gland with a small but acceptable margin and avoid excessive irradiation to the surrounding normal tissue, we are able to gradually increase the dose (dose escalation studies) and the results of this exciting research is awaited.

ii. **High Risk Localized Prostate Cancer**
Standard therapy for these patients yield poor results. Research is under way to improve the results by combining hormone therapy given before, during and/or after external beam radiotherapy. Multicentre trials are underway to look at the efficacy as well as the quality of life issues.

iii. **Metastatic Prostate Cancer**
The conventional treatment for metastatic prostate cancer is hormone therapy, i.e., castration, either by surgical or medical means. Although Androgen ablation results in rapid and often dramatic improvement in most patients, the duration of response is limited and ultimately most of them develop hormone refractory disease. Almost all of these patients with hormone refractory disease die of their disease within a year or two. Research is underway to study the mechanism of hormone refractoriness and examine the role of drug resistance markers. Ultimately the goal of this research is to develop treatment which will be effective for these patients, e.g., molecular directed therapy.

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GUT REACTIONS: AN ETHICAL ANALYSIS OF EMERGING BIOTECHNOLOGIES

For this issue’s ethics editorial, I have chosen to discuss several broad ethical considerations surrounding an article written by Glenna Cuccarolo entitled, “AT RISK FOR BREAST CANCER? The Ups and Downs of Genetic Breast Cancer Testing.” As its title suggests, her article presents potentially positive and negative aspects of the biomedical application of personal genetic information; namely selective screening for mutations in breast cancer susceptibility genes (BRCA1 and 2) and the medical management thereof. I will employ BRCA gene technology both as an example (albeit not an exemplar) of a very positive development and as a foil for potentially negative trends in the field of biotechnology.

I am a firm believer in the wisdom of the G.I. tract. It’s not that I discount more cerebral analysis, rather I consider visceral sensations seriously enough to merit investigation. When we hear the term ‘Nuclear’ and the name ‘Einstein’ in the same sentence we typically picture an eccentric, kindly-looking old man, with white hair flailing atop a head of genius. – This is our gut reaction. However, when we put the name ‘Oppenheimer’ together with “Nuclear”, few among us imagine the mysteries of the universe unraveling in the physicist’s cloud chamber. Rather, most of us picture a very different cloud over Hiroshima or Nagasaki – Another gut reaction. I propose that these gut reactions represent a valuable distinction we can take to heart when considering revolutionary discoveries and new technologies. Today, our gut reaction to the names ‘Watson and Crick’ coupled with ‘Genetics’ is most probably a pristine picture of the beautiful double helix – A positive gut reaction. I hope we feel the same in fifty years.

My gut reaction is mixed. Just as nuclear power can be a force of massive amounts of energy as well as mass destruction, genetic biotechnology holds the potential to cure disease or devalue humanity. I do feel hopeful when considering our current capacity to empower some women with valuable knowledge of their own DNA. I marvel at the prospect of curing genetic disease. But I feel uneasy when picturing the very real potential for things to go terribly awry. These are not apocalyptic scribbles on the picket sign of a street-corner fanatic. These are the views voiced by our scientists, physicians, ethicists, economists, and politicians. My concern here, is no more over the scientific discovery of the gene than over the discovery of the atom, for those cats have long been out of the bag. Furthermore, I would hardly choose to rediscover such phenomena, for I could never turn away from their immense positive potential – but my family did not live in Hiroshima, Nagasaki, Three Mile Island, or Chernobyl. As emotionally laden as the term ‘Nuclear’ is presently, I believe ‘Genetic’ may one day surpass it in sheer magnitude. Whether the direction of these emotions will be positive or negative is the subject at hand.

I believe we have a collective duty to actively promote the positive technological developments and actively denounce the negatives – or at very least contribute to public debate. Discerning the positives from the negatives is an integral part of what I believe ought to be the moral debate. The following is a fragment of the type of reasoning I believe should be involved in discriminating among ‘good’ and ‘bad’ biotechnologies. I do not purport to be providing a complete account of the issues at hand. Far from a doctrine, I offer food for the thought of physicians. I will employ the current practice of selective BRCA (1 and 2) screening as representative of an overall ‘good’ technology. I will contrast the approach taken with respect to such technology with the current approach of the Human Genome Project.

Classically trained, I’m compelled to begin my analysis by considering how a given technology fares with respect to standard ethical theories. The Utilitarian holds stock in most biotechnologies for, like most technologies, they are designed to improve outcomes thereby increasing the total happiness of the user. Selectively screening for BRCA gene mutations may certainly achieve such a goal as early diagnosis tends to improve overall outcomes. The Human Genome Project aims to construct a complete blueprint of the human genome. The Utilitarian ought to approve of this project under the condition that its results ultimately increase the total happiness of the population. Practically, this means that if information derived from the complete blueprint enables physicians to cure a given disease such as muscular dystrophy, then the Utilitarian would be swayed towards approval.

Thus far, both our candidates are doing well. However, the moral status regarding the order (or lack thereof) in which the Human Genome Project currently uncovers information has recently been challenged. The project has no mandate stating that we ought to first uncover the nature of the genes responsible for humanity’s most prevalent diseases, or those diseases associated with the highest mortality or morbidity. Without such a mandate, the most sought after gene patents effectively become those most economically beneficial to the researcher.

Not only might we find fault in the project’s lack of
priorities, but we may question the wisdom of mapping the entire human genome. For example, there are currently Biotech Corporations searching among the Icelandic genome for the blond hair, blue eyed cash-cow. The not-so-futuristic images of eugenics, or the bioengineering of 'perfect' people, ought to be disturbing. But the Utilitarian may be less faint of heart, for it is a contingent matter whether a homogeneous 'master-race' may indeed promote the greatest happiness. This virtual reductio-ad-absurdum demonstrates why we cannot entertain a unidimensional, or purely Utilitarian analysis - our gut reactions ought to be negative.

Justice demands that no biotechnology marginalize a group of people or create greater unfairness. Selective screening, such as the aforementioned BRCA protocol, ultimately bridges fairness gaps by empowering and indirectly promoting the physical health of those at high risk of disease. There is always a concern however, regarding the question of who gets screened and who does not. Currently, those who fulfill the screening criteria (i.e. those at highest risk) are offered funded screens while those who are at a lesser risk may purchase the screen. This raises the specter of unequal health care, for the wealthy woman can effectively purchase empowerment in the form of more informed decisions with respect to a wide variety of health care management strategies. While this is an important issue to be worked out, it is not a challenge particular to biotechnologies but rather to health care in general.

The results of the Human Genome Project on the other hand, will probably not only shares this problem in spades, but may allow parents of the future to purchase 'perfect' designer children. The quest for 'perfection' is the issue here. The process of attaining perfection forces us to identify, stigmatize, and devalue 'imperfection'. This may lead to the marginalization of those who fail to meet the standards; a haunting theme often revisited in novels formerly known as fictional.

Finally, Kantian (or more broadly, Deontological) ethics demand respect for human dignity. Selective screening for oncogenic BRCA mutations promotes human dignity by giving women greater control over their health, and enabling them to possibly avoid a crippling disease. Uncovering all human genetic information may ultimately detract from the self-respect and dignity of the 'imperfect'. Several questions ought to be considered, "Can the search for non-disease-causing genes be halted? What counts as a disease-causing gene? For example, is Tourette's sufficiently disabling to merit research with the goal of eradicating the disease from future generations? Is meiopia? How about short, or even average stature?" We ought not promote the reduction of human value, or dignity, to the sum of our attributes.

The allure of biotechnologies resides in our overwhelming, pervasive, and most easily accessible Utilitarian leanings. 'Success' is typically judged by practical outcomes, accurately measured and precisely calculated to the nth decimal place. Utility is conducive to science. Justice and human dignity are not. They cannot be quantified. Some therefore interpret them as being invaluable, others see them as having no value at all. It thus stands to reason that we must see beyond science if we are to appreciate what is at stake in evaluating biotechnologies. We must embrace our roles as physicians qua persons, and physicians qua political entities, lest our legacy be a gut feeling of the worst kind.

Einstein was once quoted in conversation with colleague H.A. Lorentz saying, "One must divide one's time between politics and equations. But our equations are much more important to me." Einstein often spoke in a Kantian way by referring to duty. He recognized that there can be no such thing as a complete, exclusive, scientist qua scientist; for all scientists are persons, and all persons are, by definition, moral beings. Due to the nature of their work, physicists of that time ought to have openly expressed political commitments as well as scientific ones. Physicians today are in a very similar position.

The purpose of the opening to this editorial was not to demonize Oppenheimer, for I hold him in high regard. Rather it is to illustrate how exclusive scientists qua scientists, even great ones, cannot fulfill their social obligations. While Oppenheimer may have had the best of intentions and the most noble of beliefs, he nevertheless went unheard. Einstein on the other hand, is known for his objections to the very project for which he constructed the theoretical groundwork.

The types of warnings we currently hear regarding biotechnologies resemble those voiced by Einstein. His insight and public assertions helped separate his persona from Oppenheimer's. Let us ensure that when we look back upon Watson and Crick, our gut reactions leave us with a pleasant satiety rather than a bellyache and a feeling of impending doom. Let us be more gourmet than gourmand. I'm dedicated to the belief that the outcome of medical biotechnology lies in the hands of the physicians that employ it. Some believe that since they did not make the world the way it is, they cannot be held accountable for upholding the status quo. In truth, I believe we all make the world the way it is.

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Like any other medical field, oncology has an appreciable representation on the Internet. This is not surprising, as cancer is one of the leading causes of mortality in developed nations like Canada (www.statcan.ca/Daily/English/980416/d980416.htm). Therefore it is important as medical practitioners, to rely on sources of information that are reliable and evidence-based. As may be expected, a short article cannot do justice to all the Internet sites on oncology. However, the beauty of the Internet lies in the presence of ‘hyperlinks’ that connect sites to one another. Therefore, if one can begin an adventure of web surfing by looking up a few sites on a particular topic, then one is bound to be infinitely linked to a plethora of additional sites, each containing vast amounts of enlightening information.

As a medical student, perhaps the most important question in my mind is one of resource allocation. The word ‘cutbacks’ has become an anthem to most Canadians and especially to physicians who bear the brunt of government cutbacks in health-care. When dealing with oncology, my first impulse would be to ask how accessible is specialized cancer treatment for people in rural areas. The Internet holds the answer to this dilemma by uniting information from around the world at your fingertips. Perhaps the first web-site to visit for such information is the Cancer Care Ontario (CCO) page (www.cancercare.on.ca). CCO is an agency formed by the government of Ontario to provide leadership to various cancer-care services in Ontario. The web-page has much information regarding government initiatives in oncology including such recent news as the opening of new cancer centres in Oshawa, Mississauga and Kitchener-Waterloo as well as the long waiting lists for radiation therapy. It also contains hyperlinks to the eight regional cancer centres in Ontario which are located in Hamilton, London, Toronto, Windsor, Kingston, Thunder-Bay (North-Western Ontario) and Sudbury (North-Eastern Ontario). Web-sites for each of these regional cancer centres contain a wealth of information on the services available at each of these localities, the research being carried out there, and various medically relevant material. All eight cancer centres can be accessed from the CCO web page and would be an excellent starting point to appraise the facilities available in rural regional cancer centres. It would also be a good way of getting in touch with health care professionals at different community based cancer centres.

After this, the next step would be to find out more about the therapeutic and research aspects of oncology. Basically, surgical excisions of tumors, chemotherapeutic intervention, radiation therapy or combinations are currently used to treat most malignancies. Physicians specializing in each of these areas (surgical oncologists, medical oncologists and radiation oncologists respectively) carry out the different therapeutic strategies. The Oncolink web-site at the University of Pennsylvania has a detailed section devoted to each of the therapeutic modes (www.oncolink.upenn.edu/speciality). The site also keeps track of frontier therapeutic research such as monoclonal tumor-specific antibodies conjugated to toxins or anti-tumour cytokines.

On the commercial side, Genentech, a biotechnology company experimenting with several anti-cancer therapies, maintains a very informative oncology site (www.biooncology.com). One area they advertise is a novel therapeutic agent Herceptin®, a monoclonal antibody used to treat breast cancer. This site also includes information on upcoming meetings, an oncology glossary and links to other equally informative sites. Entremed, the company that holds patents for Angiostatin and Endostatin, has a web site (www.entremed.com) with much information on new therapies including updates on when human clinical trials are expected to begin.

To enhance our knowledge of the ongoing advances in the world of oncology even further, we can surf over to the Oncology Therapeutics Network web site (www.otnet.com) or visit the immunotherapy and gene-therapy weekly news releases at www.newsfile.com. I also suggest visiting the medicine-online web site at www.meds.com where one can find an online cancer library and a database of chemotherapeutic agents. This site also has an online calculator for calculating the dosages of various chemotherapeutic drugs.

Another idea for the net surfers would be to visit the websites of various cancer centres in the United States. Some of them are definitely involved in novel therapies that may be of interest to us in Canada. All the American cancer centres are listed with the NIH at www.nci.nih.gov/cancercenters/centers1.htm.

Keeping up with clinical research is highly important for oncologists. The Oncolink site has a devoted a section to ongoing clinical trials (www.oncolink.edu/clinical_trials). One could even subscribe to an automated electronic mailing list giving updates on recent novel anti-tumour therapies. Another list of clinical trials in the United States can be accessed at www.centerwatch.com. Furthermore, the American National Cancer Institute (NCI) site
Medicine on the Internet

cancernet.nci.nih.gov/nci.htm at NIH has interesting sections in various branches of oncology for both a basic-science researcher, and a clinician.

In keeping with the need for physicians to be well informed of their patient population, it is essential to be aware of the statistics associated with cancer incidence and mortality. Such statistics are readily obtained by doing a search on the Statistics Canada web-site (www.statcan.ca) for cancer, oncology or indeed any other health related item. After a few seconds, the search responds with numerous documents, charts, and tables summarizing a multitude of relevant Canadian statistics. However, if one wants even easier access to such figures specifically for cancer, I suggest consulting the Statistics section of the National Cancer Institute of Canada (www.cancer.ca/stats) where updated 1998 statistics can be obtained.

The internet sites mentioned so far are only a few examples of what is available out there. For those interested in visiting as many web-sites as possible, I suggest consulting a site maintained by the University of Newcastle in England which has a compilation of cancer links from around the world (http://www.ncl.ac.uk/~nchwww/guides/clinks1.htm). They have done an excellent job of cataloguing the sites into categories based on regions and types of cancer. In addition, they have indicated the usefulness of these sites for patients, families, physicians and researchers. If you are interested in cancer and enjoy surfing the Internet, a visit to this web page may begin a long journey into the multi-dimensional nature of oncology.

Lastly, I would like to point out a few sites that are good references for our patients. Most of the reputable sites I have indicated so far contain a special section directed specifically to patients and their families. These include the Oncolink site at the University of Pennsylvania and the American NCI site at the NIH. Among Canadian resources, the eight regional cancer centres all have some sort of information for patients. However, I found that the London Regional Cancer Centre (LRCC, www.lrcc.on.ca) and the Toronto-Sunnybrook Regional Cancer Centre (TSRCC, www.tsrcc.on.ca) are excellent in this regard, directing patients not only to credible information resources but also to community resources that patients may want to access. The TSRCC has a searchable ‘community cancer resource guide’ which covers such issues as prevention, home-care, caregiver relief, and women and cancer. A similar cancer resource directory exists at the LRCC. In addition, the Canadian Cancer Society (www.cancer.ca) and the American Cancer Society (www.cancer.org) have vast amounts of general information on cancer. Finally, clinical centres often have links to sites created by support groups comprised of cancer patients and their families. A good example of these support groups can be seen at www.willow.org (mainly for breast cancer patients) and at www.cancerkids.org (for families of children suffering from cancer). These resources would be useful to cancer patients and their families in providing information, advice and much needed support.

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Cancer morbidity and mortality is the major problem facing North American public health today. Chemotherapy and radiation therapies have been successful in improving the quality of life for many patients, but a definitive cure remains elusive.

Partly in search for a cure, and partly to improve the quality of life for patients non-responsive to conventional therapies, sage and quack alike are touting alternative therapies. Alternative therapies, including herbs, nutrition, chemicals and electromagnetic stimulation, have rapidly arisen over the past 25 years. Only a few of these treatments have been rigorously tested, and even fewer have been validated. As a result, a great debate has emerged between skeptics who await firm evidence before using them and those who stress that there is no time to waste waiting for scientific authorities to come around while cancer patients are suffering.

The use of non-conventional therapies has also sparked many legal battles against the companies and persons that supply them. The case of Charles Pixley and the drug 714-X is a particularly salient example.

714-X is trimethyl bicyclo nitro-amine heptane-cl, a nitrogenous camphor product developed by biochemist/microbiologist Gaston Naessens. He reasoned that cancer cells use “co-cancerogenic K factor” to suppress the immune system and harness the body’s nitrogen to replicate. By providing an exogenous source of nitrogen, cancer cells could still replicate, but would not release “co-cancerogenic K factor” because there would be no need to capture endogenous nitrogen. This would keep the immune system strong and allow for immunity to effectively out-compete slow cancer growth and defeat the cancer.

Gaston Naessens received his microbiology training in France. In the 1960’s, he developed an ultraviolet and laser light microscopic technique capable of viewing live blood with high magnification and resolution. Around 1962, Naessens reported the discovery of a previously unknown microorganism using his microscope. This he termed “somatid”. His descriptions of the findings correspond to *Mycoplasma*, discovered by American researchers in the same year. Working out of Canada, Naessens applied his knowledge of the “somatidian” life cycle, gathered with use of his new microscope, to cancer cells and patented 714-X as an anti-cancer agent in Canada in August 1980. He developed a protocol using homeopathic reasoning, 714-X is not intended to attack cancer cells specifically. It provides nitrogenous compounds to the cell and in so doing, suppresses production of what Naessens termed “co-cancerogenic K factor”, an anti-immune toxin. The agent is made more dilute before administration since homeopaths reason the dilution process to potentiate the medicine.

Naessens’ protocol involves daily intralymphatic injection (1/day) for 21 days, followed by 2 days rest. This is repeated on a cyclical basis until adequate results are achieved. Vitamins E and B12 should not be taken concurrently. A study by Bigelson, MD has shown that 714-X, in combination with other alternative therapies, results in 60-80% effectiveness at reversing cancer.

In 1989, Naessens was charged with 4 counts of illegal practice of medicine and one count of contributing to the death of a person (a patient taking 714-X). He was acquitted on all charges. The same year, his drug was approved in the United States under the *Emergency Drug Relief Act* for use among desperate terminally ill patients.

Since 1990, Charles Pixley’s company *Writers and Research Inc.* has marketed 714-X in the United States, with prescriptions being filled by direct order from Naessens’ private lab in Rock Forest, Quebec. Advocates of 714-X claimed 75% effectiveness in treating cancers using the Naessens protocol.

In 1992, the happy state of affairs was brought to its first crisis point. The Food and Drug Administration, in a move contradicting its own personal import policy on non-conventional remedies, issued an import alert on 714-X even as 5000 orders were to be filled. Pixley countered in 1993 by establishing an Institutional Review Board, a vehicle mandated by Congress to make unapproved drugs available to the public in preliminary trials. Dietmar Schildwaechter, MD, PhD was placed as chief medical investigator. To satisfy the law on informed consent and to ensure proper understanding, the IRB put out a protocol guide entitled *Do No Harm*.

The FDA was not completely satisfied, however. Pixley complied by deleting all mention of the IRB from the protocol and eliminating the link with physicians established under the *Emergency Drug Relief Act* by filling orders directly to individual customers from the lab in Canada.

In 1994, Canada’s Health Protection Board concluded that 714-X is unsafe and refused official drug status. Under the terms of the *Canadian Investigational and Emergency Drug List*, the agent was nevertheless accorded availability on compassionate grounds in Canada. This to date has not been rescinded. We note that in 1994, 714-X was available, albeit under limited terms, in both Canada and the United States.

The Institutional Review Board did not escape the eye of the FDA for long. In 1996, charges were brought against the IRB in circuit court for impeding an FDA investigation into its operations and for illegal importation of a drug.
into the United States. Pixley and his associates were tried, convicted and sentenced and the IRB was disbanded and its publications suppressed. Most recently, Pixley is actively fund-raising to mobilize an appeal before the Second Circuit Court of Appeals to be headed up by the famed lawyer Alan Dershowitz.¹

The ongoing saga of 714-X is only surprising in that government action has been relatively swift and decisive. An immense body of alternative and natural agents geared towards cancer and many other illnesses exists and is being used by patients, in potentially unsafe ways. The claims of their producers vary from baseless to fairly reasonable, as in this case. Given the tremendous amount of concern these ill patients express, and their vulnerability to opportunistic manufacturers or wishful thinking, it is advisable that the onus for proving efficacy be put on the advocates of alternative treatments before their products can be marketed as having any medicinal value. Criminal penalty should be the consequence for infringement.

These recommendations will admittedly prejudice small-scale producers who cannot challenge the monopoly held by the big pharmaceutical companies. However, it is feasible that small-scale producers could cooperate with academia to validate their products scientifically in exchange for profit sharing or government research funding given on a merit basis to groups with alternative therapy proposals. It is crucial that sound scientific evidence about medicinal treatments be sought in a timely fashion, and then translated into safe products with therapeutic potential.

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In traditional cultures, health and healing have been unified with the concepts of religion and morality. Historically, healing practices have been ritualistic and religious. Similarly, sickness has been linked to the violation of established moral norms. In many cultures, physical illness has been associated with a disharmony between the individual and the universe. The concepts of bad karma in Hinduism and the connection in Christianity of illness and sin are examples of how moral digressions can be considered to manifest in physical disease. Thus, in traditional cultures, sickness has distinct causation. Tradition cultures also often have specific types of healers that can cure illness through ritualistic or religious methods. This article is a brief review of disease causation and disease cure in traditional cultures.

DISEASE CAUSATION

Theories of disease causation in traditional cultures usually involve personalized agents that afflict the unlucky or morally transgressive individual. Many traditional cultures share the view that all natural objects, even those that are inanimate, possess a soul. The soul is especially potent in living things, and even more so in human beings. This belief is termed animism (from anima, soul). Those who believe in animism consider the world to be alive, and all objects in the world to have a will and personality. Bad things, such as sickness, occur because they are willed by another, often for personal reasons. By calling sickness the result of a disharmonious interaction with another, it is framed in a moral context. The ill person has insulted or offended someone, usually a deity, an ancestor, or another human being.

Deities exist in most traditional cultures. They are responsible for the creation of both human life and the rules that human life must abide. Violation of these laws invites punishment from the god or gods, in the form of misfortune, sickness and death. Both Judaic and Islamic traditions, for example, have very detailed and rigid codes of conduct that are maintained by a system of reward and consequence. In some cultures, specific diseases are even directly linked with a god. For example, offence of the Hindu goddess Shitala is thought to lead to smallpox.

Offense can also be given to the dead, who in many traditional cultures are believed to have the ability to exist in a noncorporeal form. In these cultures, the dead take great interest in the living, particularly in the activities of their descendants. Those that die in an unhappy state may be transformed into ghosts or demons, who in their frustrated state, try to avenge themselves on the living.

These traditional cultures believe that illness is caused by not respecting and revering deceased relatives, or through the maleficence of angry and listless ghosts.

Traditional cultures also often view sickness and bad luck as the consequence of more mundane interactions. There often exists a belief that inconsiderate behaviour to others can cause illness. This is epitomized by the concept of the mal ojo or evil eye. Sickness is directly correlated with the hatred, jealousy, envy or wrath of an offended human being. The offended party may cause the individual to become sick themselves or they may consult a master of charms, such as a witch or sorcerer.

Whether an illness is triggered by an angry human, an offended spirit, or a crossed deity, there are usually repeating themes in traditional cultures of how this energy is spent to cause actual disease. Soul loss, object intrusion, spirit intrusion and disease sorcery are the most common theories of how illness is immediately caused.

Soul loss involves a relationship between the weakening of the body and the weakening of the soul. If the soul is in poor health, the body reflects this and cannot heal. Whereas common North American beliefs place greater importance in the existence of a body (no body, no person), traditional cultures view the soul as the main requirement for existence. Somewhat hypocritically, though, most North Americans will not find it unusual to blame a person’s illness on a “lost will to live”.

Sickness caused by object intrusion is due to a foreign substance that has been introduced into the body. Many traditional cultures propose that some object has been injected into the afflicted; indeed, sorcery is based on the ability to do so. If the object is not removed, it makes the person ill and then kills them. Spirit intrusion is a similar concept, involving the possession of the ill person by a spirit or ancestral ghost. It is often considered the mechanism of mental illness. Even modern North American culture colloquially refers to the concept of spirit intrusion: “He’s not himself today, something has gotten into him.”

Disease sorcery is an example of a traditional belief in which the immediate and ultimate cause of illness are the same. In this belief, a witch or sorcerer is able to channel psychic power or the energy of their will through charms and rituals. Disease causation is viewed by traditional cultures as the result of personal interactions. The conviction that all inhabitants of the earth possess a will and soul allows transgressions against that culture’s ethical norm to be translated into disease justification.
DISEASE CURE

Diagnosis and therapy of illness in traditional cultures relies heavily on the causative agent. The healer must be able to connect religion, custom and interpersonal skills to determine the cause of the sickness and thereby effectively combat it. For example, if a person has developed an illness due to soul loss, the healer must be erudite in the path that the lost soul has taken. Alternatively, if the illness is largely spiritual, the healer must be able to solve the moral and religious problem the stricken individual has. In traditional cultures, there are several types of medical specialists that appear repeatedly. These are the shaman, the spirit medium, the priest, the holy person and the prescriptionist.

The shaman is considered to be a master of the soul. He or she has the ability to travel to the spirit realm where the souls of the sick have wandered. Through this direct connection with the spirit world, the shaman has the ability to see the soul and ask the help of a spirit or healing ally. In most traditional cultures, the shaman is a part of the divine as much as the world of healing.

The motif of a spirit medium used to cure the sick is also one that commonly appears in traditional cultures. The spirit medium can summon spirits and allow them to act through his or her body to affect the material world. Unlike the shaman, however, the medium is simply a passive tool of the spirit, who instigates the actual healing.

The theme of consulting spiritual powers is repeated in another type of traditional healer: the priest. If the illness has been triggered by offense or insult to a deity or spirit, the priest can help appease the offended party. Only trained priests know the prayers and rituals that supplicate angry deities and spirits. Holy people derive their healing powers from a similar bond with deities, however, they have an innate sacredness and healing power due to their goodness and piety. It may be believed that a god is working through the holy person.

A prescriptionist, in traditional cultures, specializes in preparing medicines. In addition to being learned in the natural attributes of plants, they have a special connection to the spirits of plants. The medicine is almost always composed with the practice of rituals, or the saying of prayers. The ill person may also be given stringent rules about taking the preparation, and prayers to recite.

Disease cure has certain repeating themes in traditional cultures. The healers all possess special talents that allows them to be in intimate contact with the spiritual world. This allows the healer to use his or her knowledge about the culture’s beliefs and traditions in an attempt to correct the disharmony that is causing sickness.

The concept of religion and moral consequence being combined with sickness and health is quite prevalent in traditional cultures. What extent those ideas are manifest in our North American culture’s view of health and healing is a topic that warrants further consideration. Does modern medicine also imply a connection between human behaviour, cause and cure? An understanding of the cultural environment that surrounds medicine can surely serve to improve medical practice.

REFERENCES

PARKE DAVIS
STRIVING TO MAKE MIRACLES HAPPEN
A LITTLE SOONER

Miracles can happen.
But behind every miracle is hard work and determination.
The determination to make our lives a little better,
the hard work necessary to get closer to a cure.
It doesn’t happen overnight; it often takes years of
dedicated research. But when that research culminates in
a breakthrough or a new pharmaceutical,
miracles become possible.

Committed to hard work, determination and caring,
The qualities that can make miracles happen.

PARKE·DAVIS
Scarsborough, Ontario  M1L 2N3
Despite the fact that testicular tumours account for approximately 1% of all neoplasms in men, they are the most common form of cancer in men between 15-35 years old. As a result, in the last 15 years, there has been an emphasis by various groups to ensure that physicians are instructing young men on the testicular self-exam (TSE), and to ensure that men are in fact performing this exam on themselves. It appears that many groups see a parallel between breast cancer in women and testicular cancer in men and thus, they also see a parallel between the breast self-exam (BSE) and the TSE. The question arises as to just how effective the BSE and TSE are when compared to one another and if it is in fact cost-effective to implement widespread TSE education to young men and physicians.

Testicular cancer, as mentioned above, is a mainly a disease of those under 35, as 20% of cancers in this age group originate in the testicle. Thus the disease tends to affect individuals in the prime productive years of their life. The incidence of testicular cancer in Caucasians has doubled over the past 50 years and now is approximately 5.0/100,000 (in contrast, the incidence for breast cancer is 68/100,000). The age adjusted mortality rate, however, has been steadily declining, mostly due to the development of more effective treatment modalities. The current 5-year survival rate for most early stage testicular tumours is about 95%, although morbidity from treatments tends to be high.

The most important risk factor for testicular carcinoma is cryptorchidism, or undescended testes. Other risk factors of less importance include a family history of testicular cancer, high socioeconomic status, Caucasian race, gonadal dysgenesis, a congenital inguinal hernia or hydrocele and being the child of a mother who had exposure to exogenous estrogens during pregnancy.

Testicular cancers can be grouped into 2 main major pathological categories. Seminomas account for 40% of testicular tumours and tend to be radiosensitive. Non-seminomas (embryonal carcinoma, choriocarcinoma, endodermal sinus carcinoma and teratoma) make up 50% of all testicular tumours and are generally less radiosensitive. One also often sees tumours of mixed histology. Between 50-60% of seminomas and 30% of non-seminomas present at an early stage of disease. Despite this, even patients with metastatic disease have about a 90% cure rate.

Both types of testicular tumours tend to present with a painless mass within the substance of the testicle and it is with this reasoning that the testicular self-exam was developed. The exam should be done while the scrotum is warm, preferably after a bath or shower. Both hands are used to roll each testicle between the thumb and fingers. The testes, epididymis and spermatic cord should all be palpated and lumps, irregularities and any dragging sensations should be noted. It is recommended that men aged 15-40 years perform the exam monthly.

The American Cancer Society recommends that BSE be performed by all women beginning at age 20 and thus should be taught to every teenager as a method of preventative medicine. The National Cancer Institute recently found that 90% of women in the United States were aware of the BSE, although only 24% actually perform monthly self-exams. This can be contrasted with a recent study in which a survey of male college students indicated that over 41% had been taught TSE, but only 8% actually practiced TSE once a month.

It thus argued that more of an emphasis needs to be placed on teaching TSE to men in order to attempt to detect testicular cancer as early as possible, in an attempt to achieve a near 100% cure rate. Should as much emphasis be placed on the TSE as the BSE? Goldenring and Purcell suggest that with the cure rate for cancer of the testes being greater than that of breast cancer, and with the TSE being a much simpler examination technique, our current efforts are nothing short of inadequate. Their sentiments are underscored by many in many other works by public health advocates.

There has also been shown to be a documented delay between the onset of symptoms and the diagnosis of testicular cancer – usually in the order of around 3 months. Many point to this delay as support for more education with regards to TSE. Unfortunately, this delay appears to have more to do with reluctance on the part of both the physician and the patient. Patients tend to be reluctant because they fear the diagnosis, believe they are responsible (i.e. through masturbation or excessive physical activity), or fear that treatment will leave them impotent or sterile. Doctors have been shown in 1/3 of cases to be responsible for the delay, mostly due to the assumption of the mass being a more benign condition such as a hydrocele or epididymitis, or because they are reluctant to diagnose a relatively rare cancer in a young man. As a result it does not appear as if encouraging TSE education alone would be sufficient to prevent a delay, as the actual finding of a mass does not appear to be the primary problem.

Some argue against TSE by claiming that there would be a great amount of anxiety caused by the number of
false positives generated as the result of young men mistakenly assuming that benign conditions were cancerous. This has been refuted by a study by Weist and Finney which showed that training in the TSE among college and high school students was not associated with elevated anxiety states.

The biggest evidence against putting more money into the amount of TSE training comes by examining how cost effective widespread education would be. As mentioned before, there is an increasing incidence in testicular carcinoma amongst young men, but is an increasing incidence a good enough justification? The answer must be no, since screening will only affect mortality and not the actual incidence of the disease. Since mortality (as shown above) is already so low, the scope for screening to have an effect is very small. In other words, even if TSE were to reduce mortality by half, 500,000 men aged 15-34 would have to perform monthly TSE’s for one year in order to prevent one death.

The major problem with TSE is that no randomized control studies have been performed to determine its actual benefit. Moreover, it is unlikely that such a trial will ever be performed, due to the rarity of the disease, the low number of deaths from it, and the high cost of such a trial. There have also been no studies that show that men who examine their testes are more likely to detect cancer earlier or have an improved outcome than men who do not. Additionally, very few studies exist which show that teaching TSE motivates men to perform it, yet alone to perform it correctly.

It seems clear that there is a need to educate young men about the early presentation of testicular cancer in order to reduce the delay in diagnosis, but there seems to be little hard evidence supporting widespread education regarding TSE. The question then arises as to why there seems to be so much support for TSE? Is it because of the parallel being drawn with breast cancer and BSE? If this is the case, it seems imperative to stress to all health care advocates that a correlation cannot be drawn between these two diseases simply because they each affect only one sex.

If widespread TSE education is ineffective, then what should be done? It seems that if any education is to be done, it should be aimed at primary care physicians. The focus of this education should not be on the TSE, but should rather be to simply raise awareness of testicular neoplasms in general. If family physicians maintain a high index of suspicion for testicular carcinoma when dealing with any scrotal mass, we would most likely see an earlier diagnosis of these lesions. Additionally, family doctors should be aware of the use of other investigative tools, such as scrotal ultrasound, when the clinical exam proves to be equivocal.

Acknowledgement

The author would like to thank Dr. J.L. Chin for his suggestions and peer review of this paper.
You are a second year surgical resident, rotating through your two month service in otolaryngology when presented with the following clinical scenario.

On Feb 15 an otherwise normal clinic has been booked for the day. You are feeling particularly refreshed after a rare full six hours of sleep the night before. The first patient you see that day is a woman by the name of “Mrs. Smith.” On history, Mrs. Smith reveals that she was referred to the local E.N.T. specialist for her recent difficulties with hearing in her right ear.

1. Identify two classes of hearing loss and list a few of the common etiologies of each.

Upon further discussion, Mrs. Smith describes that her hearing loss has been getting progressively worse in the right ear for the past 3 years. She also mentions that it is now so severe, she is unable to use that ear when speaking on the phone.

2. Discuss other points you would want to explore during the history that would be pertinent with respect to hearing loss.

Mrs. Smith reveals that she has also been experiencing a “hum” in her right ear that has been present for approximately the same length of time as the hearing loss. She also recalls feeling unsteady at times, but denies any vertiginous episodes. The rest of the history reveals no other significant details. On examination, a Weber test lateralized to the left and a Rinne test was positive in both ears. Romberg’s sign was positive with the patient falling to the right. Further physical exam reveals no other abnormalities. The audiogram below was performed today prior to clinic.

3. Discuss the above findings with relevance to the case at hand, including analysis of the audiogram.

4. Your clinical experience to date leads you to suspect a cerebellopontine angle tumor, indicate the “gold standard” imaging modality in this scenario and list the common tumors of the cerebellopontine angle.

You have now completed your history and physical exam of Mrs. Smith and proceed to present the case to the consultant at clinic.

5. You are asked by the consultant to give the most common presenting symptoms of an acoustic neuroma and their relative frequencies.

The consultant and yourself have viewed the MRI images and discussed the findings with radiology; you feel rather confident that the problem at hand is an acoustic neuroma affecting cranial nerve VIII. You discuss with Mrs. Smith your suspected diagnoses and proceed to inform her that you feel surgical removal of the tumor is the recommended treatment modality.

6. Discuss the different surgical options available and common complications associated with each.

ANSWERS

1. The two classes of hearing loss described in the literature are conductive and sensorineural hearing loss.

   Conductive hearing loss results primarily from lesions involving the external and middle ear, including the tympanic membrane. It can be further classified as either congenital or acquired. Some examples of congenital malformations of the ear include atresia of the external ear and ossicular abnormalities. Acquired malformations include most commonly, cerumen impaction of the external canal, otitis media either supplicative or serous, chronic otitis media (cholesteatoma and erosion of the ossicular chain), otosclerosis and traumatic perforation of the drum with ossicular disruption.

   Sensorineural hearing loss is the result of a lesion to the cochlea or auditory division of the VIII cranial nerve, or both. It can also be divided into congenital and acquired, with genetic inheritance and maternal rubella being two examples of congenital hearing loss. Some examples of acquired hearing loss include, presbyacusis, noise induced hearing loss, ototoxicity due to aminoglycosides or cytotoxics, inflammatory conditions such as meningitis, measles, mumps, syphilis and chronic otitis. Neoplasms such as acoustic neuromas and idiopathic etiologies such as Meniere’s disease have also
been implicated.1

2. Other features that would be important to elicit on history include: associated otalgia or otorrhea, tinnitus, imbalance or sensation of vertigo, excessive noise exposure, pertinent drug history (ototoxic agents) and family history of hearing loss.2

3. The results of the Weber and Rinne test are indicative of a sensorineural hearing loss in the right ear. The positive Romberg’s sign can be due to a right-sided vestibular disorder. The combination of a progressive asymmetric hearing loss, tinnitus and vestibular related dysfunction is highly suggestive of an acoustic neuroma of the the right VIIIth cranial nerve.3 Audiogram analysis further validates our suspicion of a severe right sided hearing loss.

4. The gold standard for the diagnosis of an acoustic neuroma is gadolinium-enhanced magnetic resonance imaging. The sensitivity of high resolution CT to pick up acoustic neuromas of less than 15mm has been shown to be only 48%.4 It has been suggested that the increase in use of MRI has enabled the mean tumor size at the time of detection to decrease from 27.9mm in 1975 to 16.5mm in 1989.5 The common tumors of the cerebellopontine angle include 78% acoustic neuromas, 6.3% meningiomas, 6.3% cholesteatomas, 5.9% gliomas and remaining 3.5% abscesses and miscellaneous tumors.6

5. The most commonly encountered presenting symptoms in patients with acoustic neuromas were shown by Gillman and Parnes.7 This was done with a retrospective study of 83 patients, with 84 acoustic neuromas, over a 6 year period. Hearing loss was the most common presenting symptom at 91%, tinnitus 51%, imbalance 49%, headache 15%, trigeminal nerve dysfunction 13%, facial nerve dysfunction 7% and other 1%.

6. There are essentially three surgical options available when considering removal of an acoustic neuroma. They are the translabyrinthine approach (TL), middle fossa approach (MF) and Suboccipital approach. Each procedure has its own advantages and disadvantages. The goal of acoustic tumor removal is preservation of facial nerve integrity, total removal of tumor to prevent recurrence and mortality and, when possible, preservation of hearing. Preservation of hearing is only possible with MF and SO approaches as the TL approach must sacrifice hearing in the affected ear. The other two objectives can be achieved by all three of the surgical options. Other management options in certain situations include stereotactic radiosurgery and observation8 Further analysis of the surgical approaches will not be done in this case report.

Some of the more common post-operative complications include CSF leak at 11.2%, severe headache at 11.2%, wound 6%, cranial nerve injury (except VII and VIII) at 4.2% and meningitis at 2.8%.9

REFERENCES
There is an adage that "a mediocre teacher teaches, a
good teacher explains, and a great teacher inspires." 
Apparently, some lecturers believe that a mediocre
teacher preaches, a good teacher bores, and a great teacher
sedates. It is rather amusing to think of all the assorted
scenarios that can and have played out in the classroom.

Take for instance the lecturer, who when questioned,
will reply with "someone else in this course will be
teaching you this." While this certainly may be the case,
often it is not. This leaves me wondering whether the
lecturer just doesn't know the answer, or whether it might
somehow go against the alignment of the cosmic
constellations to enlighten us with the answer. I didn't
realize that a lecturer could plead the fifth.

It is also rather comical to have a lecturer who has
gotten stuck with teaching a particular class. This is
unfortunate for both lecturer and class alike. In some cases,
the lecturer is unaware of what information to emphasize,
nor are they always as capable and knowledgeable on the
given topic. As the lecturer drones on, the subconsciously
flog themselves with a Singaporean cane for agreeing to
cover their colleague's snorkeling emergency. The class
observes this unfortunate sacrificial lamb with contempt as
they enjoy their third hand of poker.

Then there is the lecturer who engrosses the class into
a sedated stupor reminiscent of a good benzodiazepine.
These lecturers are famous for inspiring impromptu
“snack-times” or regression to naptimes of a childhood
past.

One of the greater challenges in listening to lectures is
translating and decoding the rhetoric. “Don't bother
writing this down” has come to mean “You better know
this word-for-word,” and “You are the doctors of
tomorrow” is now understood to mean “God help us all.”
Then there is the easily translated “Today, we have a
very special guest for you” which has come to mean “this
was the only person we could find” and “this material is
not testable” easily translates into “you have my
permission to go home and frolic amongst yourselves.”

While my arguments may seem critical of lecturers, I
do hold them in high regard. In fact, if I could, I would
sing their praises right here, for pages and pages on end.
But sadly, I am no Pavarotti and thus will restrict my
singing to the tormenting of my brother.

PHYSICIANS NEEDED

Leamington District Memorial Hospital, situated on the beautiful shores of Lake
Erie, a short drive from Windsor and Detroit needs physicians in:
G.P. Anaesthesia
Emergency Medicine

The Hospital provides a full range of services for a catchment area of 45,000
population, including 24 hour Emergency Service, General Surgery and
OB/GYN Surgery. The Hospital Service Restructuring Commission has
mandated that the Hospital continue its present range of services.

As well, the area has been designated as underserviced and there is a need for
additional:
Family Physicians

The Town of Leamington, located in the southernmost part of mainland Canada,
enjoys numerous recreational facilities including excellent marinas and golfing,
as well as progressive schools and churches of all denominations. Point Pelee
National Park and Pelee Island are also local attractions.

If you wish to discuss these opportunities further, in confidence, please contact:

Dr. Robert Page or Warren Chant
Chief of Staff Chief Executive Officer
Leamington District Memorial Hospital
794 Talbot Street West
Leamington, Ontario
N8L 1N9
Telephone: (519) 326-2373

"We believe our first responsibility is to the
doctors, nurses and
patients, to mothers and
dathers and all others
who use our products
and services."

- From the first tenet of the
Johnson & Johnson Credo.
**LIPITOR**
(Atorvastatin Calcium)

**INDICATIONS AND USAGE**

LIPITOR (atorvastatin calcium) is a synthetic, lipid-lowering agent. It is a selective, competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is the rate-controlling step of cholesterol synthesis in the liver and by increasing the number of hepatic Low Density Lipoprotein (LDL) receptors on the cell-surface for enhanced uptake of LDL particles.

LIPITOR lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic Low Density Lipoprotein (LDL) receptors on the cell-surface for enhanced uptake of LDL particles. LIPITOR reduces LDL-Cholesterol (LDL-C) and the number of LDL particles. LIPITOR also reduces Very Low Density Lipoprotein-Cholesterol (VLDL-C), serum triglycerides (TG) and Intermediate Density Lipoprotein (IDL) as well as the number of IDL particles, but increases High Density Lipoprotein-Cholesterol (HDL-C).

LIPITOR elevates serum cholesterol due to elevated LDL-C; a major risk factor for the development of cardiovascular disease. Elevated plasma Tg is also a risk factor for cardiovascular disease, particularly if due to increased DL, or associated with decreased HDL-C or apo A1.

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur in 1 to 2 hours. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions. Mean distribution of atorvastatin in approximately 38% times. Atorvastatin is a CYP2C9, bound to plasma proteins. Atorvastatin is extensively metabolized by cytochrome P450 3A4 to other and para-hydroxylated derivatives and to various beta-oxidation products. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. Atorvastatin and its metabolites are eliminated by biliary excretion. Less than 2% of a dose of atorvastatin is recovered in urine after oral administration. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 2 to 3 hours due to the contribution of longer-lived active metabolites.

**DOSAGE AND ADMINISTRATION**

LIPITOR (atorvastatin calcium) is indicated as an adjunct to diet, at least equivalent to the American Heart Association (AHA) Step 1 diet, for the reduction of elevated total cholesterol, (total-C), LDL-C, TG and apolipoprotein B (Apo B) in hyperlipidemic and dyslipidemic conditions, when response to diet and other nonpharmacological measures alone has been inadequate, including:

- Primary hypercholesterolemia (Type IIa).
- Combined mixed hyperlipidemia (Type IIb), including familial combined hyperlipidemia, regardless of whether cholesterol or triglycerides are the lipid abnormality of concern.
- Dysbetalipoproteinemia (Type IV).
- Hyperylipidemia (Type V).
- Familial hypercholesterolemia (homozygous and heterozygous). For homozygous familial hypercholesterolemia, LIPITOR should be used as an adjunct to treatments such as LDL apheresis, or as monotherapy if these treatments are not available.

In clinical trials, LIPITOR (10 to 80 mg/day) significantly improved lipid profiles in patients with a wide variety of hyperlipidemias, and demonstrated clinical improvement in 2- to 6-week response studies in mildly-to-moderately hyperlipidemic patients (Fredrickson Types IIa and IIb). LIPITOR reduced the levels of total cholesterol (25-45%), LDL-C (35-50%), Apo B (30-50%), and TG (40-60%), and increased HDL-C levels (9-13%). Comparable reductions were achieved in patients with heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, combined hyperlipidemia, including familial combined hyperlipidemia and patients with non-insulin dependent diabetes mellitus. In patients with heterozygous Type II, LIPITOR (10 to 80 mg/day) reduced TG (25%-50%) and LDL-C levels (23%-40%). Cholesterol, which characterizes Type I and V, have not been measured in clinical studies in patients with high TG levels (>11.1 mmol/L). In an open-label study in patients with dysbetalipoproteinemia (Type III, LIPIORT 10 to 80 mg/day) reduced total-C (40%-57%), TG (40%-56%) and LDL-C: VLDL-C ratio [45%-58%]. In an open-label study in patients with homogenous familial hypercholesterolemia FH LIPITOR (10 to 80 mg/day) reduced total-C (40-48%), LDL-C (42-47%) and Apo B (41-50%) levels in 21 patients with FH. LDL-C lowering of 35% for patients not on plasmapheresis and of 31% for patients who continued plasmapheresis. A mean LDL-C lowering of 35% was observed in receptor defective patients and of 19% in receptor-negative patients (see PHARMACODYNAMIC/CLINICAL STUDIES).

For more details on efficacy results by pre-defined classification and pooled data by Fredrickson types, see PHARMACODYNAMIC/CLINICAL STUDIES.

Prior to initiating therapy with LIPITOR, secondary causes should be excluded for elevations in plasma lipids levels (e.g., poorly controlled diabetes mellitus, hyperthyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, and alcoholism), and a lipid profile performed to measure total cholesterol, LDL-C, HDL-C, and TC. For patients with TG ≤<52 mg/dL, LDL-C can be calculated using the following equation:

\[
LDL-C (mg/dL) = total-C - (0.573 \times TG) \]

For patients with TG between 52 and 400 mg/dL, this equation is less accurate and LDL-C concentrations should be measured directly or by ultracentrifugation.

**CONTRAINDICATIONS**

Hyperreactivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (see WARNINGS).

Pregnancy and lactation (see PRECAUTIONS).

**PRECAUTIONS**

Pharmacokinetic Interactions

The use of HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which may be triggered by other drugs that inhibit cytochrome P-450 enzyme system. Atorvastatin is metabolized by cytochrome P-450 3A4 and may interact with such agents as follows. See WARNINGS, Muscle effects and PRECAUTIONS, Drug Interactions and CYTOCHROME P-450-INTERACTED medications.

Hepatic Effects

In clinical trials, persistent increases in serum transaminases greater than three times the upper limit of normal occurred in <1% of patients who received LIPITOR. When the dosage of LIPITOR was reduced, or when drug treatment was discontinued, transaminase levels returned to normal. In general, these elevations were generally not associated with jaundice or other clinical signs or symptoms. Most patients continued treatment with a reduced dose of LIPITOR without sequelae.

Liver function tests should be performed before the initiation of treatment, and periodically thereafter. Special attention should be paid to patients who develop elevated serum transaminase levels, and these patients measurements should be repeated promptly and then performed more frequently.

If increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) show evidence of progression, particularly if they rise to greater than 3 times the upper limit of normal and are persistent, the dosage should be reduced or the drug discontinued.

LIPITOR should be used with caution in patients who consume substantial quantities of alcohol and/or a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of LIPITOR, if such a condition should develop during therapy, the drug should be discontinued.
Patients with mild to moderate hypercholesterolemia. LDL-C reduction was greater when LIPITOR 10 mg and colesterol 20 mg were coadministered (40% vs. 35% for LIPITOR and 20% for coadministration).

Patients with severe hypercholesterolemia. LDL-C reduction was similar (53%) when LIPITOR 40 mg and colesterol 20 mg were coadministered when compared to that with LIPITOR 60 mg alone. Plasma concentration of atorvastatin was lower approximately 28% when LIPITOR 40 mg plus colesterol 20 mg were coadministered with LIPITOR 40 mg alone.

However, the combination drug therapy was less effective in lowering the triglycerides from LIPITOR monotherapy in both these hypercholesterolemic subtypes than other statins (see PHARMACODYNAMICS). When LIPITOR is used concomitantly with colesterol or any other resin, an interval of at least 2 hours should be maintained between the two drugs, since the absorption of LIPITOR may be impaired by the resin.

Fibrillar Derivatives (Gemfibrozil, Fenofibrate, Bezafibrate) and Niacin (Nicotinic Acid). Although there is no experience with the use of LIPITOR given concurrently with fibrin derivatives and niacin, the benefits and risks of such combination therapy should be carefully considered. The risk of myopathy during treatment with other drugs in this class, is increased with concurrent administration (see WARNINGS, Muscle Effects).

Coadministration: LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy (see SELECTED BIBLIOGRAPHY).

Coadministration: Coadministration of multiple doses of LIPITOR and digoxin increased steady-state plasma digoxin concentrations by approximately 20%. Patients taking digoxin should be monitored closely and appropriately.

Oral Contraceptives: Coadministration of LIPITOR with an oral contraceptive, containing 1mg norethisterone and 30ug ethinyl estradiol, increased plasma concentrations and AUC levels of norethisterone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive.

Antacid: Administration of aluminum and magnesium based antacids, such as Maalox® TC Suspension, with LIPITOR did not diminish plasma concentrations of LIPITOR by approximately 30%. LDL-C reduction was not altered but the triglyceride-lowering effect of LIPITOR may be affected.

Coadministration: Administration of comedine with LIPITOR did not alter plasma concentrations or LDL-C lowering efficacy of LIPITOR. However, the triglyceride-lowering effect of LIPITOR was reduced from 34% to 26%.

Cytocochrome P-450-Related Interactions: Atorvastatin is metabolized by the cytochrome P-450 3A4 enzyme, CYP 3A4. Ethinylstron, a CYP 3A4 inhibitor, increased atorvastatin plasma levels by 40%. Coadministration of CYP 3A4 inhibitors, such as galepamulfur, macrolide antibiotics (including erythromycin and clarithromycin), iminodiazepines (enzopicron, azep amfargfic salts (i.e. trimipramine, ketocnazole), or the antiretroviral rifabutin may have the potential to increase plasma concentrations of HMG-CoA reductase inhibitors, including LIPITOR (see SELECTED BIBLIOGRAPHY). Care should be taken to administer co-use of these agents (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects, PRECAUTIONS, Renal Insufficiency and End-Organ Function, DOSAGE AND ADMINISTRATION, SELECTED BIBLIOGRAPHY).

In a small number of healthy subjects, concomitant administration of maximum doses of both atorvastatin (80 mg) and terfenadine (120 mg, a CYP 3A4 substrate, was shown to produce a modest increase in terfenadine AUC. The QT interval remained unchanged, however, since an interaction between these two drugs cannot be excluded in patients with pre-existing factors for arrhythmia (e.g. pre-existing prolonged QT interval, severe coronary artery disease, hypokalemia), caution should be exercised when these agents are coadministered (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects, PRECAUTIONS, DOSAGE AND ADMINISTRATION).

Antipyrine: Antipyrine was used as a specific non-model drug for metabolised by the microsomal hepatic enzyme system (cytochrome P-450 system). LIPITOR had no effect on the pharmacokinetics of antipyrine, thus interactions with other substrates metabolised via the same cytochrome isoenzymes are not expected.

Enzymeinduced in healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of LIPITOR and oral contraceptives, a known inhibitor of CYP 3A4 sees WARNINGS. Muscle Effects).

Other Concurrent Therapies: In clinical studies, LIPITOR was used concomitantly with antithrombin agents and estrogen replacement therapy without evidence to date of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted.

Patients with Severe Hypercholesterolemia: Higher drug dosages (80 mg/day) required for some patients with severe hypercholesterolemia. Dosage recommendations are associated with increased plasma levels of atorvastatin. Caution should be exercised in such patients who are also severely receiving impaired, elderly, or are concomitantly being administered digoxin or CYP 3A4 inhibitors (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects, PRECAUTIONS, Drug Interactions, DOSAGE AND ADMINISTRATION).

LIPITOR may elevate serum transaminase and creatinine phosphokinase levels (from skeletal muscle). In the differential diagnosis of chest pain in a patient on therapy with LIPITOR, cardiac and noncardiac factors of these symptoms should be determined.

ADVERSE REACTIONS

LIPITOR is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies (placebo-controlled and active-controlled comparative studies with other lipid lowering agents involving 2525 patients, <2% of patients were discontinued due to adverse experiences attributable to LIPITOR. Of these 2525 patients, 1729 were treated for at least 6 months and 1252 for 1 year or more. Adverse experiences occurring at an incidence >1% in patients participating in placebo-controlled clinical studies of LIPITOR and reported to be possibly, probably or definitely drug related are shown in Table 1 below.

Table:<br>TABLE 1. Associated Adverse Events Reported in >5% of Patients in Placebo Controlled Clinical Trials

<table>
<thead>
<tr>
<th>Lipitor (%)</th>
<th>Placebo (%)</th>
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<tbody>
<tr>
<td>Constipation</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
</tr>
<tr>
<td>MUSCULAR SYSTEM</td>
<td>2</td>
</tr>
<tr>
<td>Pain</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>&lt;1</td>
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</tbody>
</table>

The following additional adverse events were reported in clinical trials, not all events listed below have been associated with LIPITOR treatment. In general, the adverse experiences associated with the use of the LIPITOR were similar to monotherapy, myopathy, pancreatitis, pericarditis, pleurisy, neuropsychiatric events, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, anuria, pruritus, rash, impotence, hyperglycemia, and hypothyroidism.


For a copy of the Product Monograph or full Prescribing Information, please contact: Porker Canada Inc., 1500 Canada Mills, Scarborough, ON M1L 3M3.
THE MUTAGENICITY OF SURGICAL SMOKE IN ELECTROSURGICAL PROCEDURES

By Sandy Widder, MEDS 2001

Recently, the safety of surgical smoke generated by electrosurgery devices has become a topic of much concern. Electrocautery is used to dissect tissue or cauterize blood vessels with a high radio frequency electrical current. During the cauterizing process, copious amounts of visible smoke are produced. The smoke is malodorous and tends to irritate operating room personnel by producing burning, watery eyes, respiratory problems and nausea. Many animal studies have demonstrated the ill effects of electrocautery smoke plume, though its specific effects have yet to be determined in humans.9

SURGICAL SMOKE STUDIES

The combustion of animal tissues leads to the formation of carcinogenic amines.2 Heterocyclic amines have also been identified from environmental components like airborne particles and cooking fumes.3, 4, 5, 6 Animal studies have shown that the mutagenic agents in smoke from cooking fish and meat cause tumor formation in rodent organs such as liver, lung, large intestine, and mammary gland.7

In recent years, electrocautery smoke has been demonstrated to possess mutagenic properties. Analysis of electrocautery smoke determined that its chemical composition consisted of significant levels of benzene, ethyl benzene, styrene, carbon disulfide and toluene.8 Individually, these chemicals have all demonstrated carcinogenic effects in both animal and human studies. Styrene exposure in humans causes irritation of the eyes and respiratory tracts; some studies have even indicated increases in the frequency of lung and other cancers with styrene exposure, though the studies are considered inadequate by some.9 Carbon disulfide has been shown to cause mutagenesis of human germ cells and to induce embryonic growth retardation.10, 11 Toluene exposure in humans has led to increased risks of various gastrointestinal cancers as well as lung cancer.9 Benzene exposure is strongly associated with an increased risk of leukemia.12 As well, a large Chinese cohort study linked benzene exposure to a greater risk of lung and nasopharyngeal cancer.13

Gatti et al. tested airborne smoke particles for mutagenic potential in two strains of Salmonella typhimurium (TA 98 ands TA 100) and found that smoke induced by an electrocautery knife was mutagenic to the TA 98 strain.14 The aforementioned study supports an older, similar experiment by Tomita et al., which concluded that the mutagenicity of electrocautery smoke condensates was comparable to that of cigarette smoke.15

SMOKE SAFETY MEASURES

Currently employed surgical masks filter 5 micrometer size particles.16 However, more than 77% of the particulate matter contained in surgical smoke is less than 1.1 micrometers in size.16 As a result, other methods are necessary in order to diminish exposure to electrocautery smoke.

The National Institute for Occupational Safety and Health in the United States has demonstrated several methods whereby airborne contaminants generated by electrocautery can be controlled. It is recommended that a combination of general room and local exhaust ventilation be used. Smoke evacuation methods may consist of the simple attachment of a suction apparatus to the cautery hand piece or having an assistant with a high flow suction tip.17 Additional means include commercial smoke removal systems and high filtration surgical masks/respirators worn by members of the surgical team.18

Unfortunately, though several studies have proven the deleterious effects of surgical smoke plume, many members of the perioperative team are indifferent or negatively inclined towards the use of protective ventilatory devices (general or local).16 The most likely reasons for the aforementioned attitudes are as follows19:

- Some individuals believe that smoke plume is not a hazard to one's health.
- There is a perception by many surgical personnel that surgical masks provide adequate ventilation.
- It is also thought by some that evacuating equipment may interfere with surgical procedures or the surgeon's dexterity.
- Lack of resources available to purchase a smoke evacuator.
- Lack of the availability of personnel needed to hold an evacuator wand.

CONCLUSION:

Surgical smoke plume contains known carcinogens and irritants, which can produce watery, burning eyes, dermatitis, central nervous system effects, hepatic and renal toxicity, and bronchitis or emphysema-like...
conditions.\(^8\)\(^{16}\) Though there have been no formal studies determining the exact effects of inhaling mutagenic surgical smoke in humans, it has been proven that electrocautery smoke condensates collected during surgery have genetically altered strains of *Salmonella bacteria*. Further studies ought therefore to concentrate on the specific hazards of surgical smoke plume by determining the level of exposure by the surgeon and surgical staff; longitudinal studies would also be valuable in assessing any detrimental effects which might be suffered as a consequence of electrocautery smoke contact. Until such additional studies are investigated, simple techniques such as high filtration masks and local electrocautery smoke suction ought to be employed in order to minimize electrocautery smoke exposure in the operating room setting.

ACKNOWLEDGMENT:

The author wishes to thank Dr. R. Holliday, Department of Surgery (S.S. LHSC), for his constructive suggestions.

REFERENCES:


ANGIOGENIC INHIBITORS: NEW POSSIBILITIES FOR CANCER THERAPY

By Tisha Joy, MEDS 2001

BACKGROUND

The formation of new blood vessels, known as angiogenesis, is a critical component of tumour biology, in both local tumour growth as well as distant metastatic spread. Without neovascularization, tumours have been found to be unable to grow beyond a size of 2 to 3 mm³ due to an equilibrium present between the cellular proliferative rate and the apoptotic rate. Thus, these tumours may persist for months, or even years, in a “dormant” state until a particular subset of malignant cells converts to an angiogenic phenotype. The exact mechanism involved in this conversion is still not completely understood. Yet, it involves some form of variation in the local balance between positive and negative regulators of angiogenesis.

Shedding of tumour cells to distant sites has been demonstrated to begin only after a tumour has become vascularized. In fact, it has been shown that the greater the vascular density of a tumour, the greater the chance for malignant cells to enter the circulation. Interestingly, proliferating capillaries of the tumour neovascularure have been found to consist of fragmented basement membranes, resulting in these capillaries being more leaky than mature vessels and thus, more conducive to entry of malignant cells into circulation. This correlation between vascular density and metastasis, relapse, or mortality has been shown in several neoplasms, such as breast cancer and colorectal cancer, and has been a key factor in the recent interest in angiogenic inhibitors as a form of cancer therapy.

Angiogenic inhibitors or antiangiogenic agents were first proposed as a form of antitumour therapy in 1971. Since the primary target of antiangiogenic agents is the proliferating endothelium, there are many advantages to the use of these agents, as summarized in Table 1. One important advantage is that these agents are less likely to result in resistance because endothelial cells are diploid cells possessing a stable genome. Thus, the potential for angiogenic inhibitors as an effective cancer therapy is enormous. This article will focus on two classes of angiogenic inhibitors, namely tumour-derived inhibitors and matrix metalloproteinase inhibitors.

TUMOUR-DERIVED INHIBITORS

Angiostatin and endostatin are two angiogenic inhibitors that have received a lot of media attention recently. Angiostatin is a 38 kD fragment of the precursor, plasminogen. Although plasminogen itself is not antiangiogenic, angiostatin is indeed a potent inhibitor of endothelial cell proliferation and migration as well as a circulating angiogenesis inhibitor. Angiostatin is actually a tumour-derived inhibitor since it only appears in the serum in the presence of the primary tumour, and upon removal of the primary tumour, angiostatin disappears from circulation, resulting in growth of metastases. However, even though angiostatin is tumour-derived, it is not thought to be produced by the tumour cells per se, but instead to be the result of cleavage of plasminogen by proteases produced or activated by certain tumours, such as prostate cancer.

Treatment of certain cancers with angiostatin has shown promising results. In mice xenotransplanted with three human cancers (breast, colon, or prostate), systemic treatment with angiostatin inhibited the growth of breast cancer by 95%, colon cancer by 97%, and prostate cancer by 100%. The mechanism of growth inhibition in these tumours involved a marked increase in apoptotic rate in the treated mice, while the proliferative rates in both the untreated and treated mice were the same. Interestingly, no toxic side effects were observed. However, cessation of angiostatin therapy resulted in relapse of the dormant tumours.

Endostatin, a fragment of the non-angiogenic precursor collagen XVIII, is another potent tumour-derived inhibitor of endothelial cell proliferation and angiogenesis. Systemic treatment with endostatin has been shown to cause significant regression of primary tumour size as well as inhibition of metastatic growth, without development of toxicity or of drug resistance. Like angiostatin, the mechanism of action is via an increased tumour cell apoptotic rate. Discontinuation of endostatin, however, was shown to result in relapse. Interestingly, combination therapy involving both endostatin and angiostatin seems to cause complete tumour regression, even after therapy is discontinued.

Recent studies have investigated viral-vector mediated angiostatin therapy (via adenovirus or retrovirus) to deliver high local concentrations of angiostatin. This has been termed "targeted angiogenesis" and has been found to cause a significant arrest of tumour growth in vivo via an increased tumour apoptotic rate. This will have important applications for the therapy of tumours that are locally invasive but not necessarily metastatic, such as gliomas. It is important to note, however, that this targeted angiostatin therapy did not cure the mice tested, but

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In mice xenotransplanted with human ovarian cancer, tumour size, local/regional invasion, as well as metastases in mice xenotransplanted with human colon cancer.

Importantly, no significant side effects with batimastat therapy were found. Based on these findings, batimastat was one of the first MMP inhibitors to be tested in cancer patients, primarily those with malignant effusions. Unfortunately, batimastat was found to have poor oral bioavailability and thus, could only be given to the cancer patients via intraperitoneal or intrapleural suspensions.

Marimastat, a compound similar to batimastat, is an orally active drug that is able to inhibit cell invasion, metastasis, and angiogenesis. This drug is currently in the process of clinical trials, which have shown that the most significant side effects are musculoskeletal complaints. Despite this, marimastat seems to have potent biological activity in patients with advanced ovarian, prostatic, pancreatic, or colorectal cancer, and thereby, demonstrates substantial promise for acceptance as a novel form of anticancer therapy in the near future.

**CONCLUSION**

MMP inhibitors (TIMPs, batimastat, marimastat) and tumour-derived angiogenic inhibitors (angiostatin, endostatin) are just two classes of angiogenic agents that have shown significant findings for future cancer therapy. In fact, it is interesting to note that several anticancer agents already in clinical use (such as tamoxifen) have been found to have antiangiogenic activity. Even certain non-cancer pharmacologic agents such as thalidomide also have demonstrated antiangiogenic activity and are currently being investigated as a form of cancer therapy. Although it seems that treatment with angiogenic inhibitors will not necessarily cause complete regression of tumours, combination therapy of angiogenic agents with conventional chemotherapy has been found to reduce tumour metastases to a greater degree than when either therapy is used alone.

Thus, angiogenic inhibitors seem...

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Therapeutic advantages of angioinhibitory therapy</th>
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<tbody>
<tr>
<td>• Are quiescent in normal tissues of the adult whilst they are activated, proliferating and migrating within the stroma of invasive tumours</td>
<td>• Little toxicity on normal vasculature</td>
</tr>
<tr>
<td>• Are genetically stable, normal diploid cells that are required for tumour growth</td>
<td>• Their genomic and phenotypic characteristics are stable in time</td>
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<tr>
<td>• Have similar characteristics in different solid tumors</td>
<td>• Represent a uniform target</td>
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<tr>
<td>• Are easily targeted by systemic administration of antiangiogenic agents</td>
<td>• No difficulties related to the amount of drug that can reach the cellular target</td>
</tr>
<tr>
<td>• Proliferate under the stimulus of partially known endothelial growth factors</td>
<td>• Pharmacological neutralization of the angiogenic peptides is a possible therapeutic strategy</td>
</tr>
<tr>
<td>• Proliferation and migration can be inhibited by endogenous angiogenesis inhibitors</td>
<td>• Therapy with endogenous antiangiogenic peptides is feasible and well tolerated</td>
</tr>
</tbody>
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**Table 1**

Favourable characteristics of endothelial cells as a target for anticancer therapy

merely prolonged their survival. Improvement in vectorization efficiency will be required for eventual attainment of maximal clinical benefits and hopefully, the synergistic effect of angiostatin combined with endostatin for complete tumour regression may also one day be achieved with vector therapy.

**MATRIX METALLOPROTEINASE INHIBITORS**

Neovascularization is dependent on not only the proliferation of endothelial cells but also the migration of the endothelial cells through the surrounding extracellular matrix. This requires degradation of the components of the tissue matrix via the enzymes, matrix metalloproteinases (MMPs). These enzymes are upregulated in proliferating endothelial cells and thus, assist in the neovascularization and ultimate growth of a tumour.

TIMPs (tissue inhibitors of metalloproteinases) are naturally occurring MMP inhibitors and are all inhibitors of angiogenesis. TIMPs inhibit both tumour growth as well as metastasis, most likely due to their ability to suppress matrix degradation.

TIMPs have also been shown to directly block the proliferation of tumour and endothelial cells *in vitro*. Thus, this dual mechanism of action makes them very potent antitumour agents. In fact, one study found that retroviral-mediated transfer of TIMP into a limited population (only 13%) of tumour cells in mice was still sufficient to inhibit tumour growth and limit local tumour invasion.

These findings show the great potential for these agents in cancer therapy.

Synthetic MMP inhibitors also exist. Batimastat and marimastat are two such compounds, and they act by binding reversibly to the zinc in the active site of MMPs. In the mouse model, batimastat was shown to increase the survival of mice xenotransplanted with human ovarian cancer by 5- to 6-fold. These results were supported the following year by an experiment demonstrating that treatment with batimastat causes reductions in primary...
to be quite promising for cancer therapy, and it is possible that we may soon see the incorporation of angiogenic inhibitors into the standard treatment protocol of various cancers.

ACKNOWLEDGEMENT

The author gratefully acknowledges Dr. M. Vincent, medical oncologist at the London Regional Cancer Centre and Assistant Professor in the Department of Oncology, University of Western Ontario, for his helpful comments and generous contributions to this article.

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BACKGROUND

Breast cancer and melanoma occur at high frequency in Canada. In fact, breast cancer is the leading cancer diagnosed in Canadian women, accounting for about 30% of all new cases.1 There has been a dramatic increase in the incidence of cutaneous melanoma associated with damaging sun exposure during childhood. The incidence rate for melanoma has tripled since the late 1960s, from 3.2 per 100,000 population in 1969 to an estimated rate of 10.5 per 100,000 in 1998.2 Fortunately, early diagnosis has reduced the death rate from almost 90% earlier this century to less than 20% today.2

For most patients with solid tumours, the most powerful and predictive prognostic factor of one’s survival is the status of one’s regional lymph nodes.3 Patients with malignant melanoma with no lymph node metastases have a 10 year survival rate of 70-80%, while those with nodal involvement have a 10 year 20-30% survival rate.4 In breast cancer, regional nodal metastases decrease the 5 year survival by 28-40%.4 Hence, it remains important to identify those patients with nodal involvement in order to differentiate those patients that will clearly benefit from systemic treatment from those who will not.

The management and staging of breast cancer usually include an axillary lymph node dissection. Likewise, melanoma patients with palpable regional lymph node metastases undergo a therapeutic nodal dissection. However, the approach to melanoma patients who may have lymph node micrometastases has been quite controversial - ranging from complete node dissection to simply “watch and wait”.4

THE SENTINEL NODE CONCEPT

The sentinel node is that lymph node in a given lymphatic basin that first receives lymphatic flow from a primary tumour.5 As a result, the histology of the sentinel node usually reflects the histology of the basin. If the sentinel node is cancer free, there is greater than 98% likelihood that the remaining nodes in the basin are negative, but if there is cancer in the sentinel node there may be metastatic disease in other nodes.5 Assuming the sentinel node can be reliably identified and histopathologic exam reveals no cancer cells, the remaining nodes in the basin should be clear as skip metastases are rare.6 Thus a total resection of the lymph node basin with its associated surgical morbidity (such as parasthesia, wound infection, seroma, drain discomfort, acute and chronic lymphoedema, as well as potential delays in adjuvant therapy) can be avoided.7 Particularly, chronic lymphoedema can pose a significant morbidity.

Sentinel node lymphoscintigraphy (SNL) has been developed for this purpose. It involves injecting radiopharmaceuticals (specifically radiolabeled colloid of suitable size and properties) just outside the periphery of the primary tumour site where they are transported by lymphatics and localize in drainage lymph nodes. This allows one to trace the path of lymphatics from a cutaneous melanoma or breast lesion to the regional node basin. Using the nuclear images as a road map, gamma probe guided surgery (with a hand-held, wand-like instrument that detects gamma rays emitted by the radiocolloid) successfully locates the sentinel node, allowing a directed dissection and minimizing tissue disruption. When a pathologist is given a sentinel node instead of many nodes to examine, a thorough examination with more sectioning or with the use of specific staining methods or PCR-based assays is afforded, which contributes to more accurate disease staging.8

Furthermore, lymphatic mapping and sentinel node biopsies direct dissection to all lymph node beds that potentially receive or have received tumour cells. Not infrequently, a sentinel node that shows micrometastases is in a lymph node bed that would not have been predicted to receive lymphatic drainage from the primary tumour based on conventional estimates. In fact, the classic concept of a lymphatic watershed described by Sappey’s lines (anatomic coordinates governing the direction of lymphatic flow from any point on the trunk) has been shown by lymphoscintigraphy to be inaccurate in many patients.8

The Ideal Radiocolloid

Debate exists regarding the most appropriate radiocolloid for use in SNL. The rate of colloid transport and movement through lymphatic pathways is most strongly related to the size and surface charge of the colloid. Those larger than 0.004μm to 0.005μm are preferred, as smaller particles have been reported to penetrate the capillary membranes and are therefore

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unavailable to migrate through the lymphatic channels resulting in obscured images. Particles smaller than 0.1µm show the most rapid disappearance from the interstitial space into the lymphatic vessels and have significant retention in the lymph node. Large colloid particles (>0.5µm) show a much slower rate of clearance from the interstitial space with significantly less accumulation in the lymph nodes. 

Three important questions must ultimately be answered in the assessment of a colloid's suitability for SNL. Firstly, is a stable, safe and efficacious product made during the radiolabelling process? Next, how will the body deal with a charged particulate, taking into account its many other physical properties? Lastly, will this particulate be biochemically altered, metabolized and excreted? Research is currently taking place at London Health Sciences Centre in the development of suitable radiolabeled colloids and assessing them in cancer patients after appropriate animal biodistribution studies.

**SENTINEL NODE LYMPHOSCINTIGRAPHY IN MALIGNANT MELANOMA**

In patients with malignant melanoma, the sentinel node(s) is (are) resected and biopsied and, if free of metastases, radical nodal dissection is not required, thus avoiding potential morbidity which could result from radical nodal dissection. If the sentinel node is involved with malignancy, radical nodal dissection of the affected basin is then performed. Such an approach is currently an accepted practice.

The use of a variety of radiotracer agents for lymphoscintigraphy and intraoperative gamma probe localization of sentinel nodes in patients with stage I/II melanoma (ie. no evidence of tumour spread) is firmly documented in the literature. For example Berman et al reported on 135 patients with malignant melanoma of the head, neck, shoulder and trunk. A discordancy rate of 41% was found between drainage that would have been predicted by the surgeon based on location of the primary skin lesion and what was found on imaging. Surgical management was changed in 33% because of the lymphatic drainage revealed on lymphoscintigraphy.

Uren et al reported on 209 patients with high risk melanoma of the trunk. They found that lymphoscintigraphy was 94% sensitive in detecting sentinel nodes that contained metastases. Similarly, Krag et al reported on 121 patients with invasive malignant melanoma and clinically negative lymph nodes. Before surgical lymph node resection, these patients had intradermal administration of 99mTc sulfur colloid around the primary melanoma. A gamma probe was used in the operating room to identify radiolabeled nodes which were then selectively removed. Patients with identified metastatic lesions then underwent regional lymphadenectomy. Radiolabeled sentinel lymph nodes were successfully resected in 98% of cases. Fifteen patients had pathologically positive sentinel lymph nodes and in 10 of those, the sentinel node was the only node with metastases.

Glass et al reported on 132 patients with intermediate thickness malignant melanoma. Sentinel nodes were excised and examined for metastases by light microscopy with conventional stains and immunohistochemistry. Only patients with micrometastases received complete lymph node dissection. Sentinel nodes were identified in all patients while micrometastases was found in 23%. Of those with metastases the sentinel node was the only node with tumour in 83% based on subsequent complete nodal dissection.

O'Brien et al studied 97 patients with cutaneous head and neck melanoma using preoperative lymphoscintigraphy to identify sentinel nodes. Sentinel nodes were identified in 95 of 97 scintigrams. Lymphoscintigraphy was discordant with clinical prediction in 34% of cases.

The sentinel lymph node biopsy is a particularly appealing surgical management strategy for patients with stage I/II melanoma because of the controversy about the alternative surgical intervention - namely elective lymph node dissection (ELND). Approximately 80% of patients with stage I/II disease do not have nodal tumour involvement demonstrated by ELND. Thus the expense and morbidity of the dissection would be unnecessary in that group.

**SENTINEL NODE LYMPHOSCINTIGRAPHY IN BREAST CANCER**

In the case of breast cancer, surgical management, over the years, has evolved from radical and mutilatory surgery to the less extensive simple mastectomy or lumpectomy with radical nodal dissection still being performed on a significant number of patients. The sentinel node localization and biopsy should eventually, after validation by large clinical trials, lead to the elimination of unnecessary radical nodal resection, another step towards optimizing the surgical management of this disease.

Uren et al reported on 34 patients with breast cancer who were studied with lymphoscintigraphy. Unexpected drainage across the centre of the breast to axillary or internal mammary nodes was reported in 32% of patients with inner-or outer- quadrant lesions; drainage to supraclavicular or infraclavicular nodes in 20% of upper quadrant lesions; drainage to ipsilateral axilla in 85% of cases where a single sentinel node was seen. Furthermore, Solin has shown that the frequency of internal mammary node metastases in breast cancer parallels metastases to axillary nodes and correlates with the size of the tumour. The implications of drainage to unpredicted lymph nodes for patient surgical management are profound. In a large number of centres, current management of breast cancer does not include lymphoscintigraphy to identify lymphatic drainage from the breast cancer site. However, it does include ipsilateral axillary node dissection for staging invasive breast cancers regardless of location. The therapeutic impact of sentinel node localization, excision and biopsy directed by lymphoscintigraphy in all potential nodal beds involved with tumour is being evaluated. If the frequency of metastases to axillary, internal mammary, and other nodal groups is proportional to the frequency of lymph drainage to those node groups, then surgical management should probably be modified to include internal mammary and other nodal bed dissections.
CONCLUSION
Like all currently practiced radionuclide procedures, interstitial lymphoscintigraphy is easily performed, well tolerated by patients, and is free from either local or systemic toxicity. Patient discomfort or inconvenience with the procedure as well as allocated resources are small considerations relative to the potential benefits. Greater familiarity with the technique will enhance its role in the investigation and treatment of patients with melanoma and breast cancer.

ACKNOWLEDGEMENTS
I would like to acknowledge Dr Adel G Mattar (Chief of Nuclear Medicine, London Health Sciences Centre) and Pamela Zabel (Radiopharmacist and Director of the London Regional Nuclear Pharmacy) for their input on my paper.

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Imagine you have just taken your seat on the third balcony, front row centre. From far below, a colourful hum of notes rises towards you as a string quartet begins to play. You are impressed by the clarity of the sound as it fills the four-storey-high atrium. The hall with such remarkable acoustics is, in fact, the London Regional Cancer Centre (LRCC). And the musicians are participants in the LRCC Live Music Program.

Music has been a part of medicine for many centuries, and the establishment of the LRCC Live Music Program shows an increasing awareness of this relationship today. It is the goal of this article to review the role of music in medicine, and to describe the LRCC program based on our experiences at the Cancer Centre as a piano-cello duo.

Medicine, religion and the arts were closely connected in many ancient cultures. The use of music and other healing modalities reflected a culture's view of illness. For example, chants and magic songs were used by various Native American tribes who viewed disease as being due to the intervention of spiritual forces. Ancient Greek mythology and historical literature contain many references to the use of music in healing, for instance, in the works of Homer and Plutarch. During the Renaissance period, many philosophers tried to develop a scientific approach to the relationship between music and the human being. For example, the four musical voices (bass, tenor, alto, soprano) were related to the four temperaments (melancholic, phlegmatic, sanguine, choleric), and the four humours of the body (black bile, phlegm, blood, yellow bile). The first English book on the use of music in medicine was Robert Browne's Medicina Musica: A Mechanical Essay on the Effects of Singing, Musick, and Dancing on Human Bodies (1729).

Of significance, Browne put forth several postulates that still serve as a basis for music therapy today. He proposed that music can change and evoke moods, influence physiological processes, does not require the attainment of a certain level of proficiency when used therapeutically, and could be useful in preventive health care.

Music therapy is the modern term for the use of music in medicine. Music therapy can be defined as the "controlled use of music, its elements and their influences on the human being to aid in the physiologic, psychologic, and emotional integration of the individual during the treatment of an illness or disability." It involves listening, singing, playing instruments, improvising, and composing.

Most people have an intuitive awareness of the relaxing and calming effect of music. Background music is commonly used in hospital waiting areas, delivery suites, operating rooms, and in occupational and physiotherapy. In the medical setting, attentive listening can distract from the "here and now" of an illness. Specifically, music can divert a person's attention away from the pain, stress, anxiety, and isolation of his or her illness and hospitalization.

Furthermore, it is important to recognize that illness is an experience that goes beyond reason and words. Finding a way to express this experience may prove crucial to the patient's sense of well-being: "For the patient, expression of unspeakable concerns not infrequently provides renewed creative energy that is usually lost in the process of an illness. This not only enriches the quality of life at such a time but may provide the impetus to live." As such, improvising, singing, composing, and playing an instrument can provide an avenue for expression and creativity.

At this time, it is important to point out that the term music "therapy" suggests a procedure that has an effect on the disease process itself. Is this justifiable? Physiological processes, to some extent, can reflect our emotions. We hold our breath when we are anxious and exhale when the moment of tension passes. We blush when we are embarrassed. Yet can the experience of music directly influence physiology and possibly disease as well? Some basic evidence-based research in this area has begun. For instance, in Munro and Mount's study of chronic pain, they found that music could decrease the intensity of the pain experience. Music has also been shown to decrease heart rate, systolic and diastolic blood pressure. Of interest, music played at the tempo approximating that of the heart rate is thought to promote relaxation.

In this century, music therapy was initially used in the mental health services. Norma Sharpe, who worked at St. Thomas Psychiatric Hospital in Ontario, was one of the pioneers of music therapy in Canada. In fact, some of the inaugural conferences of the Canadian Association for Music Therapy took place in St. Thomas (1974) and...
London, Ontario (1976). However, most of the current literature about the use of music in medicine involves the field of palliative care and oncology.

Regarding the use of music in cancer care, it is felt that "the diversity of its potential is particularly suited to the diversity of the challenges - physical, psychosocial and spiritual - that these [cancer] patients present." The way in which music can help cancer patients at various stages of the disease deserves an entire discussion of its own. However, in general, music helps those afflicted with cancer in the process of coping and acceptance through relaxation, distraction, and expression of feelings.

One of the most established music therapy programs in Canada is the 20-year-old program of Montreal's Royal Victoria Hospital palliative care service. Music used in this setting has been shown to help patients with advanced malignant disease. In particular, case reports from this service document the importance of the power of association that music can invoke. Specifically, "music can reduce feelings of loneliness by producing familiar, comforting stimulation reminiscent of family, homeland, or past experiences." Music may also be beneficial as an adjunct to antiemetic agents used to treat chemotherapy-induced nausea and vomiting. Music not only helps to decrease the anxiety that may precipitate the nausea and vomiting, but also the degree and length of this unpleasant side effect.

While most of the literature deals with adult oncology, the use of music in pediatric oncology, particularly in the United States, is well documented. The use of music therapeutically shares a similar concept to that of art and play therapy - to provide a diversion and help to enhance self-expression of the child. The latter is particularly important for children who, as a group, are less capable of expressing their feelings in concrete terms. Of interest, there has also been some documentation of potential physiological therapeutic effects of music used in pediatric settings. These include decreased crying, decreased respiratory rate, and even increased oxygen saturation. Nonetheless, as music therapy is slowly but surely being discovered by other medical specialties, it is becoming apparent how music can benefit patients in almost all illness situations.

It is interesting to note that most of the literature written about music in oncology and medicine revolves around its use as taped background music. There is little written about the use of live music. Yet, a live performance has much to offer patients. In contrast to taped background music, live music provides the human presence that can enhance the musical experience of the audience. A live performer is able to present the music to the listener in a personal way which can be very meaningful to the patient. Moreover, an advantage of live performance is that the musician is continuously aware of the audience's response and can spontaneously tailor the choice of music and to some extent the style of the performance, to the listener.

These benefits were recognized by Jan Searle, a flautist and cancer survivor from Stratford, Ontario, and Shelley Markland and Dr. Leslie Levin of the LRCC. In 1997, they organized trial performances with the flute and harp in an attempt to make the LRCC "a softer, gentler place." These performances met with an overwhelmingly positive response. Although some staff members initially found it more difficult to get the patients' attention when it was time to see the doctor, most were supportive of the live music. The unique program developed quickly, aided, for instance, by the donation of a piano. The program currently involves music students, community musicians, and most recently, patients themselves, who play for one to two hours during clinics.

When we first heard about the program, it immediately appealed to us but we did not quite know what to expect. At our first performance at the Cancer Centre a year ago, we were initially intimidated by the hushed, impersonal silence that pervades the LRCC. Would we dare to - or even want to - introduce some sound here? Everything seemed so subdued and quietly functioning. However, as we gingerly began to play and the LRCC revealed its true acoustical qualities, our doubts were dispelled. The atmosphere became lively as the patients, previously following various trains of thought, turned their attention to the new presence.

Importantly, we were well aware of the fact that many patients were in an emotionally demanding situation and therefore, we would have to choose our music carefully. What type of music would be most appropriate for the LRCC? We played as wide a spectrum of music as we could to cater to the different musical tastes of the patients. A chronological progression seemed to work well, from Bach and Vivaldi, to Brahms, Schubert and Chopin, to the "hits" of the 1950's and 1960's and some soft contemporary music.

In addition to choosing the music carefully, we learned that we had to pay special attention to the intervals between pieces. Interestingly, we found that it was especially important to be aware of the moments immediately after the end of a piece. The patients at the LRCC tended not to applaud by clapping. Instead, a remarkable, attentive silence usually followed the last note. It was as if the music continued to linger on in the minds of the patients. In particular, Brahms' Waltz in A Major and Chopin's Claire de Lune were usually followed by such a "listening" silence, completely different from the "frozen" silence that preceded the performance. Remarkably, it often took several minutes before the usual background noises and movements resumed.

Perhaps one of the most rewarding aspects of playing at the cancer centre was experiencing the patients' gratitude. They appreciated not only the music itself, but also the fact that we were taking the time to play for them. We felt that the supportive smiles and appreciative comments the patients gave us benefited them as much as it did us. Many patients were especially appreciative of the fact that we volunteered our time. This tells us what an important part of the live performance the musicians' personal dedication is to this audience.

However, in our opinion, one of the greatest achievements of the Live Music Program is the involvement of the patients in the performances. As mentioned earlier, some cancer patients are now themselves performing at the LRCC. Experiencing the progressive illness, and perhaps many rather impersonal, standardized procedures such as MRI, CT, chemotherapy, and radiation protocols, can easily give a patient a feeling
of powerlessness. Becoming active and creative is empowering and can serve as a strong support during such an uprooting life experience.

Although most patients do not perform themselves, they often express an active interest in the live performance. How often have we been told about the patients’ own musical backgrounds, or about a relative’s accomplishments? It was as if the performance offered a much-needed opportunity for personal communication and conversation.

Our experience at the LRCC has given us an appreciation of the tremendous potential of music in cancer care. As we discovered, music has the unique ability to fulfill a need that arises during an illness experience. Thus, we would encourage everyone to contribute their talent whenever there is an opportunity, to help secure and expand the role of music in medicine.

ACKNOWLEDGEMENTS

We would like to thank Shelley Markland and Nancy Campbell of the LRCC, and Jan Searle in Stratford, Ontario for providing us with background information about the Live Music Program. Many thanks also to Shelley Markland for reviewing the manuscript, and to Isabel Mangold of the Lukas Cancer Clinic in Arlesheim, Switzerland for providing us with references on the use of music therapy in cancer care.

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**FUNCTIONAL BRAIN MAPPING AND THE REMOVAL OF BRAIN TUMOURS**

By Peter Howard, MEDS 2000

Whether malignant or benign, tumours that lie within the brain pose a treatment dilemma. Surgical removal of the tumour may jeopardize surrounding brain tissue, thus causing a profound neurological deficit. In order to minimize the neurological deficit that will result from a tumour's resection, the function of the brain tissue surrounding the tumour must be identified. We shall start by briefly sketching the typical organization of brain functions within the human cerebral cortex, which provides an approximate guide to the functions that may be threatened by a tumour. Definitive identification of the functions threatened by a particular tumour is made possible by the techniques of functional mapping. We shall briefly discuss the standard technique for functional brain mapping, which involves applying an electric current directly to the brain's surface to stimulate the cortex. We shall then focus on an experimental method of functional brain mapping with magnetic resonance imaging. Finally, we shall present a single case in which both techniques of mapping were used prior to the resection of a cavernous hemangioma.

The brain is the most complex organ in the human body, both in terms of structure and function. One of the ongoing challenges of neuroscience is to relate the anatomical structure of the brain to the cognitive processes that occur within it. Historically, there have been two rival theories of the relationship between the structure of the human cerebral cortex and its function. At one extreme is the view that the cerebral cortex is homogeneous, with all regions capable of contributing to all mental tasks. At the other extreme is the view that each mental process is "localized" to a discrete anatomical area specialized for the task. The model supported by today's evidence combines elements of these two views. The primary sensory and motor functions of the brain are certainly localized to characteristic areas in the normal human. For instance, the visual area is in the posterior occipital lobe, the primary auditory area is in the superior temporal gyrus, and the sensorimotor areas lie on the banks of the central sulcus. Even the more abstract function of language has a dedicated area surrounding the left sylvian fissure in most individuals. It is worth noting, however, that this characteristic arrangement of functional areas in the brain can be dramatically reconfigured in response to injuries, particularly those that occur during development of the nervous system. This indicates that there is a fair amount of homogeneity between areas of the cerebral cortex at least in their potential to perform various cognitive tasks.

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The areas of the brain that are specialized to process motor output and linguistic activity are of particular concern when the surgical resection of a tumour is planned, since the surgeon wants at all costs to avoid leaving the patient hemiplegic or aphasic. Because each brain may show significant idiosyncrasies in the location of functional areas, vital functions can be spared only if they are mapped prior to surgery. Between the 1930's and 1950's, Dr. Wilder Penfield of the Montreal Neurological Institute pioneered functional mapping of the brain as a guide to neurosurgery. His technique involved performing brain surgery under a combination of local and neuroleptic anaesthesia, so that the patient remained conscious and responsive during the operation. The surface of the cortex was stimulated with a small electric current. Motor areas were identified by observing the contraction of muscles in response to the current. Sensory areas were identified by asking the patient to verbally describe any sensation that the electrical stimulation evoked. Finally, speech areas were identified when stimulation of the area caused a temporary arrest in the flow of a patient's speech. Once these critical areas were labeled (see figure 1 upper left), surgery could proceed giving them as wide a berth as possible.

The recent development of functional magnetic resonance imaging (fMRI) provides another method of creating functional brain maps. FMRI exploits the deoxygenated hemoglobin normally found in the blood as a "contrast agent" indicating brain activity. In magnetic resonance imaging, the signal emanating from each small block of tissue is produced by the precession of protons within the tissue. The rate of each proton's precession is proportional to the strength of the magnetic field acting on the proton. Since deoxyhemoglobin contains iron with free valence electrons, each molecule of deoxyhemoglobin creates its own magnetic field. High numbers of deoxyhemoglobin molecules in a small block of tissue therefore create many small distortions in the magnetic field within the tissue block. In the presence of such distortions, the protons in the tissue precess at different rates, thereby losing phase with one another. The resulting MR signal is diminished by the loss of phase in the same way that two water waves of different phase will partially cancel one another. The key result is that high deoxyhemoglobin concentrations within a tissue cause a darkening of that tissue on appropriately acquired MR images. When an area of brain is activated, it extracts more oxygen from its blood supply, thus creating deoxyhemoglobin. However, an increase in blood supply to the active area more than compensates for the increased oxygen extraction, so the concentration of deoxyhemoglobin within the venous microvasculature of the active brain area drops. The net effect on MR images is that active cerebral cortex is approximately four percent...
brighter than the same cortex at rest. If a series of images are taken while a subject alternates between rest and task performance, the brain areas responsible for the task can be identified by their significantly increased brightness during task performance. FMRI has been used to map primary sensorimotor and visual activity, higher order motor and visual processing, and even complex cognitive functions such as learning and language use.\textsuperscript{5-13}

The following case illustrates the use of fMRI in conjunction with electrical cortical stimulation for the purpose of brain mapping. A 52 year-old lady presented with a history of headaches and with simple partial seizures involving the left thumb. Clinical MR images suggested that the lesion was a cavernous hemangioma in the middle portion of the central sulcus of the right hemisphere, located in the depths of the sulcus. The surgeon's preoperative assessment was that removal of the lesion might cause a deficit in hand and arm movement. FMRI was used to map the brain regions responsible for left finger to thumb opposition, solo left thumb movement, left wrist flexion and extension, and left to right tongue movements. Extensive cortical stimulation mapping was performed at the time of surgery, locating a range of sensory and motor activities in the upper limb, head, and neck.

The volume rendered fMRI data was oriented to resemble the view of the brain obtained at surgery. The fMRI rendering is sufficiently detailed to identify all of the gyral contours visible in the operative photograph. Comparisons of the fMRI maps to the operative data are made in figure 1. From figure 1, it is evident that finger to thumb opposition caused fMRI brain activity within 3 mm of operative label A, where electrical stimulation caused the patient to clench her left hand. Furthermore, finger to thumb opposition caused activation in the postcentral gyrus in the areas identified with finger and thumb sensation during surgery. The task of finger to thumb opposition would be expected to activate both sensory and motor components of the primary sensorimotor cortex responsible for the fingers and thumb. We thus conclude that the fMRI and cortical stimulation maps agree on the location of the hand sensorimotor cortex. Wrist movement caused fMRI activation at label C, which marked forearm pronation and hand movement during surgery. These are closely related movements that also involve the wrist joint. Tongue sensation could only be elicited during surgery by probing beyond the edge of the craniotomy at U. This region is within 3 mm of the activation shown by fMRI during tongue movement, a task that will also elicit tongue sensation. In this patient, then, fMRI and cortical stimulation create comparable maps of the functional areas found along the banks of the central sulcus.

The ability to identify the function performed by an area of brain tissue is of obvious benefit to a surgeon considering the resection of that tissue to facilitate the removal of a tumour. Cortical stimulation mapping has long been used successfully in this capacity. Early experimental results such as the case study described suggest that fMRI may play a role in this type of brain mapping in the future. FMRI has several features that make it an attractive method of brain mapping. First, since it is non-invasive, fMRI can be performed on patients both before and after neurosurgery. This gives fMRI the potential to show the plasticity of brain function in...
Prostate cancer is ranked among the most common causes of cancer-related death in men. In 1997, it surpassed lung cancer as the most frequently diagnosed cancer in Canadian men and its estimated incidence per year has exceeded that of breast cancer in Canadian women. Prostate Specific-antigen (PSA) has been available as a screening test in Canada since 1986, although its use did not become widespread until the early 1990's. Screening guidelines for prostate cancer in the United States include PSA testing, however no such guidelines have been established in Canada. Why have screening programs for prostate cancer, like those of breast cancer, not been implemented in Canada? There are no clear cut answers, however, an understanding of PSA as a screening tool will help physicians determine how to best apply this tool in the management of their patients.

**Prostate Specific Antigen; Historical Aspects**

The search for a prostatic tumor marker more specific and sensitive than *prostatic phosphatase* began in the 1960's. By the 1970's several groups of researchers had discovered antigens specific to the prostate. Work on these antigens continued in hopes of developing forensic identifiers in rape cases (never very effective) as well as tumor markers for prostate cancer. In 1971, Hara et al. isolated PSA from seminal plasma and named it γ-spermoprotein. Soon afterwards, Li and Beling characterized E1, an antigen from seminal plasma using a series of protein chromatographic techniques. In 1978, Sensabaugh identified PSA in human semen and called it p30. When it was discovered that antiserum to the partially purified antigens did not react with extracts from tissues other than the prostate, the term prostate-specific antigen or PSA was coined.

In 1981, Wang et al. reported isolates of prostatic antigen from seminal plasma and prostatic antigen purified from prostatic tissue were identical. Almost a quarter of a century after the three separate antigens were initially discovered, investigation revealed that the three antigens where in reality a single specific antigen – prostate-specific antigen. PSA is an organ-specific serine protease, produced by prostatic epithelial cells lining the acini and ducts of the prostate gland. Functionally, this protease is known to cause liquefaction of the seminal coagulum.

**Current Screening Techniques for Prostate Cancer**

There are several criteria a clinical test should meet before being considered as a disease screening test: (1) the disease must be an important health problem; (2) the disease must have a recognizable early stage; (3) treatment at an early stage should be more beneficial than treatment at a later stage; (4) the test must be convenient and acceptable to society; (5) necessary facilities must exist for diagnosis and treatment; (6) the cost of screening must be acceptable to society. Currently there are four potential screening tests used for prostate cancer. These include the digital rectal exam (DRE), prostatic phosphatase (PAP), trans-rectal ultrasound (TRUS); as well as, the seromarker prostate-specific antigen (PSA) approved in 1986 by the Food and Drug Administration for the use as an aid in the prognosis and management of patients with prostate cancer.

Although PAP is also a seromarker for prostate cancer, unlike PSA, PAP levels do not become elevated until the disease has reached an advanced stage. This gives PAP no advantage over a DRE screening exam. Thus, PAP is not used for screening but for staging the disease only after it is diagnosed. Performing a TRUS of the prostate as a screening test is not an effective screening test because a TRUS can not differentiate many small cancers from surrounding benign prostatic tissue. TRUS' most appropriate use is in directing biopsies in men who have abnormal findings on DRE and/or PSA testing. Although inexpensive and time tested, DRE-based trials in pre-PSA eras showed that only 33% of DRE-detected prostate cancers had pathologically organ-confined disease. Thus, 67% of men were diagnosed at a stage of prostate cancer associated with a very poor 10-year prognosis. If men with organ-confined prostate cancer undergo radical prostatectomy, they are essentially cured of the disease and have a survival rate equivalent to that of age-matched men without the disease. In contrast, prostate cancer that is not organ confined is incurable. PSA screening has shown itself to be a very effective tool in finding organ confined and thus curable prostate cancer. PSA testing is convenient, tolerable and inexpensive. Serum PSA testing meets most established criteria's for a clinical test be considered as a screening tool.

**Physiologic Reasons for PSA Elevation.**

The physiology by which elevated levels of PSA enter the blood stream has lead to some inaccurate assumptions regarding the specificity of elevated serum PSA levels. Serum PSA levels deviate from reference values for two basic reasons: (1) an increase in PSA production, such as in the case of benign prostatic hyperplasia, which creates a shift in the diffusion gradient; (2) a change in the membrane permeability or normal physiological barriers, for example prostate cancer and prostatitis.

Early research indicated the potential for false-positive
response to changes during surgery. Secondly, many complex cognitive tasks that cannot be investigated using cortical stimulation can be investigated with fMRI. Finally, while cortical stimulation gives access only to the brain’s surface, fMRI can show functional areas deep within the brain. Thus, there is reason to be optimistic that the difficult surgery currently performed to remove cerebral tumours will in the future benefit from advances in functional mapping techniques.

ACKNOWLEDGEMENTS

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elevations in serum PSA levels after prostatic manipulation and/or ejaculation. However, Chybowski et al. via a prospective randomized controlled trial, showed that the median serum PSA elevation caused by DRE represented a clinically insignificant increase in the serum PSA level. Thus the authors concluded that the serum PSA concentration in the immediate post-DRE period is accurate and would not compromise clinical value of the marker. Similarly, Yuan et al. found that DRE, prostatic massage, and TRUS, produced some elevations in serum PSA levels; however, the authors concluded that the elevations were not statistically significant and that these exams had minimal effects on serum PSA levels in most patients.

PSA levels may become elevated by age (therefore, age specific ranges of values are employed), acute urinary retention and urethral catheterization. The use of Finasteride can lower PSA levels by approximately 50%.

**Sensitivity and Specificity of PSA**

The fact that prostate cancer has recently become one of the most prevalent cancers in our society is primarily due to increased diagnosis as a direct result of the use of PSA as a screening tool. Of the cancers now detected, 95% that are detected are clinically localized. While sensitivity is relatively high at 92%, specificity is lower because of the other ways in which PSA can be raised. When other conditions or reasons for the elevation of PSA are suspected, the finding of a low percentage of free, unbound PSA increases the specificity. Also, PSA velocity can be followed. While it is increased by factors such as age, it should not increase by more than 0.75 ng/ml per year. PSA density (ng/ml/ml) can also be followed for screening. Regardless of its limitations, serum PSA is currently the best screening tool available for prostate cancer. If there is sufficient suspicion of prostate cancer based on PSA levels, then TRUS guided biopsy of the prostate can be performed for a definitive diagnosis.

**Management of Prostate Cancer**

There is currently some controversy surrounding the widespread use of serum PSA levels as a screen for prostate cancer. As noted previously, PSA is currently the best method for detecting prostate cancer. It is highly sensitive, and since PSA testing began, there has been a lower incidence of metastatic disease at the time of diagnosis. This is important, as there is a realistic chance for cure of prostate cancer only if it is detected and treated early in its course. Arguments against the widespread use of PSA for prostate cancer screening are not based on whether or not PSA is a reliable tool for the detection of cancer. This has already been proven and accepted. What those opposed to PSA screening question, is whether or not there are effective treatments available to patients which will increase their quantity and/or quality of life once the cancer has been diagnosed.

There are currently four approaches to the management of prostate cancer. The first and simplest approach is watchful waiting. This may be the most appropriate management for prostate cancer diagnosed in men 75 or older, as 84% of these patients will survive 10 years without treatment and its associated risks. Another option for older patients is hormonal therapy such as a luteinizing hormone-releasing hormone agonist or an antiandrogen. This is an acceptable option to many older patients who will not accept watchful waiting. While it may not affect their life expectancy, many patients feel that watchful waiting is an unsatisfactory treatment course for cancer. The gold standard treatment for prostate cancer is surgery. A radical prostatectomy is associated with a 10-year survival rate of up to 94%. However, this is only an option if the tumor is confined within the prostate capsule. Finally, radiation therapy is an option. It is associated with a lower 10-year survival rate than a radical prostatectomy (74%), but this is largely due to the fact that radiation therapy is reserved for patients with larger tumors and higher PSA levels.

**Widespread Use of PSA as a Screening Tool**

There are several arguments that fuel the controversy of PSA screening. An important question that must be addressed before screening for prostate cancer is, "What grade or stage of prostate cancer is worth treating in order to improve quality of life?" At 55 years of age, a man without prostate cancer has a life expectancy of 21.4 years. If the same man has a well-differentiated, microscopic cancer and does not undergo treatment, his life expectancy will still be 21.4 years. However, a moderately differentiated cancer will cut life expectancy by four years. As widespread screening will identify cases in which treatment will benefit the patient as well as cases in which treatment will have no benefit, the willingness of patients to leave a cancer untreated, no matter what the studies indicate, must also be questioned.

It is likely that a large number of patients, even when counseled that treatment will have no effect on life expectancy will go forward with management to remove the cancer from their bodies. This desire to treat prostate cancer regardless of the fact that it may not alter life expectancy is a primary argument against widespread screening. Treatment may not only be of little benefit, it is associated with several side effects which can diminish a patient's quality of life. Radical prostatectomy is associated with a 30% risk of incontinence and impotence as lingering patient problems. Radiation therapy is associated with stress incontinence in 50% of patients, sexual dysfunction in 30% and chronic proctitis in 10%. Hormonal therapy is associated with hot flashes, decreased libido, and breast tenderness although these effects are usually short-lived. Only watchful waiting is without treatment-induced side effects.

A second important argument against PSA screening

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**Table 1 Age-specific reference ranges for serum prostate-specific antigen.**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Serum PSA (ng/ml)</th>
<th>PSA density (ng/ml/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>0.0-2.5</td>
<td>0.0-0.08</td>
</tr>
<tr>
<td>50-59</td>
<td>0.0-3.5</td>
<td>0.0-0.10</td>
</tr>
<tr>
<td>60-69</td>
<td>0.0-4.5</td>
<td>0.0-0.11</td>
</tr>
<tr>
<td>70-79</td>
<td>0.0-6.5</td>
<td>0.0-0.13</td>
</tr>
</tbody>
</table>
is cost-effectiveness. As with all aspects of health care in today’s society, cost-effectiveness is a great concern. Analyses by Krahn et al. and Fleming found that there was little or no clinical benefit derived from treating clinically localized prostate cancer. While these studies received a good deal of attention from the media and were well-cited in medical literature, their selection of patients has been questioned. In their studies, the average age of the men studied was 72 years, whereas the recommended age for screening is 50-70 years. Also, 34.2% of the men with cancer in the study had moderately or poorly differentiated disease, whereas in the U.S., screening trials have shown that over 77.6% of men diagnosed with cancer had the same level of disease. As well, several studies have shown that men treated by radical prostatectomy have the same life expectancy as age-matched men without prostate cancer, whereas there is no available data demonstrating the number of years lost if these same men were not treated for their cancer.

There are studies both for and against the cost-effectiveness of PSA screening; however, conclusive data from long-term randomized clinical trials will not be available for another ten years.

Conclusions

Widespread screening for prostate cancer by PSA has not yet been accepted in Ontario, evidenced by our lack of Canadian guidelines for screening, as well as the fact that PSA testing is not covered by OHIP. The American Cancer Society, the American Urological Association and the College of Radiology (U.S.) currently recommend that men over the age of 50 years should undergo an annual DRE and serum PSA for the purpose of detecting early prostate cancer. Annual screening should begin at the age of 40 years in African-American men or patients with a known family history of prostate cancer.

Currently in Ontario, laboratory testing is covered by both public and private sectors. Private laboratories recover their costs by billing OHIP for insured tests covered by the provincial plan. Public laboratories operate mainly within hospitals and testing costs are recovered from hospital budgets. Therefore, patients must pay for the PSA screen if it is requested outside of a hospital setting (i.e. in a family physician’s office). The fact that PSA screening is not yet covered by OHIP should not be reason to withhold it from patients in the identified risk groups. The controversy of PSA screening comes at a time when cost control is a dominant concern to the health care system. In reality, cervical and breast cancer screening programs were implemented at times during which the effect of these screening programs on mortality was not known. The fact that the burden of cost for this test currently lies with the patient, coupled with the fact that Canadian guidelines do not currently support the widespread use of testing, leaves the family physician in a state of uncertainty as to whether or not to use PSA as a screening tool in their practice.

One certainty remains, prostate cancer is a highly prevalent problem in our society. While the controversy over screening and treatment continues, all patients must be educated on the significance of positive test results, different modes of treatment (including watchful waiting) and potential benefits and side effects of these treatments. This education must be fairly comprehensive and take place before the option of PSA testing is given to the patient. While the jury is still out regarding both screening and subsequent treatment, the magnitude of the problem is such that inaction cannot be tolerated. PSA screening must be offered to informed patients 50-70 years of age and those with risk factors 40-70 years old.

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METASTASES TO BONE

By Matthew R. G. Menon, MEDS 2000

Bony metastases are a hallmark of ominous, disseminated disease. They are more common than primary bone tumours. In fact 70% of all malignancies in bone are metastases from another primary source.1,2,3 Skeletal metastases are present in up to 85% of all people with terminal carcinoma.1,3 These metastases are frequently the presenting complaint from which the disease is discovered.

Almost all malignant neoplasms have been described to metastasize to bone at some point.3 However, carcinomas of the breast, prostate, lung, kidney and thyroid comprise 90% of bony metastases.1,2,3,4 Less common primary tumours include carcinomas of the skin, esophagus, oral cavity, stomach, cervix and colon. Only 23% of terminal colon cancer cases show bony metastases on autopsy.5 In men, prostate cancer is responsible for 60% of bony metastases and bronchogenic carcinoma is responsible for 25%.5 In women, breast cancer produces 70% of bony metastases with kidney, thyroid and uterus causing nearly 30%. In children under five years old, neuroblastoma is the most common primary neoplasm metastasizing to bone.

The most common site for bony metastases is the thoracic spine. This is followed by the lumbar spine, pelvis, femur, rib, sternum, proximal humerus and skull.5 It is rare to see bony metastases distal to the elbows or knees. When these so called acral metastases are present, lung is the most common primary.1,3

Tumours arrive at bone usually via hematogenous spread, although local invasion is possible. The spine in particular is surrounded by an anastamosing vascular network known as Batson’s Plexus.1,2,5 This rich plexus of veins has no valves.6 This fact allows for retrograde flow of blood that bypasses the caval system and facilitates the seeding of tumour cells in the spine. The hematopoietic marrow of the axial skeleton is also supplied by rich sinuosoids. These may also play a role in metastases formation.

In the early stages, bony metastases are usually asymptomatic.7 They often progress to pain, tenderness and swelling, increasing insidiously for weeks or months.7 This pain is usually worse at night. In the much rarer case of sudden onset of pain, a pathological fracture is usually responsible. Other possible presenting complaints may be related to nerve root or spinal cord compromise. Up to 10% of patients with bony metastases will develop a clinical picture similar to hyperparathyroidism, due to the production of parathyroid hormone-like osteoclast-activating factor.7

Bony metastases can be either osteoblastic, osteolytic or both.5 Osteoblastic lesions constitute 15% of all bony metastases. They carry a better prognosis than osteolytic tumours.1 They are frequently painless and have a lower chance of pathological fracture. In men, prostate and testicular seminoma are most often the primary tumours.2 In women, breast, ovary and uterus are usually responsible for blastic metastases.

Osteoblastic tumours produce cytokines that activate osteoblasts.5,6 There is also an association with increased alkaline phosphatase levels and causing hypocalcemia. A plain film of an osteoblastic lesion may show increased bone density or sclerosis. However, a bone scan is usually used to detect these lesions.

Seventy-five per cent of bony metastases are osteolytic. Common primaries of lytic lesions include kidney, breast, lung, gastrointestinal and thyroid tumours.7 These lesions are more often associated with hypercalcemia. Osteolytic lesions result when tumours produce substances that cause bone resorption such as prostaglandins or vitamin D-like steroids. These tumours may also produce cytokines that induce osteoclast activity. (eg. interleuken 1 and tumour necrosis factor).

Most tumours may produce both lytic and blastic metastases. Ten per cent of all lesions are actually a mixture of both blastic and lytic components.2 Some carcinomas, such as hypernephroma, multiple myeloma and thyroid carcinoma, can induce vascularity at a metastatic site producing an aneurysmal lesion.1 It is important to note these as they may need to be embolized prior to surgery.

APPROACH

It is not unheard of for a cancer to present as a focus of bony metastases. In these cases, the presenting complaint is usually that of progressive spine pain that may or may not progress to include neurological symptoms. Less often, the presenting problem may be that of a pathological fracture. In either case, a full work-up to diagnose the primary lesion is indicated.

The recommended investigation into bony metastases of unknown origin begins with a detailed history and physical exam.1,6 In the female, concentration should be on the breast exam and Papanicolou smear. In the male, a prostate exam and Prostate Specific Antigen are of special interest. Breast and prostate should be the first thought in a diagnostic investigation. The thyroid gland should also be palpated thoroughly and an I-131 isotope study of the thyroid is often indicated. A complete blood count, electrolytes, urinalysis and alkaline phosphatase levels are the initial laboratory investigations of choice.6 Pathology examination of a biopsy of the metastasis may provide a diagnosis if the above investigations fail to yield the needed information.

Imaging is more helpful in finding the primary lesion than it is at detecting bony metastases. A chest x-ray,

ABOUT THE AUTHOR

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THERAPEUTIC CLASSIFICATION
Bone Metabolism Regulator

INDICATIONS AND CLINICAL USE
Tumour-induced hypercalcaemia following adequate saline rehydration.

Prior to treatment with AREDIA, renal excretion of excess calcium should be assessed and, where necessary, maintaining adequate fluid balance and urine output.

- Conditions associated with increased osteoclastic activity, predominantly lytic bone metastases and multiple myeloma.
- Symptomatic Paget's disease of bone.

CONTRAINDICATIONS
Known or suspected hypersensitivity to AREDIA, or to any of its components (see COMPOSITION IN PHARMACEUTICAL INFORMATION section).

WARNINGS
AREDIA SHOULD NEVER BE GIVEN AS A BOLUS INJECTION SINCE SEVERE LOCAL REACTIONS AND THROMBOPHLEBITIS MAY RESULT FROM HIGH LOCAL CONCENTRATIONS.

AREDIA SHOULD NOT BE ADMINISTRED AND ADMINISTERED AS A SLOW INTRAVENOUS INFUSION (see DOSAGE AND ADMINISTRATION). REGARDLESS OF THE VOLUME OF SOLUTION IN WHICH AREDIA IS DILUTED, SLOW INTRAVENOUS INFUSION IS ABSOLUTELY NECESSARY FOR SAFETY.

PRECAUTIONS
It is essential in the initial treatment of tumour-induced hypercalcaemia that intravenous rehydration be instituted to restore urine output. Patients should be treated adequately throughout treatment but overhydration must be avoided.

In patients with cardiac disease, especially in the elderly, additional saline overhydration may precipitate cardiac failure (left or right heart failure or congestive heart failure). Fever (influenza-like symptoms) may also contribute to this deterioration.

Although AREDIA is excrated unchanged by the kidney, the drug has been used without apparent increase in adverse effects in patients with severe renal impairment. However, patients undergoing renal replacement therapy with both hemodialysis and peritoneal dialysis. Experience with AREDIA in this group of patients is limited (serum creatinine >440 μmol/l, or 5 mg/l, in 71 patients; <180 μmol/l, or 2 mg/l, in 63 patients) and therefore the safety and efficacy of AREDIA in this patient group has not been established.

Central nervous system: Occasional: headache. Rare: symptomatic hypercalcaemia (paresthesias, tetany), agitation, confusion, diziness, paresis, myoclonus, convulsions, hyperreflexia, cold sweats, or cardiac arrhythmias.

Musculoskeletal system: Occasional: transient bone pain, arthralgia, myalgias, peripheral neuropathy, Raynaud's phenomenon.

Gastrointestinal tract: Occasional: nausea, vomiting. Rare: anorexia, abdominal pain, diarrhea, constipation, dyspepsia.

Hypersensitivity: Occasional: urticaria.


Renal system: Isolated cases: haematuria, acute renal failure, deterioration of pre-existing renal disease.

Dermatological system: Occasional: rash. Rare: erythema multiforme, bullous eruption.

Gastrointestinal: Occasional: nausea, vomiting. Rare: anorexia, abdominal pain, diarrhea, constipation, dyspepsia.

Haematological system: Occasional: thrombocytopenia, leucopenia or a decrease in white blood cell count.

Neurological system: Occasional: convulsions, seizures, visual disturbances, tremors, transient drowsiness.

Other: Occasional: infections of herpetic simplex and herpes zoster.

Biochemical changes: Frequent: hyperglycaemia, hypercalcaemia, hyperuricaemia, hyperkalaemia, hypomagnesaemia.

Infusion site: Rare: pain, redness, local tissue oedema, infection.

Infusion reaction: Occasional: fever, flushing, rigors, rash, hypotension, tachycardia, dyspnoea, angina.

Pain: Infusion site: occasional; rare: abdominal pain, renal colic, chest pain, muscle pain, arthralgia.

SYMPTOMS AND MANAGEMENT OF OVERDOSE:
In the event of overdose, intravenous calcium gluconate, 10% should be administered. Appropriate supportive measures should be taken to correct hypocalcaemia and hypokalaemia.

Intravenous calcium gluconate, 10% solution should be given as a bolus injection (see WARNINGS).

In addition, supportive measures should be taken to arrest the progression of acute renal failure.

For severe calcium excess within 6 hours calcium administration should be held and magnesium should be administered. Where appropriate, additional supportive measures should be taken to correct hypocalcaemia and hypomagnesaemia.

In the event of severe magnesium excess, supportive measures should be taken to correct hypocalcaemia and hypomagnesaemia.

The total dose of calcium gluconate to correct hypocalcaemia should not exceed 2 g in a single bolus injection, or 5 g in 24 hours, to prevent potential cardiovascular toxicity.

It is not known whether administration of calcium gluconate will enhance the clinical response to intravenous calcitonin or vitamin D metabolites.

DOSAGE AND ADMINISTRATION
Dosing recommendations differ for tumour-induced hypercalcaemia, acute hypercalcaemia, and multiple myeloma. For patients suffering from TH and multiple myeloma, see the TH dosage guidelines.

AREDIA should never be given as a bolus injection (see WARNINGS).
PREVENTING SKELETAL COMPLICATIONS WITH AREDIA

FROM THE 1st SIGN OF METASTASES

WITH MORE THAN 2 YEARS OF CONTINUOUS, PROVEN EFFICACY

AREDIA OFFERS 3 SIGNIFICANT BENEFITS:

• Delayed time to first skeletal complications.†
• Reduced bone pain and analgesic use.‡
• Maintained quality of life.‡‡

† In a study of 382 women with metastatic breast cancer and lytic bone lesions receiving 90 mg pamidronate every 3 to 4 weeks.
‡ At the last measurement (month 9 or last visit), quality of life worsened with chemotherapy alone, while there was no significant deterioration vs baseline in Aredia-treated patients.
The most common adverse reactions are arthralgia, fatigue, and myalgia.
Aredia is indicated in conditions associated with increased osteoclastic activity: predominantly lytic bone metastases and multiple myeloma.
AREDIA (pamidronate disodium) MUST NEVER BE GIVEN AS A BOLUS INJECTION.
Please refer to the Product Monograph for additional prescribing information.

*Registered trademark
†Mfd. by Genentech
‡Evidence-based solution
‡‡Novartis Pharmaceuticals Canada Inc.
Dorval, Quebec H9R 4P1

AREDIA
(pamidronate disodium)
Evidence-based solution
ARE-98-12-4440E
abdominal CT and pelvic CT are usually indicated in disseminated neoplastic disease. Plain films of the bones where metastases are suspected are often of little value. Osteolytic lesions tend to show up on plain films only after the cortex has become involved. Usually, tumours embolize to marrow first and only invade the cortex after some growth (usually at least 1 cm diameter) has occurred. This invasion of the cortex produces the so-called "cookie-cutter" lesion on a plain radiograph. Typically, 30% to 50% of cortical bone mineral must be lost before the lesion shows up on x-ray. Therefore, bone scans often show positive metastases up to four months before plain films.

In 3% to 4% of cases of isolated bony metastases, a primary is not found. Although most bony metastases are from prostate or breast, those that remain unknown are not likely to be from either of these two common cancers. These are both easily examined and local symptoms are usually present. Undiagnosed primaries are more likely to be from deeper visceral organs such as kidney or lung. If the aforementioned investigations do not yield a diagnosis, further investigation is likely not indicated. The disease is severe and the prognosis is already known to be poor. It should seriously be considered to treat this patient palliatively and spare them the discomfort of further aggressive tests.

MANAGEMENT

The pain caused by bony metastases should not be underestimated. Palliative pain management is often necessary to reduce the morbidity of the disease. Hormonal regulation plays a role in controlling the symptoms of bony metastases. Also effective for these common tumours is local radiation therapy consisting of 3000 cGy for ten days. More radioreistant tumours, such as renal cancer or melanoma, may respond favourably to 4000 cGy to 5000 cGy for ten days. This has been shown to significantly reduce pain one month post-treatment in 80% of cases. This is also associated with a change from an osteolytic picture to an osteoblastic one.

Pathological fracture of a bone due to metastatic disease is most often an indication for surgical treatment. Twenty years ago, the mean survival following a pathological fracture was 7.8 months. Due to the development of better surgical techniques and radiotherapy, the current mean survival following all pathologic fractures is 18.8 months. Specifically, the mean survival following fracture due to prostate cancer is 30 months, breast cancer is 22.6 months, kidney cancer is 11.8 months. The worst prognosis follows pathologic fracture due to lung cancer with a mean survival of 3.6 months.

75% of all pathological fracture surgery is performed on the hip. The most common site for fracture is intertrochanteric followed by the femoral neck. Often a metastasis to the femur is identified before fracture occurs. In this case it is the responsibility of the Orthopaedic Surgeon to decide whether prophylactic internal fixation is necessary prior to local radiation. The current criteria for prophylactic stabilization consist of one of: 50% cortical lysis; 2.5 cm diameter femoral lesion; avulsion fracture of the lesser trochanter and persistent pain four weeks after local radiation therapy. Other sites of pathological fracture that commonly require surgical stabilization include the shafts of the femur and humerus and the acetabular area.

Metastases to the spine produce further issues in management. The presenting complaint of spinal metastases is that of progressive pain persisting for weeks to months. Most spinal metastases can be adequately managed with local radiation therapy and medication. However, in the event of neurological symptoms such as motor or sensory changes, radicular pain or alterations in bowel and bladder function, more aggressive treatment needs to be instituted. The mid-thoracic spine is the most common site for spinal metastases. The narrow vertebral canal in this area also makes it more prone to spinal cord compression. This is followed by the thoracolumbar area. The cervical spine is more rarely affected partially due to the wide vertebral canal at this level. Prostate and breast cancers usually appear at multiple sites along the spine whereas lung cancers often metastasize to one focal point.

Spinal cord compression occurs in 5% to 10% of all cancer patients. Cord injury occurs when metastases from the vertebral body or pedicles encroach upon the spinal canal and compress the dura. Alternatively, it is possible for a tumour from the paravertebral area to invade into the spinal canal through the intervertebral foramina.

If neurological symptoms present with back pain, an emergency work-up for cord compression is indicated. Upper motor neuron findings (ie, upgoing toes, spasticity and hyper-reflexia), sensory loss and loss of autonomic sphincter control may all be present. MRI is the investigation of choice to diagnose cord compression. If cord compression is suspected on history and physical exam, dexamethasone can be given immediately (dose 6 mg po q6h, can be doubled if necessary). The goals of therapy are to reduce pain and to preserve neurological function. This is usually accomplished with radiation therapy and glucocorticoids. With this protocol, 75% of those patients who are ambulating on presentation will remain ambulatory. However, only 10% of those who have lost their ability to walk will regain it.

Surgical decompression and stabilization is required in some cases of vertebral collapse and cord compromise. The current indications for surgery are: a radioreistant tumour; local radiation failure; pathological fracture; and rapidly developing neurological symptoms. Formerly, a laminectomy alone was the procedure of choice: however this led to a destabilized spine, kyphosis and further cord damage. Now, an anterior decompression with pins and bone cement or a femoral allograft is used if this aggressive anterior thoracotomy can be tolerated. This is a particularly effective procedure as most lesions are actually anterior to the cord itself. In the lumbar area, due to the large amount of force that the spine must bear, posterior stabilization is also necessary. Bone grafting is contraindicated as local radiation therapy follows surgery.

Cancer is a disease that no physician can avoid dealing with. A large component of cancer treatment consists of treating the complications of the disease. In the case of bony metastases, correct identification, approach
and treatment can significantly improve the morbidity and mortality from the primary disease.

REFERENCES


Prevacid is indicated for short-term treatment of reflux esophagitis and maintenance therapy of healed reflux esophagitis.

* After the first day of therapy, significantly more patients (p < 0.05) on Prevacid 30 mg (n = 402) reported less day and night heartburn compared with omeprazole 20 mg (n = 418).†

Most common side effects (>3%) in short-term studies are headache and diarrhea.

Doses higher than 30 mg per day should not be administered to patients with impaired hepatic function and the elderly.‡
OVERVIEW OF THE PALLIATIVE ROLE OF RADIOTHERAPY

By Eric Wong, MEDS 2002

INTRODUCTION

Radiotherapy plays major roles in both radical and palliative cancer treatments. Radical radiotherapy is a more aggressive form of management that targets cancer patients who have limited tumours and a reasonable chance of cure. Meanwhile, palliative radiotherapy manages incurable patients, with the goal of alleviating their cancer-associated symptoms. Radiotherapy is further categorized by techniques of delivery into two groups: external beam therapy and internal therapy. Modern external beam therapy primarily utilizes megavoltage teletherapy, which includes linear accelerators that produce proton and high-energy electron beams, and cobalt-60 units that emit gamma rays. It is suitable for many superficial and deep-seated malignancies. Internal therapy is divided into brachytherapy and systemic therapy. Brachytherapy refers to the direct implantation of sealed radioactive sources or intracavitary source placement, and is mainly used for surface treatment, tumors in the intracavitary spaces (cervix, uterus), and interstitial implants within tissues (breast and tongue). Systemic therapy uses unsealed radioisopes. Its major applications include thyroid carcinoma and hyperthyroidism, polycythemia vera, and cancers of the peritoneal cavity.

BASIC PRINCIPLES

Radiotherapy is an important palliative tool because of its ability to remarkably relieve certain symptoms of advanced-stage cancers. It is often prescribed to effectively manage pain from bone metastases and ulceration, visceral obstruction, bleeding, neurological deficits, pathological fractures, and other systemic symptoms. However, since radiotherapy is not the only modality that can alleviate symptoms associated with advanced-stage tumours, indications and contraindications have been outlined to guide its usage (see Table 1).

Besides directing the appropriate usage of palliative radiotherapy, the indications and contraindications in Table 1 also emphasize the goals of palliative radiotherapy. These include achievement of reasonable symptom relief with shorter duration of therapy than radical radiotherapy, complete and durable palliation, minimization of patient inconvenience and discomfort, and minimization of toxic effects and hospital stay. Other palliative modalities, such as surgery, chemotherapy, and analgesics, may contribute to symptom management as adjuvant palliation.

COMMON USAGES

There are specific clinical manifestations for which palliative radiotherapy has proven to be effective. The more dominant ones include skeletal or bone metastases, spinal cord compression, brain metastases, and mediastinal metastases.

Skeletal Metastases

Metastases found in the bone are mostly multiple, and originate primarily from tumors of the breast, prostate and lung. The main role radiotherapy plays in these situations is the relief of pain. Radiotherapy is used only when the patient is symptomatic, and this occurs in three-fourths of patients with skeletal metastases. Pain is the result of two processes triggered by the tumour cells: osteolysis and osteosclerosis. There are two main mechanisms of osteolysis. In the direct method, tumor cells either resorb bone themselves, or activate osteoclasts through the release of chemicals such as growth factors, prostaglandins, and cytokines. On the other hand, the indirect mechanism involves stimulation of immune cells by the tumour cells to produce the same chemicals that induce osteoclastic activity. Pain produced by osteosclerosis rarely occurs, and is usually limited to metastases from prostate cancer, and in about 10% of breast cancer.

Once the bone pain has been confirmed to be the result of bone cancer, a therapeutic decision is often made between surgery and external beam therapy. Surgery is required if bone has already been fractured, or if there is an impending fracture in the affected long bones. In cases where surgery is not required, local ionizing radiation alone has proven to be very effective in managing skeletal symptoms. Moller's meta-analysis of 19 retrospective studies observed that 40% to 50% of patients reported complete pain relief in response to localized irradiation, while an additional 30% reported partial pain relief. These results agree with those of a randomized trial conducted by the Radiation Therapy Oncology Group (RTOG) between 1974 and 1980. The RTOG trial found that 90% of all patients treated with local external beam therapy received partial pain relief while 64% received complete pain relief.

Although the success of local external beam therapy in alleviating skeletal symptoms is unquestionable, there is controversy over which type of treatment module is most effective and efficient. Main variations in treatment plans include dosage of radiation and fractionation schedules. Moller analyzed six prospective randomized studies and concluded that there was no consensus on the optimal type of treatment delivery module based on these variations.

ABOUT THE AUTHOR

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in the presence of multiple bone lesions, local external beam therapy becomes less applicable, and is usually replaced by hemi-body irradiation. The upper body and lower body are usually treated sequentially, with a 2 to 4 week interval to allow for the recovery of bone marrow. Although shown in several studies to provide faster pain relief, this method of delivery results in more prominent toxic effects than conventional, local irradiation. The side effects usually involve the lungs, gastrointestinal tract, and mucous membranes. Emesis is the most common one, which affects up to 80% of patients who receive a single high dose of radiation to either half of their bodies. Pneumonitis is a possible side effect, but can be avoided by using lower dosage to the upper body. Pretreatment hospitalization with drug prophylaxis is also used to minimize patient discomfort.

When bone metastases are too numerous, or when they are unresponsive to external beam therapy, the patient can be managed with systemic therapy, a less widely used treatment. Metastases from the prostate and breast respond most avidly to this form of radiotherapy. Presently, two main types of radionuclei are used for the alleviation of symptoms associated with skeletal metastases: phosphorus 32 and strontium 89. They are both introduced into the body intravenously, and are absorbed more efficiently by tumours and bone tissues than normal tissues. Results from randomized studies on symptom alleviation have been encouraging for both radionuclei. Approximately 70% of patients treated with phosphorus 32 report some degree of pain relief, although myelosuppression was a major side effect. Strontium 89 has also been associated with significantly greater pain relief than placebo, but with less severe myelosuppression. One setback for strontium 89 is its long half-life, which results in a longer latency period than phosphorus 32 before pain relief begins.

**Spinal Cord Compression**

Metastases to the vertebral column that result in spinal cord compression occurs in 5-10% of cancer patients. Like metastases to other parts of the skeleton, breast, prostate, and lung cancers are usually the common primary tumours in these cases. The thoracic vertebrae is the most common site of metastasis, accounting for 70% of all vertebral metastases. Because vertebral body involvement is frequent, most compressions associate with the anterior aspect of the spinal cord. Consequently, compromised motor functions represent dominant, early symptoms. Other classical symptoms of spinal cord compression include back pain, bladder and bowel dysfunction, and numbness.

Spinal cord compression requires prompt management because a patient's neurological function is at stake. Radiotherapy is highly indicated as treatment unless the patient expresses vertebral instability, compression due to bony deformity, high cervical cord compression that jeopardizes respiratory function, or unresponsiveness to radiotherapy. In the presence of these scenarios, surgery is the alternate treatment. Prior to local external beam irradiation, patients are usually prescribed corticosteroids (e.g. dexamethasone) to reduce neurological symptoms due to vasogenic edema. Localized external beam therapy that includes 1 or 2 vertebrae above and below the cord block to be treated is extremely effective in relieving pain. From an analysis of several studies, Moller reported a 50% to 95% pain relief for patients treated with external beam therapy alone. Meanwhile, reversal of neurological deficits depend largely on pretreatment neurological status. If a patient could ambulate independently at the start of treatment, there is a 70% to 90% chance that mobility can be maintained. This contrasts with a 10% to 30% chance of regaining ambulatory ability after irradiation for patients who were paralytic prior to treatment.

**Brain Metastases**

Patients with brain metastases have extremely poor prognosis. Untreated, their median survival time ranges from 1 to 2 months. The most common source of brain metastases is lung cancer. Prevalent symptoms include headache, focal weakness, behavioural change, seizures, ataxia, and aphasia. At times, more serious conditions such as hydrocephalus, herniation of cranial contents, and vasogenic edema often complicate treatment. Like treatment of spinal cord compression, initial therapy includes corticosteroids, which is effective in extending survival to about 2 to 3 months if prescribed alone. And complications, such as seizures and hydrocephalus, must be stabilized before radiotherapy can be initiated.

### Table 1. Indications and Contraindications for Usage of Palliative Radiotherapy

<table>
<thead>
<tr>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>relief of pain</td>
<td>availability of more effective therapy</td>
</tr>
<tr>
<td>relief of neurological deficits</td>
<td>availability of more easily administered therapy</td>
</tr>
<tr>
<td>restoration/preservation of function/cosmesis</td>
<td>unreasonable risk of sequelae</td>
</tr>
<tr>
<td>relief of obstruction</td>
<td>low probability of success</td>
</tr>
<tr>
<td>control of bleeding</td>
<td>pregnancy</td>
</tr>
<tr>
<td>restraint of tumor growth</td>
<td></td>
</tr>
<tr>
<td>maintenance of skeletal integrity</td>
<td></td>
</tr>
<tr>
<td>prevention of fistula</td>
<td></td>
</tr>
<tr>
<td>relief of systemic symptoms</td>
<td></td>
</tr>
<tr>
<td>Promotion of healing</td>
<td></td>
</tr>
</tbody>
</table>

50

U.W.O. Medical Journal 69 (2) 1999
External beam therapy for the whole brain is an effective method in relieving symptoms and increasing survival time for both solitary and multiple cerebral metastases. Surgery is usually indicated prior to radiation treatment in the presence of solitary metastases. Together with the administration of corticosteroids, whole brain irradiation typical yields survival time between 3 to 5 months.6-8 Collectively, studies have shown that external beam therapy as a primary treatment of cerebral metastasis relieves symptoms and improves neurological status in 50% to 90% of patients.2,4-6-7 There is also indication that postoperative whole brain irradiation is able to increase durability of palliation from surgery and median survival time, and decrease recurrence rates.4-6-7 However, this only applies for patients who have one or few brain metastases that are accessible by surgery, and who are generally in good conditions.7 One major imperfection in whole brain irradiation is the high recurrence rates, which often require patients to be re-irradiated. Even though re-irradiation from several studies points to a 69% to 79% improvement in all patients treated, the concern for acute and subacute sequelae arises.

Patients generally tolerate toxic effects of whole brain irradiation quite well.9 Acute adverse effects from whole brain irradiation include fatigue, epilation, and skin erythema.9 Subacute toxicity usually arises within 3 to 10 weeks after radiation treatment, and may consist of the somnolence syndrome, or transient neurological deterioration that usually resolve in an additional 6 weeks.7 Late sequelae are less common because of the limited life expectancy of the patients, but dizziness, headache, short-term memory loss, and severe dementia have been noted. Moreover, cortical atrophy, ventricular dilatation, and hypodense white matter have also been observed.6-7 A more aggressive form of treatment, like stereotactic radiosurgery, may also be of value for patients with solitary or few cerebral metastases. It involves the delivery of high doses of radiation to limited volumes of tissue using a cobalt-60 gamma knife. Although further studies are required to study its benefits and setbacks, stereotactic radiosurgery has been associated with high local tumour control, 64% to 99% in several investigations, and with few morbidity.2,4-6 Brain toxicity becomes a concern only when there are more than a few metastases to be treated.4

**Mediastinal Metastases**

Metastasis to the mediastinum is a common complication of advanced lung cancer. Common mediastinal metastases include obstructions of the esophageal, bronchi, and superior vena cava. Obstruction of the superior vena cava is the most frequently seen type of complication, and accounts for 75% of all thoracic metastases. The prognosis of these patients is poor, with a median survival time of only 3 months.7 Being regarded as a medical emergency, superior vena cava obstructions receive prompt interventions.

The symptoms of superior vena cava syndrome include dilatation of veins, edema in the chest, neck and upper extremities, cough, orthopnea, headache, dysphagia, dizziness, and chest pain.2,4-6 Radiotherapy is usually the first and main treatment for relief of these symptoms. It is extremely effective, having response rates from 70% to 80% that can begin subjectively as early as 3 to 4 days, and objectively between 1 to 3 weeks.4-6 Toxic effects are generally mild and tolerable, with dysphagia being the more prevalent one.7 The external beam therapy involved begins with higher doses of radiation in order to illicit greater response, and then turns to lower doses and more fractionated schedules.2-4 At times, relief of symptoms does not correlate with an increase in venous drainage through the superior vena cava. This is indicative of obstructive thrombosis, which can be readily resolved if thrombolytic therapy was prescribed promptly.4 In the event of recurrence or unresponsiveness after radiotherapy to tolerance doses, patients may be eligible for an intravenous insertion of expandable prosthesis into the superior vena cava that has been associated with high success in relieving symptoms.6

ACKNOWLEDMENT

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REFERENCES

PALLIATION OF INOPERABLE CANCER OF THE ESOPHAGUS WITH STENTS: A SYSTEMATIC REVIEW

By Gabriel Chan, MEDS 2000

The diagnosis of esophageal cancer carries a very grave prognosis. In Ontario, the median survival is less than a year and the 5-year relative survival rate is 12% for males and 15% for females. The onset is insidious and the majority of patients present at an advanced stage with pain, severe dysphagia and weight loss. Cure is only possible by surgical resection, if the cancer is detected at an early stage. When the tumor is unresectable, then the main objective of therapy is palliation.

At present, there is no definitive palliative treatment for inoperable esophageal cancer. Conventional interventions include external radiation therapy and chemotherapy. Different centers worldwide apply various other therapies, including simple dilation, endoluminal laser therapy, brachytherapy, electrocoagulation, alcohol injection sclerotherapy, photodynamic therapy and stent placement. However, most of the palliative therapies are associated with a significant morbidity and mortality.

Esophageal stents are used primarily to treat malignant dysphagia and resultant cachexia. They do not directly stem the growth of the cancer. Initial endoluminal stents were rigid plastic tubes and had to be introduced by laparotomy involving a high mortality rate. The development of laparoscopic techniques allowed for a less traumatic placement, but the delivery system was still cumbersome and resulted in many procedure-related complications. Plastic stents have the advantage of a one-time treatment and the additional ability to seal off fistulas with a modified cuff. Recently, expandable metal stents have been designed for an easier delivery, fewer complications and lessened chance of migration. The deployment is guided by Barium swallow, fluoroscopy and possibly endoscopy. Some of the current models in use include the Wallstent endoprosthesis (Schneider AG, Zurich, Switzerland), the Ultraflex device (Boston Scientific Corporation, Watertown, MA, USA) and the Gianturco stent (William-Cook Europe, Bjaeverskov, Denmark).

This article reviews the literature for randomized controlled trials comparing the effectiveness of various stents to other palliative therapies for patients with inoperable esophageal cancer. The primary focus is on the improvement of the patients’ quality-of-life, especially with regards to the dysphagia, a significant source of morbidity and mortality. The secondary focus is on the improvement of survival.

METHODS

The MEDLINE, EMBASE and CANCERLIT databases were searched for randomized controlled trials studying the treatment of inoperable esophageal cancer. The MEDLINE database was searched with the OVID program, through the years January 1, 1966 to September 11, 1997. The search parameters included the MeSH subject term, “esophageal neoplasm” the publications terms, “clinical trial, phase III” and “randomized controlled trial” and the text words, “unresectable”, “advanced” and “inoperable”. The EMBASE database and CANCERLIT database were searched for articles from 1980 to 1997 using the MeSH terms “esophageal cancer” and the publication terms “experimental controlled study”, “double blind procedure” and “single blind procedure”. The reference lists of trials and review articles were also reviewed, as were textbooks related to esophageal oncology.

Articles were included in this review if they were randomized controlled trials comparing the use of stents for inoperable esophageal cancer. Articles were excluded if they were not limited to patients with esophageal cancer, were not focused on palliation or treatment, or included surgery as part of the treatment.

Data concerning the patient population, interventions and the end-points of median survival, quality-of-life and the rate of complications were extracted. Quality-of-life data concerning the improvement of swallowing function or relief of dysphagia were used to gauge the effectiveness of the therapies.

RESULTS

The initial method intended was a meta-analysis of the published trials to reach an Evidenced-Based Recommendation for the treatment of inoperable esophageal cancer according to the protocol set out by the Cancer Care Ontario. At present, this is not feasible with the number of published trials and their heterogeneity. A systematic review of these trials was done and presented in Table 1.

DISCUSSION

Two published randomized trials compare the efficacy of plastic stents and expandable metal stents in the palliation of malignant dysphagia are reviewed. Kyririm et al compared the Wilson-Cook plastic stent to the Wallstent expandable metal stent and found no significant difference in survival, nor in the improvement of dysphagia or Karnofsky scores. Both the plastic and metal types of stent improved dysphagia scores significantly. The advantage of expandable metal stents was that complications such as...
TABLE 1. Randomized Controlled Trials with Oesophageal Stents in the Palliation of Malignant Dysphagia

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Intervention (#)</th>
<th>Median Survival</th>
<th>Swallowing Score</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knyrim 1993 7</td>
<td>Wilson-Cook (21)</td>
<td>146 ± 29 d.</td>
<td>3 → 1</td>
<td>43%*</td>
</tr>
<tr>
<td></td>
<td>Wallstent (21)</td>
<td>167 ± 28 d. a</td>
<td>3 → 1</td>
<td>0%*</td>
</tr>
<tr>
<td>DePalma 1996 8</td>
<td>Wilson-Cook (20)</td>
<td>6.2 mo.</td>
<td>3.0 → 1.0</td>
<td>22.2%*</td>
</tr>
<tr>
<td></td>
<td>Ultrafluew (19)</td>
<td>6.6 mo.</td>
<td>2.9 → 0.5</td>
<td>0%**</td>
</tr>
<tr>
<td>Adam 1997 10</td>
<td>Nd:YAG Laser (18)</td>
<td>56 d.</td>
<td>3 → 2</td>
<td>11%*</td>
</tr>
<tr>
<td>Uncovered Strecker (19)</td>
<td>60 d.</td>
<td>3 → 1</td>
<td>5%*</td>
<td></td>
</tr>
<tr>
<td>Wallstent or Gianturco (23)</td>
<td>48 d.</td>
<td>3 → 1</td>
<td>9%*</td>
<td></td>
</tr>
<tr>
<td>Alderson 1990 9</td>
<td>Nd:YAG Laser (20)</td>
<td>12 wk.</td>
<td>85%</td>
<td>20%*</td>
</tr>
<tr>
<td>Celestin or Atkinson (20)</td>
<td>16 wk.</td>
<td>85% f</td>
<td>5%*</td>
<td></td>
</tr>
<tr>
<td>Reed 1991 12</td>
<td>Atkinson (10)</td>
<td>119 ± 82 d.</td>
<td>+ 2.3 ± 1.1</td>
<td>50%*</td>
</tr>
<tr>
<td>Atkinson + RT (8)</td>
<td>72 ± 62 d.</td>
<td>+ 1.8 ± 1.0</td>
<td>100%*</td>
<td></td>
</tr>
<tr>
<td>Nd:YAG Laser + RT (9)</td>
<td>169 ± 92 d. a</td>
<td>+ 1.4 ± 0.5</td>
<td>0%*</td>
<td></td>
</tr>
<tr>
<td>Nicolaou 1982 11</td>
<td>Celestin + CT* (12)</td>
<td>182 d.</td>
<td>(not recorded)</td>
<td>100% b</td>
</tr>
<tr>
<td>Celestin (12)</td>
<td>117 d.</td>
<td></td>
<td>(not recorded)</td>
<td></td>
</tr>
<tr>
<td>Albers 1992 13</td>
<td>Celestin or PL + CT* + RT (10)</td>
<td>11 wk.</td>
<td>(Semi-solid)</td>
<td>70%*</td>
</tr>
<tr>
<td>Celestin or PL (10)</td>
<td>19 wk. (P=0.03)</td>
<td>(Semi-solid)</td>
<td>(not recorded)</td>
<td></td>
</tr>
<tr>
<td>Schmid 1993 14</td>
<td>Celestin or PL + RT (41)</td>
<td>9 wk.</td>
<td>(not recorded)</td>
<td></td>
</tr>
<tr>
<td>Celestin or PL + CT* (40)</td>
<td>11 wk.</td>
<td></td>
<td>(not recorded)</td>
<td></td>
</tr>
<tr>
<td>Celestin or PL (46)</td>
<td>9 wk.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(PL: Procter-Livingstone plastic stent; RT: radiation therapy; CT: chemotherapy)
a expressed as mean survival
b Doxorubicin 40 mg/m² + Cyclophosphamide 700 mg/m², Complications related to chemotoxicity such as alopecia, nausea, vomiting, leukopenia, thrombocytopenia, fistulas, weight loss, esophagitis
c 5-Fluorouracil 500 mg/m² + Cisplatin 15 mg/m²
d Trimetrexate 12 mg/m² or, Ifosfamide 1.2 g/m² + Mesna 20% or, %-Fluorouracil 425 mg/m² + Leucovorin 20 mg/m²
e Median dysphagia score (pre-/post-treatment)
f Swallowing scale (post-treatment): 0 (normal) – II (dietary modifications)
g Mean increase in swallowing score
h Complications include perforation, migration, aspiration pneumonia, obstruction and hemorrhage.
** Other complications not included were tumor ingrowth and overgrowth

perforation, migration and aspiration pneumonia occur less frequently. The only major reported complications of the metal stents were tumor in-growth and outgrowth. DePalma et al compared the Wilson-Cook plastic stent with the Ultrafluew Ti-alloy metal stent and also found that there was no significant difference in median survival or in the improvement of dysphagia. Plastic stents were shown to have a higher rate of complications, and a higher mortality related to stent placement. Major complications encountered with the plastic stent included migration, perforation and hemorrhage. Tumor in-growth was the only major complication to occur more often with the metal stent. These limited numbers of trials demonstrate that expandible metal stents are equally effective treatments for malignant dysphagia and a safer, more effective alternative to plastic stents.

Two published trials comparing stent to laser therapy are reviewed. Alderson et al studied the endoscopic treatment of esophageal cancer with Celestin or Atkinson plastic tubes and Nd:YAG laser ablation. Unfortunately, it should be noted that this trial was under-powered. Both groups were found to have similar improvements in swallowing function and low complication rates. The authors make the suggestion that laser ablation and stent placement should be considered as complementary rather than mutually exclusive treatments.

A trial by Adam et al compared three treatment modalities, Nd:YAG laser therapy, the Strecker covered metal stent, and the Wallstent or Gianturco uncovered metal stent. No survival advantage was demonstrated for any of the three modalities. Improvement of dysphagia was similar for the two types of stents, covered and uncovered, and both provided superior relief to laser therapy. Patients receiving the uncovered stent were found to have substantially fewer complications than the other two groups. Covered stents were prone to reflux, and to migration if placed in the lower esophagus. Uncovered stents were prone to tumour in-growth that was amenable to treatment with laser ablation, showing a role for adjuvant laser therapy in stent placement, as also suggested by Alderson et al. Although the evidence in favour of stent placement is not unequivocal, the improvement of stent technology, as was used in the trial by Adam, should be accounted for as a significant advancement from the Alderson trial. A plastic stent was used in the Alderson trial whereas an expandible metal stent was used by the Adam trial, possibly suggesting that a metal stent may provide superior palliation to laser therapy, while a plastic stent is comparable to laser.

The focus of the other trials published studying esophageal stents is on improving the palliation of the stent with chemotherapy, radiotherapy or a combination
of both. Nicolaou et al. conducted a randomized trial of intubation using the Celestin tube alone versus intubation with combination chemotherapy (Doxorubicin and Cyclophosphamide). A small increase in median survival was noted in the group receiving the additional chemotherapy. However, the results are not significant because the study was under-powered. The chemotherapy was well tolerated with minimal side effects, although the complications of the control group were not recorded.

A trial by Reed et al. divided the patient population into three groups, intubation with the Atkinson tube alone, with radiation therapy, and laser therapy with radiation therapy. It was found that the post-treatment swallowing scores were similar for all three groups. The addition of irradiation offered no survival advantage over intubation alone and had the added complications of radiation toxicity.

A trial by Alberts et al. had significant negative findings. The addition of combination chemotherapy (with 5-Fluorouracil and Cisplatin) and radiation therapy to a Celestin tube resulted in severe to lethal toxicity and a decrease in the median survival as compared to intubation alone. This trial was terminated early.

A trial by Schmid et al. also found that there was no difference in survival or degree of palliation of dysphagia between the groups of intubation with Celestin tube alone, with adjuvant chemotherapy and with adjuvant radiotherapy. Neither of the adjuvant treatment regimens were found to alter the natural course of the disease and are not justified because of additional toxicity.

**CONCLUSION**

The current state of research into the treatment of inoperable esophageal cancer is insufficient to support a meta-analysis and an Evidence-Based Recommendation. There are simply not enough homogeneous trials to provide significant statistical power.

The management of malignant dysphagia has seen the emergence of expandable metal stents. The limited number of trials shows that they are as clinically effective as the previous generation of plastic stents in the relief of malignant dysphagia. The advantages are in an easier deployment, and significantly fewer functional and technical complications.

Studies have shown that laser ablation of the obstructive tumor can be clinically effective. One disadvantage is the multiple sessions required to maintain patency. An increased morbidity and a prolonged hospital stay may not be justified in a patient whose median survival is less than one year and receives no survival benefit from the treatment. One suggestion made by two of the investigators [9, 10] merits some attention: A role of laser ablation as an adjuvant treatment of expandable metal stents that experience complications of tumour in-growth and overgrowth, with lasers ablating cancerous tissue extending into the lumen of the stent. This complementary role requires further research to clarify the clinical effectiveness of lasers used in the presence of stents.

The literature also shows that other adjuvant treatments such as radiotherapy and chemotherapy do not improve the efficacy of stents. They in fact may negatively affect morbidity and mortality because of the associated toxicity resulting in more complications.

Despite many treatment options being available, none of them significantly improve upon the dismal median survival of esophageal cancer patients. As the incidence of this type of cancer increases, research should encompass extending survival times, effective palliation and improving diagnosis at an early stage.

**ACKNOWLEDGEMENTS**

The author would like to acknowledge the guidance and supervision of Dr. R. A. Malthaner, Assistant Professor of Surgery.

**REFERENCES:**

Anemia, defined as a decrease in red cell mass, is often associated with cancer and cancer treatment. Indeed, anemia is the most common hematological aberration occurring in cancer patients, ranging in severity from asymptomatic to life-endangering, and can result in a decrease in the patient's overall quality of life. All of this occurs at a time when the patient, along with his or her family and loved ones are trying their best to cope with this utterly devastating disease. Many causes for anemia have been postulated, including: blood loss (acute or chronic); bone marrow involvement by the cancer; chemotherapy or radiation therapy resulting in marrow suppression; red cell aplasia; hemolysis including autoimmune hemolysis and microangiopathic hemolysis; hypersplenism; folate or B12 deficiency; and a disease entity known as the anemia of chronic disease.

Anemia of chronic disease (ACD), also named the anemia of cancer, refers to a specific type of anemia most commonly seen in patients with malignant conditions. Current estimates reveal that over half of all patients with some form of neoplastic disease are anemic during the course of their illness, either as the result of ACD or iron deficiency, and almost all patients undergoing chemotherapy or radiation therapy become anemic. Like myelophthisic anemia, iron deficiency secondary to blood loss, and megaloblastic anemia, ACD is a form of hypoproliferative anemia resulting from decreased red blood cell (RBC) production. However, with its characteristic changes in erythrocyte survival time and iron metabolism, ACD is quite different from these other forms of anemia. Specifically, ACD most likely involves the accelerated destruction of erythrocytes, suppression of erythropoiesis, and diminished iron utilization by the erythron, leading to hypoferremia despite adequate or even increased iron stores. The exact pathogenesis of ACD is not completely understood although suggested mechanisms include decreased RBC life span, impaired reutilization of hemoglobin iron, erythropoietin deficiency, impaired responsiveness, and ineffective erythropoiesis. Interestingly, ACD has many clinical similarities to anemias present in patients with chronic inflammation or infection, including chronic renal, hepatic, and endocrine diseases. ACD is also one of the most common anemias presenting in general practice, and is the most prevalent form of anemia in the hospitalized patient population. Thus, a clear understanding of the mechanism underlying ACD, along with treatments such as human recombinant erythropoietin, is crucial not only to the physicians caring for cancer patients, but those in a more general setting as well.

CLINICAL FEATURES

Usually mild and nonprogressive, ACD is often a diagnosis of exclusion, developing insidiously within the first 1 or 2 months from the onset of the illness. Due to its mild nature, ACD is commonly overlooked in the clinical evaluation, and many patients, even those with hematocrits as low as 30%, are often asymptomatic. It is believed that the patient's inactivity, as well as the body's natural ability to increase oxygen delivery to the tissues, results in this lack of symptoms. In the setting of advanced malignancy, weakness, pallor, and fatigue are often seen, and can be the result of ACD or the cancer itself. More severe manifestations of ACD include dyspnea, peripheral edema, angina, palpitations, and other signs of cardiovascular insufficiency, but are rarely seen in patients with packed cell volumes (PCV) below 25%. Skin temperature is often reduced, and the skin, mucous membranes and conjunctivae, are pale.

LABORATORY FEATURES

ACD is usually a normocytic, normochromic anemia, although microcytic, hypochromic red blood cells can be seen. In fact, up to one third of patients may have slight to moderate microcytosis. Unlike iron deficient anemia, however, hypochromia develops before microcytosis in ACD. When the physician is contemplating the diagnosis of ACD, the other common causes of normocytic and microcytic anemias must be ruled out, including: blood loss; nutritional deficiencies; infection; renal insufficiency; and malabsorption. In terms of specific laboratory characteristics of ACD, hemoglobin is usually between 8 and 12 g/dL, and the PCV is usually between 26% to 38%. Studies have also shown a reduction in the Mean Cell Hemoglobin Concentration (MCHC) of 44-64%. The absolute reticulocyte count is normally not increased, and the white blood cell (WBC) and platelet counts are normal or even slightly increased. Bone marrow is normocellular or hypocellular, and the erythroid/myeloid ratio is often normal or slightly decreased. Although body iron stores are normal or increased in patients with ACD, serum iron levels are often substantially decreased, alone with transferrin. Indeed, transferrin saturation in ACD normally falls between 5% and 16%, compared to values of 20% or higher seen in healthy individuals. As serum ferritin concentration is usually increased in ACD, this provides an easy way to help distinguish it from iron deficient anemia.

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PATHOPHYSIOLOGY

ACD is thought to be the result of a number of factors, including accelerated erythrocyte destruction, and an inadequate bone marrow response to this loss of RBC in the form of deficient erythropoiesis.1 Normally, the lifespan of a red blood cell is approximately 120 days. In ACD, however, erythrocytes are produced in the setting of infection or inflammation, resulting in their rapid destruction by an activated RES.1 Interestingly, red cells from ACD patients have been found to survive normally when transfused into normal subjects, suggesting that the ultimate cause of the increased erythrocyte destruction must be a property of the cell’s environment and not the cell itself.1 Normal bone marrow can increase erythropoiesis at least three times the basal rate, however, so the increased loss of RBC alone should not lead to anemia.2 Thus, a key factor in the pathophysiology of ACD is an inappropriate or lack of increase in RBC production to compensate for the increased loss of erythrocytes.

In terms of erythropoietin production in ACD, recent radioimmunoassay studies for erythropoietin have found relatively normal levels in ACD patients.1,2,3 Alexian similarly reported normal erythropoietin levels in ACD patients.2,10 Thus, the notion of insufficient erythropoietin production also is an unlikely reason for the impaired bone marrow response in ACD. Instead, research now reveals that inadequate or deficient erythropoiesis may play an integral role in the pathophysiology of this disease.1

This concept was first proposed by Zucker et al in 1974 who found that erythropoietin induced a significantly lower amount of erythropoiesis in patients with cancer compared to normal patients with anemia resulting from infection or inflammation.3 They concluded that the functioning of cells responsive to erythropoietin and responsible for increased red cell production must somehow be diminished by a humoral and/or cellular immune interaction with malignant cells.2 In support of this theory, immune cytokines such as interferons alpha, beta, and gamma, along with Tumour Necrosis Factor (TNF), are known to be produced in the setting of malignancy and have been demonstrated to decrease erythropoiesis.1,2,9 Furthermore, an anemia very similar to ACD has been shown to develop in mice following chronic exposure to TNF.1,12 As a result, it would appear that the impaired marrow response in ACD is the result of an activated immune system leading to a decreased response to erythropoietin.1 This, combined with an inability to compensate for increased red cell destruction, ultimately culminates in a nonprogressive, mild, asymptomatic anemia.1

CONCLUSION

In the past, treatment of ACD has focused on the underlying malignancy, with little attention being focused on the anemia itself.4 However, exciting new therapies provide hope for the future, including eopoetin alpha, a form of human recombinant erythropoietin which may be beneficial in improving the patient’s symptoms and quality of life.20 In those patients resistant to eopoetin therapy, blood transfusions provide another treatment option.5 Clearly, until we have a better understanding of the etiology and pathogenesis of ACD, it will remain one of a plethora of unpleasant and potentially life-threatening effects of cancer and its treatment.

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ONCOLOGIC EMERGENCIES: FEBRILE NEUTROPNENIA

By Ian MacDonald, MEDS 2000

INTRODUCTION

Infectious complications in the neutropenic host are a major medical issue. Cancer patients receiving chemotherapy are at risk of neutropenia due to the toxic effect antineoplastic agents exert on rapidly proliferating bone marrow cells. The neutropenic patient who develops a fever is at risk of developing rapid and fatal sepsis. Prompt administration of empiric antibiotic therapy is, therefore, standard practice in the management of these episodes. A variety of regimens have been shown to be effective, including a multidrug approach as well as monotherapy. Controversy exists as to which method is superior.

THE NEUTROPENIC HOST

The neutropenic patient who becomes febrile has a 60% or greater chance of being infected. However, fever often presents without clinical signs of localized infection in these patients. The diminished white count precludes signs of inflammation such as edema, erythema, and purulent discharge. In a study of over 1000 febrile episodes in neutropenic patients with cancer, the physical exam was unable to reveal any sign of infection in 55% of patients with known bacteremia. The febrile state is defined as a core temperature > 38.5 C or an axillary temperature > 38.0 C. Severe neutropenia, defined as an absolute neutrophil count < 500/mm³, is the single most important risk factor for developing infection. The duration and rapidity of onset of neutropenia are also risk factors. Neutropenic episodes of < 7 days have been shown to confer a better prognosis than those with longer duration.

The risk of infection is also increased in the presence of other predisposing factors. These include mucous membrane damage secondary to cytotoxic chemotherapy, skin lesions present at intravenous injection sites, the use of indwelling central venous catheters, and neoplastic obstruction complicated by secondary infection of colonizing organisms. The risk of infection is also higher in patients with hematological malignancies than in those with solid tumours. Post-mortem studies estimate that infection is the direct cause of death in up to 50-80% of patients with acute leukemia and up to 50% of those dying with malignant lymphoma. In patients with solid tumours, infection is the primary or an associated cause of death in about 50% of cases.

The infecting organisms involved in the neutropenic patient are classically the endogenous Gram-negative bacilli arising from the GI tract, primarily P. aeruginosa, E. coli, and Klebsiella. Mortality in neutropenic patients with Gram-negative bacteremia can approach 40% due to the tendency towards systemic dissemination. Empirical antibiotic therapy is tailored to providing broad spectrum coverage against these pathogens. However, Gram-positive organisms have emerged in the past decade as a common cause of infection in the febrile neutropenic patient. In particular are S. epidermidis, S. aureus, and Streptococcus species. Recent studies have shown that at present Gram-positive organisms account for 60% of bacteremias.

INVESTIGATION

The physical exam of the febrile patient is often unremarkable in light of the absence of localized findings. However, it is important to consider the common sites of infection in febrile neutropenics: mouth and pharynx (25%), the lower respiratory tract (25%), skin and intravascular catheters (15%), and the gastrointestinal tract (15%). The remaining proportion is made up of the perineal region, the urinary tract, and the nose and sinuses. Oropharyngeal infections can occur in the patient being treated with chemotherapy as bacterial flora colonize mucosal ulcerations. Local invasions in these patients are at risk of becoming systemic rapidly. The physical exam should also assess for the presence of any long-standing intravascular catheters which can be the source of catheter-related infections.

Investigations in the febrile neutropenic patient should include a CBC and differential, BUN/Cr, and electrolytes. Before starting antibiotics, blood cultures should be drawn on samples taken from both the indwelling catheter and a peripheral vein. The threat of catheter-related bacteremia is increased when the catheter is heavily colonized. Cultures from a presumed site of infection include a urine culture and sensitivity. Sputum cultures may be included if produced and pulmonary infection is suspected. However, chest x-rays in the early stages of fever or in very neutropenic patients may not reveal significant lung findings.

TREATMENT

The concept of starting antibiotic therapy before knowing the results of blood cultures is based on the high mortality associated with Gram-negative bacteremia. Therefore, empiric therapy is directed at providing broad spectrum coverage against these organisms. In particular, any empiric regimen should provide antipseudomonal activity in light of the significant morbidity and mortality associated with this organism. Antimicrobial therapy should simultaneously produce high serum concentrations of bactericidal agents, while displaying good tissue perfusion and pose minimal toxicity to the

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In terms of approach, there is still much debate about optimal empiric treatment with respect to combination versus single-agent therapy.

Combination therapy is a widely adopted approach in the management of the febrile neutropenic patient. The traditional combinations involve an antipseudomonal β-lactam plus an aminoglycoside. These include either an extended-spectrum penicillin, such as piperacillin, or a third generation cephalosporin, such as ceftazadime, plus gentamicin or tobramycin. The main argument in favour of combination therapy is that it provides broad spectrum coverage, limiting the potential for secondary superinfections and the emergence of resistant organisms. Combination therapy also provides a synergistic effect that is greater than either agent alone. The major drawback associated with this therapy is the increased likelihood of toxicity at therapeutic levels, specifically nephrotoxicity and ototoxicity associated with aminoglycoside administration. At this point, the comparison of clinical trials has failed to demonstrate any significant difference in response rates between the different combination regimens.

The concept of empiric monotherapy is relatively new in the treatment of febrile neutropenia. These agents include the third-generation cephalosporins and the carbapenems, which offer coverage against gram-positive and gram-negative organisms, including Pseudomonas species. The theoretical advantages of monotherapy over combined therapy include reduced toxicity and improved ease of administration. Among the third generation agents, ceftazadime is employed for monotherapy due to its significant antipseudomonal activity and low toxicity. Several studies have indicated its effectiveness in the empirical treatment of fever in neutropenics based on response rates. A recent concern with ceftazadime monotherapy is the potential for the emergence of resistant organisms. The carbapenems, a new class of potent beta-lactam antibiotics, offer a broader spectrum of activity than the third-generation cephalosporins. Randomized trials have demonstrated that empirical monotherapy with imipenem is as effective as ceftazadime alone. The primary concern with imipenem therapy is its association with seizures in patients with CNS disease and/or renal failure.

The controversy between monotherapy versus combined therapy continues. Present evidence suggests that at the end of the neutropenic period there is little difference in terms of survival between febrile neutropenic patients given empiric monotherapy and those who received combination therapy. The European Organization for Research on Treatment of Cancer (EORTC) Trial XI was designed to answer the question of the efficacy of monotherapy versus combination therapy. The results published in 1996 demonstrated that among the 958 randomized patients, treatment success rates were similar in both arms of the study. A recent international trial showed that ceftazadime was as effective but also safer than the combination of piperacillin and tobramycin. Available data suggests that monotherapy appears to be a suitable option at least in low-risk patients (neutropenia > 500/mm³ with expected duration < 7 days).

**MODIFICATION OF THERAPY**

Given the increasing prevalence of gram-positive bacteremias in the febrile neutropenic host, the addition of the glycopeptide vancomycin to the empirical regimen may be indicated. This strategy may be beneficial in light of the increasing incidence of MRSA in certain institutions, the selection for gram-positive superinfections associated with ceftazadime monotherapy, and in neutropenic patients at high risk for gram-positive sepsis, such as those with indwelling central venous catheters. However, EORTC Trial V showed that in neutropenic patients with gram-positive infections the use of vancomycin from the onset of fever did not result in a more rapid defervescence. Thus, it has been suggested that the inclusion of vancomycin in empirical regimens is a reasonable approach for individual patients, patients with signs of infection at the vascular catheter site, and upon documentation of infection with MRSA.

The optimal duration of therapy in febrile neutropenic patients is controversial, although the absolute neutrophil count is considered the most important measure. The febrile patient with a negative blood culture and neutrophils ≥ 500/mm³ may discontinue antibiotics after 5 to 7 days of therapy. However, some authors suggest that antibiotics can also be stopped in the presence of persistent neutropenia (< 500/mm³) if the patient is febrile and blood cultures are negative. In the case of fever persistence or recurrence seven days after commencement of antibiotics, there is a general agreement regarding additional treatment with empirical antifungal therapy such as amphotericin B, even in the absence of symptoms or signs of systemic mycosis. Systemic fungal infections have been found in up to 33% of febrile neutropenic patients who remain unresponsive after 1 week of therapy and this approach has been shown to decrease the incidence and mortality of these episodes.

**CONCLUSION**

Significant progress has been made in the treatment of febrile neutropenia in the past 20 years. Recognizing the value of initiating empirical therapy in the neutropenic patient with a fever and the availability of new antimicrobial agents has had a significant impact on survival rates in this population, reducing mortality figures by infection to as low as 6%. However, infection remains the principal cause of morbidity and mortality in febrile neutropenic patients. The management of these episodes has been complicated by the changing spectrum of pathogens from gram-negative to gram-positive and concern for the emergence of resistant species, fuelling the debate over combination therapy versus monotherapy. Consequently, the approach to empirical therapy is determined by the circumstances surrounding the individual patient and knowledge of local patterns of infection and resistance.

**ACKNOWLEDGEMENTS**

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PRACTICE CONCENTRATED IN U.S.
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The following information regarding genetic testing for individuals at high risk was obtained through an interview with Dr. Peter Ainsworth, Director of Molecular Genetics, Victoria Hospital Campus, LHSC.

With recent advances in genetic technology, we are reaching a point where individuals may determine their risk for developing a disease one, ten or fifty years in the future. The field of oncology is no exception. Individuals with a strong family history of breast cancer can be screened to determine if they carry a mutation in one of two breast cancer susceptibility genes, BRCA1 or BRCA2. If found to carry such a mutation, females may have as high as a 50-85% lifetime risk of developing breast cancer, about half this risk of ovarian cancer and, for both males and females, a small but definite increase in the risk of colon and other cancers.

As always, with advancement comes risk. We are facing a situation in which otherwise healthy individuals can be told, with some degree of certainty, that they may have up to an 85% chance of developing breast cancer in their lifetime. As future physicians, we need to be aware of the whole picture surrounding this type of revelation, and what may be ahead for these individuals.

Who should be screened?

As with all medical tests, the cost, effectiveness and predictive value of a test is related to the level of risk of the group being tested. Family medical history guidelines exist to determine which individuals are at high risk, and thus suitable for screening. However, many individuals may wish to be screened even if they are not at high risk, to put their mind at ease. This type of screening may not be covered and would only be performed at the patient's expense. It is also important that screening of lower risk individuals should not interfere with screening of those at high risk.

Individuals should be referred according to the following guidelines (adapted from Ontario Cancer Genetics Network):

3 or more closely related individuals on the same side of the family
Early age at diagnosis (<50 years)

Multiple generations affected
Multiple primary tumours (e.g. bilateral breast cancer, or both breast and ovarian cancer)
One or more cases of ovarian cancer
Men with breast cancer (BRCA2)
Jewish ethnic background (approximately 1:50 carry a mutation compared to 1:400 in the general population).

What are the medical and non-medical considerations of detecting a BRCA mutation?

Genetic testing of members of a family known to have a BRCA1 or BRCA2 gene mutation that has been characterized, would divide them into two groups: those that carry the familial mutation and those found to be non-carriers. For the latter group, genetic screening would serve as a reassurance that they are not plagued by the same genetic fate as their relatives who may or may not be already affected by cancer. For mutation carriers, screening serves to allow for increased surveillance and hopefully early detection and treatment. For each family member there would be a 50% chance of falling into either group, by virtue of genetic inheritance.

Increased surveillance involves early mammography, starting in the late twenties or early thirties and this should be combined with regular clinical and self-examination of the breasts. The value of ovarian surveillance techniques is more controversial and prophylactic surgery may be considered in the peri- and post-menopausal period, while pre-menopausal women may be placed on birth control medication to decrease the risk of ovarian cancer. Newer treatments such as prophylactic tamoxifen may be used to reduce breast cancer risk in the future, and for some women, there may also be the possibility of prophylactic mastectomy. The increased risk of colon cancer in mutation carriers should be addressed by colonoscopy which ideally would begin at age 45.

However, what seems to be an obvious and simple management plan for early detection and surveillance carries the additional burden of the extent of prophylactic or preventive treatment which a patient should or could undertake. Oophorectomy is recommended to post-menopausal women, but is not an option for women of childbearing years intending to extend their family. Birth control can be prescribed to decrease the incidence of ovarian cancer in pre-menopausal women but cannot be used while a women is attempting to conceive. There is also the controversial question of prophylactic mastectomy: will a women feel compelled to remove her breasts without which her risk of cancer is nearly decreased to that of the general population? Will she blame herself for not accepting a more radical prophylaxis if she is later diagnosed with breast cancer? Will she feel

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alienated from the parts of her body which make her uniquely female? These questions, which may arise upon determining one's genetic risk, cannot be answered and lie outside the realm of medicine to address.

In addition to the medical controversy surrounding genetic screening, a patient's potential risk for breast cancer can be used outside the medical realm as a source of discrimination. Although current law forbids medical information to be disclosed to employment centers, banks, or life insurance companies without the patient's consent, it does not forbid the questioning surrounding these areas. Thus, once an individual's genetic status has been determined, those individuals applying for life or health insurance may be discriminated against for rates or even acceptance to the policy. An individual's ability to immigrate may be denied. Bank loans or mortgages may be refused if the client is high risk. Furthermore, the children of high-risk patients may be denied access to education loans and funds on the basis that these funds may not be repaid if the individual develops the disease.

On another perspective, early detection of a high genetic risk may make an individual hesitant to marry and have children, for fear that their lifespan may be shortened and that their family will be burdened with the disease. Others may fear passing on the mutation to their children and feel that it is morally irresponsible to have children when there is a 50% chance that they will be subjected to the same fate as themselves. In addition, since this type of testing is still relatively new, there is little evidence regarding the long term effects of pre-symptomatic testing, in which an individual can find out potentially years in advance, their risk for developing a disease in the future. A minority become more susceptible to depression and may require assistance from a social worker.

Currently all individuals who are referred for counseling regarding genetic screening are allowed ample time and several visits before making a decision to be screened. In general most individuals do choose to undergo the screening, but the information they are provided with, and the amount of time allotted, protects against making a hasty decision on the part of the patient. Patients found to be at high risk have several resources available to them to guide them through their plan of action. Most patients take a pro-active role in their health care and tend to improve their lifestyle, when found to be at high risk for cancer.

In the next few years, we will all be faced with advances in genetic technology which will allow individuals to know years in advance their potential for developing a terrifying disease such as cancer. There are several known, and likely many more unknown, consequences to delivering this type of information to the patient. However, the value of increased surveillance and early detection cannot be underestimated in relation to its potentially life-saving ability. As a society, we need to ensure that there will be a system in place to deal with the non-medical consequences of determining one's genetic status.

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This article was reviewed by Dr. Peter Ainsworth, Director of Molecular Genetics, Victoria Hospital Campus, LHSC.
INTRODUCTION

The mandible is essential for oral function and facial aesthetics. Partial or complete loss of the mandible may have severe physical and emotional consequences. The management of patients with oromandibular malignancies has evolved with advances in surgical technique. Mandibular resection poses a formidable reconstructive challenge. While many tumours of the oral cavity can be removed leaving the mandible intact, segmental mandibular resection is often required for advanced stage tumours. Previously, resection of the mandible for cancer commonly resulted in significant disability with regard to mastication, swallowing, speech and cosmesis. Microsurgical technique has revolutionized the current approach to the management of patients undergoing mandibular resection. Mandibular reconstruction using free vascularized bone transfer at the time of oncologic resection is now the treatment of choice for these patients. It has minimized many of the wound healing problems associated with previous methods of reconstruction that used prostheses, non-vascularized bone grafts or pedicled osteomyocutaneous flaps. With immediate wound problems largely overcome, attention has shifted to improving functional and aesthetic results for the patient.

OPTIONS FOR RECONSTRUCTING THE MANDIBLE

Initially, oromandibular defects were addressed with no bony reconstruction. Soft tissue was repaired either primarily or with a skin graft or local flap (e.g. tongue, buccal mucosa). Large anterior mandibular defects managed in this fashion were referred to as "Andy Gump" deformities. Free bone grafts and alloplastic prostheses were later attempted in order to improve functional outcome. However, these procedures were associated with poor wound healing, high rates of infection, extrusion of plates and screws, and considerable soft tissue contraction, especially when performed as secondary procedures (Figure 2). The jaw often required prolonged periods of immobilization. For these reasons, bone grafts currently enjoy only limited use.

Continued improvements in cure rates following ablative cancer surgery provided a stimulus for a reconstructive era beginning in the 1960s. In addition to metal plates and free bone grafts, tray devices which housed particulate bone grafts were used in order to restore jaw integrity. The advent of the pedicled myocutaneous flap in the 1970s provided well-vascularized soft tissue coverage for these bony bridges. Regional flaps such as the pectoralis major, latissimus dorsi and trapezius consist of muscle and overlying skin rotated about their constituent arterial and venous supply. These flaps permitted single stage reconstruction of virtually any head and neck defect.

In the late 1970s, autogenous bone such as rib and clavicle began to be incorporated into myocutaneous flaps and became the predominant method used in mandibular reconstruction. Autogenous bone was recognized as the material least likely to be extruded, and its use became more widespread. Reasonable success rates could be expected in limited cases, such as short defects in non-irradiated patients. However, their disadvantages included limited pedicle lengths and arcs of rotation, excessive soft tissue bulk and donor site morbidity. Furthermore, the inability to provide bone of sufficient length with a reliable blood supply stimulated a search for alternative techniques.

The establishment of a reliable blood supply via microvascular anastomosis was made possible by the advent of microvascular surgery in 1973. Consequently, tissues distant from the defect and based on an appropriate axial blood supply could be successfully transferred for reconstruction. Such "free flaps" emerged as a new approach for mandibular reconstruction. The most important advantage of the free tissue transfer is its superior vascularity and improved tissue survival. These flaps are free from a distinct limitation of myocutaneous flaps, namely their vascular pedicle length and arc of rotation. Moreover, the wide variety and versatility of donor tissue allows customization of the reconstruction to the specific requirements of the defect. These refinements in primary reconstruction provide the cancer patient with optimal functional and cosmetic rehabilitation.

FREE FLAP DONOR SITE SELECTION

The requirements for optimal reconstruction of the mandible include adequate bone length, consistent shape along the length of the bone, and a vigorous and predictable blood supply. There is usually also a requirement for the bone to have adjacent muscle and skin

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THE FREE FIBULA FLAP FOR OROMANDIBULAR RECONSTRUCTION

By Joe A. Mai, MEDS 2001, Dr. Jonathon Tritas, Dr. John Yoo, LHSC
of the proper volume and inserting flexibility to allow reconstruction of associated soft tissue defects. Common donor sites for this application include the iliac crest, radius, scapula, and more recently, the fibula flap. There is no single donor site that can be used for all situations. Donor site selection should be determined by the specific bone and soft tissue requirements of the defect.

The length of bone supplied by the radius usually does not exceed 10 cm and is of poor quality. Donor site morbidity from radial fractures is a major disadvantage. The scapula provides up to 14 cm of bone and an abundant skin flap which lends itself to three dimensional contouring. The bone is wider and longer but thinner than the radius. However, flap harvest requires repositioning the patient intraoperatively, precluding a simultaneous two-team approach. The iliac crest supplies an abundant amount of quality bone which closely approximates the height of the native mandible. However, contouring the bone may be less precise than with other flaps. A major disadvantage of this flap is the associated soft tissue, which has excessive bulk and an unreliable blood supply.

The fibular free flap has become the flap of choice for mandibular reconstruction. The flap is based on the peroneal artery, a terminal branch of the posterior tibial artery, and its venae comitantes. The caliber of the vessels and length of the pedicle allows for reliable microvascular anastomosis. The versatility of this bone flap rests on its dependable feeding periosteal blood supply. This allows multiple osteotomies, which are required to reproduce the three-dimensional shape of the resected mandible. It is the only free tissue transfer that provides a bone stock up to 24 cm. This allows near-total mandibular defects to be
repaired using a single flap. It has a consistent shape throughout its entire length, and sufficient bone stock to support osteointegrated implants for dental rehabilitation. The fibular flap can incorporate a skin paddle from the lateral aspect of the leg that measures up to 25 cm in length and 5 cm in width (Figure 3). The flexor hallucis longus muscle lies adjacent to the fibula and thus can be harvested for soft tissue reconstruction. Other advantages include minimal donor site morbidity and its distant location which facilitates a two-team approach. These distinct advantages have made the free fibular osteocutaneous flap the raw material of choice for segmental mandibular reconstruction.

OUTCOME

Free tissue transfer is a highly reliable method of head and neck reconstruction. Shpitzer et al recently reviewed their series of mandibular reconstructions using fibular free flaps in 47 patients. Successful flap transfer was achieved in 95% of patients. There were no perioperative deaths however nine patients had perioperative complications that required medical or surgical intervention.

Accurate long-term assessment of diet, oral continence, speech and cosmesis was possible in 39 patients. Dietary habits were normal in 58%, 32% tolerated a soft diet only and 10% were dependent on a feeding tube. Oral continence was normal or almost normal in 55%. Thirty-five percent had moderate drooling and those who remained dependent on a feeding tube had severe drooling (10%). Speech was easily intelligible in 90% and understandable with effort in 10%. Cosmetic results were evaluated by both the patient and the treating surgeon. Sixty-two percent were categorized as having excellent results, 33%, acceptable, and 5%, poor.

The fibular donor site healed adequately with minimal morbidity in 46 of the 47 patients. Immediate postoperative donor site infection occurred in one non-compliant patient because of insufficency on early ambulation and discharge. Patients were able to ambulate between 2-10 weeks with 5 weeks being the average. On follow-up, all patients were able to engage fully in daily recreational activities. Eight patients (17%) had mild lower extremity muscle and joint weakness, stiffness, or instability. One patient reported donor site pain. It was concluded that long-term morbidity was minimal and their lifestyle was not altered.

CONCLUSION

Head and neck surgeons must address two basic issues when planning the surgical treatment of advanced oromandibular carcinoma. The first issue is the extent of resection required for oncologic clearance. The second issue concerns the optimal method of functional and aesthetic restoration. The resection can be performed more confidently based on the ability to reconstruct complex defects involving bone and soft tissue. In particular, the ability to reconstruct large mandibular defects has improved the functional and aesthetic outcome for patients with advanced disease (Figure 4).

Free tissue transfer has dramatically enhanced the quality of life for many patients undergoing resection for head and neck cancer. Although no one flap is ideally suited to repair all defects, the fibular flap is arguably the best method for reconstructing anterior or large defects of the mandible.

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WHILE MERLIN SLEEPS: CAMELOT YIELDS
A review of the biology of neurofibromatosis type 2 and the role of merlin as a tumour suppressor

By David Skidmore, MEDS 2000, & Gregory M. Kelly, Assistant Professor, Department of Zoology; UWO

INTRODUCTION
Neurofibromatosis type 2 (NF2) is a rare, dominantly inherited genetic disease which has become the subject of considerable interest; possibly disproportionate to the medical significance of the disease itself. Excitement over NF2 is due in part to the discovery that the disease is caused by the loss of expression of a tumour suppressor gene dubbed merlin. Merlin, a widely expressed protein, is also at the centre of several types of sporadic malignancies. The study of the genetics and molecular biology of NF2 provides us with the opportunity to arrive at an improved understanding of the role tumour suppressors play in cell homeostasis and how this control breaks down in leading to the development of a malignant state.

The NF2 gene was discovered independently by two groups. The gene at chromosome 22q12 encodes merlin, a protein with significant homology to members of the Protein 4.1 superfamily, especially Ezrin, Radixin, Moein (the ERM subfamily). The homology to Protein 4.1, the prototype in a superfamily of proteins associated with the cytoskeleton-plasma membrane interface, was a surprise since most other tumour suppressor genes were known to be nuclear proteins. Since merlin’s discovery, other cytoplasmic tumour suppressor proteins have been identified. How merlin and these proteins act in the cytoplasm to directly and/or indirectly regulate gene transcription and cell cycle has been given a great deal of attention. Insight from this research will undoubtedly increase our comprehension of both NF2 and the mechanisms by which tumour suppressors act.

Neurofibromatosis Type 2
Symptoms of NF2 which manifest themselves during middle age constitute the less severe Gardner subtype, whereas patients with the disease in their mid-twenties (the severe Wishart subtype) usually do not survive past 40 years of age. NF2 is the most commonly mutated gene in benign tumours of the human nervous system. Of these cases, approximately half occur in families with no prior history of the disease. Due to the high penetrance of this disease, it is held that sporadic cases are due to de novo mutations, and suggests that this region (a hotspot) of the genome has a relatively high rate of spontaneous mutation. The hallmark of NF2 is the development of bilateral acoustic schwannomas (also called acoustic neuromas). These tumours are benign and slow growing, but due to their location can be very difficult to treat surgically. Affected individuals are also at risk of developing multiple tumours of other tissues of ectoderm lineage, especially spinal schwannomas, menigiomas and less common ependymomas. A high incidence of posterior lens opacities has also been reported. Pathological examination of afflicted individuals has demonstrated that spinal nerve roots are studded with asymptomatic tumourlets. These tumourlets are expansile lesions which are similar to schwannomas, yet histologically distinct. Whether these tumourlets, which are unique to the NF2 syndrome, represent developmental lesions or are a precursor stage in the development of full-scale schwannomas is a point of some debate. It should be noted that while NF2 tumours are benign, the compression they cause can lead to significant functional impairment, regardless of the individual’s age. In reference to NF2, Gusella et al. stated that the resulting morbidity is of such significant magnitude to result in a measurably reduced life span.

TUMOUR SUPPRESSOR GENES
A neoplasm develops when a tumor suppressor gene loses its function. These genes play a role both in familial cancers and also in many sporadic neoplasms. At least 25 tumour suppressor genes have been cloned in the ten short years since the discovery of the first tumour suppressor, RB1 (associated with familial retinoblastoma). Familial cancers associated with tumour suppressor genes are, as a rule, inherited dominantly. Interestingly, though, studies have revealed that the presence of a single copy of a tumour suppressor gene in a cell is enough to insure normal, wild type function. This observation contradicts the Mendelian theory which states that for dominant inheritance, the expression (or lack of expression) of any mutant allele should result in the disease phenotype.

To explain the discrepancy and also the seemingly random nature of tumour development, Knudson proposed his famous “two hit” theory. It holds that for a neoplasm to develop there is an inactivated copy of a tumour suppressor gene in the germ line, the “second hit” inactivates the other copy in somatic cells leading to tumourgenesis. Therefore, in familial cancers the “first hit” would occur via germ line inheritance of one non-functional copy of a tumour suppressor and sometime during the individual’s lifetime a cell will lose this
heterozygosity, either through non-disjunction during mitosis or a random mutation, which inactivates the wild-type allele: “the second hit”.

Since the likelihood of a single somatic cell having two inactive copies of a specific gene is low, tumours would be very unlikely to occur with any regularity unless there was an inherited “hit” already present. Since the timing and the frequency with which the second hit occurs is random, this simple but eloquent “two hit” model would account for the variance in severity (expressivity) and time of onset seen among family members who inherit one copy of a mutated gene. Data from many syndromes support the theory that there is a change from heterozygosity in non-neoplastic tissue to homozygous loss of expression in actual neoplastic tissue.

To frustrate matters, evidence exists to indicate that a mutated tumor suppressor gene, whose inherited loss causes a familial syndrome with its well-defined symptoms, may be responsible for generating multiple sporadic neoplasms in tissues unaffected in the familial syndrome. For example mesotheliomas, in which the homozygous loss of NF2 is reported, do not occur with an increased frequency in NF2. This inconsistency is likely explained by the existence of other factors which play a permissive role in tumourigenesis. These factors may be constitutively present in tissues characteristically affected by the inherited syndrome, and absent in others without a second stimulus to induce them. In a mesothelioma, it is proposed that the inflammatory response to asbestos alters gene expression of one or several unknown proteins which interact with merlin. In these cases mesotheliomas develop when NF2 expression is homozygously lost (it is also believed that asbestos increases the rate of mutation). Study of other tumour suppressors in NF2 will help delineate these permissive factors and may highlight some that are amenable to prevention.

MERLIN AND NEOPLASM

The neoplasms most commonly associated with merlin’s absence are schwannomas. These tumours are benign nerve sheath tumours composed of Schwann cells which can form along any peripheral or cranial nerve. Schwannomas form with particular frequency in dorsal nerve roots and in the eighth cranial nerve. Multiple tumours of this kind are especially common in individuals with NF2. In an immunocytochemical study Stemmer-Rachamimov et al., screened pathological specimens (both sporadic and from NF2 probands) of schwannomas and found merlin was completely absent. In a follow up study the authors reported that merlin’s absence in the tumourlets, characteristic of NF2, might not only be absolute, but an early requirement in the progression to schwannoma formation. It is interesting to note that independent studies have shown that merlin is absent in only 78% of schwannomas. Thus, while the evidence clearly indicates that merlin expression is altered in schwannomas, more research is needed to determine the absolute frequency.

Discrepancies in the studies described above are troublesome for those using genetic tests to identify patients with NF2; a loss of merlin mRNA in only 50-60% of schwannomas is in marked contrast to Stemmer-Rachamimov and colleagues’ absolute (100%) loss. In some cases, wild type merlin mRNA was demonstrated by reverse transcription polymerase chain reaction analysis. This discrepancy suggests that some form of a genetically undetectable translational or posttranslational modification to merlin may play a role in up to 40% of the schwannomas. In contrast, Gutmann found that while merlin was present in some schwannomas, that the absence of merlin mRNA correlated with the absence of the protein. In this case one would have to agree that current tests are adequate, but obviously further study is needed. Meanwhile, the conflict in the frequency of merlin loss between various studies prevents us from determining the sensitivity of genetic tests for NF2. Therefore, unless the specific lesion associated with a family inheritance has been identified, current methods of genetic testing for NF2, while extremely specific, are not sensitive in up to 40% of all cases.

The absence of merlin has been noted in other types of tumours. Merlin expression is often absent in meningiomas in a subtype specific pattern. Normal expression, however, was observed in 80% of sporadic meningothelial meningiomas, indicating that merlin has no role in the genesis of this type of tumour. Conversely, merlin’s absence in sporadic fibrous and anaplastic meningiomas, suggests an involvement of merlin in these tumour subtypes. In support, Hitosumatsu et al. reported that most meningiomas in NF2 patients are of the fibrous subtype. In contrast, despite the occasional occurrence of ependymomas and other astrocytomas in NF2 patients, merlin expression in sporadic tumours of the fibrous subtype was normal in the vast majority of. The authors suggest that other tumour suppressors are responsible for these conditions. In this regard, some have noted that in many cases of colorectal cancer, deletions have occurred on chromosome 22q in the region where NF2 is located. In the majority of cases, however, merlin expression was unaffected thereby suggesting a minimal role in colorectal cancer.

Despite the absence of mesotheliomas in the spectrum of tumours observed in NF2 patients, it appears that merlin is significantly absent in malignant mesotheliomas. Although its role in the lung tissue is not known the data would suggest a specific role for merlin in preventing uncontrolled hyperplasia of lung pleura. Determining what fraction of the tumours are due specifically to merlin’s absence is an urgent research objective. Once established we can then adequately use genetic tests to screen for NF2, but if the current discrepancy between the presence of merlin mRNA and the absence of the merlin protein can be shown, then we will have to search for posttranscriptional events that influence tumourigenesis. If the discrepancy lies in the inability to detect the protein using currently available antisera then diagnostic research may depend on generating a battery of antibodies to detect several epitopes in the protein itself. In any event, these areas warrant further investigation.

MERLIN AND ERM FAMILY PROTEINS

Merlin and the ERM subfamily of the Protein 4.1 superfamily are a group of evolutionarily conserved proteins that display considerable sequence homology
across the animal kingdom. All of these proteins possess two distinct components. The domain located at the NH3-terminus forms a globular region which is known to interact with integral proteins of the plasma membrane. In particular, the ERM proteins and merlin bind the hyaluronic acid receptor, CD44. Various isoforms of CD44 exist, some of which are associated with a poor prognosis in malignancy, as they indicate an early metastatic course. Of note, immunohistochemical studies have shown that aberrant expression of merlin results in an alteration of CD44 isoforms expressed in schwannomas. This information suggests that merlin and perhaps the other ERM proteins may not only bind CD44, but may regulate its function and ultimately its ability to bind to the extracellular matrix.

The second component shared by ERM proteins is the COOH-domain which binds to cortical actin microfilaments of the cytoskeleton. The ability of ERM proteins to bind two fundamentally different targets has led to the proposal that ERM proteins serve as dynamic bridges, connecting the cytoskeleton with integral plasma membrane proteins. Immunolocalization studies reinforce this notion since the ERM proteins localize to regions under the plasma membrane, particularly to those regions rich in actin. Merlin also localizes to regions just under the plasma membrane and in some studies to perinuclear regions. By proxy, merlin probably acts like the other ERM proteins albeit the ERM subfamily has not been granted tumour suppressor status.

How merlin behaves in vivo is still poorly understood, but these interactions are likely influenced by several other proteins. At least two members of the Protein 4.1 superfamily bind calmodulin in a calcium-dependent manner. All members of the Protein 4.1 superfamily possess consensus sequences for both tyrosine and serine kinases. The epidermal growth factor (EGF) receptor can phosphorylate ezrin and when this occurs, both ezrin localization and cell morphology are altered. Merlin possesses consensus phosphorylation sites, however, unlike the case with ezrin, tissue culture cells expressing merlin are not affected by EGF stimulation. These results indicate that merlin is likely controlled by other heterophilic interactions. Recently, the ERM-merlin subfamily of proteins was shown to participate in homophilic interactions. Intramolecular bonds would allow two molecules to bind in a head to tail fashion thereby masking the sites for actin and/or integral plasma membrane proteins like CD44. Subsequent post-translational modifications by growth factor-induced phosphorylation would induce an allosteric shift, interrupting the homo-dimerization and exposing the binding sites to other proteins. Much work in this area is needed to fully comprehend how merlin behaves with itself and with other putative binding partners.

Studies with tissue cultured cells expressing merlin transgenes have revealed some interesting features of the protein's ability to act as a tumour suppressor. Merlin is known to affect cell cycle and reverse malignant phenotypes. An increase in levels of both phosphorylated and dephosphorylated merlin in cell confluency studies can be correlated to the decrease in mitotic rate induced by these conditions. On the other hand, overexpression of the carboxy-terminal half of merlin induces cell death in NIH3T3 cells. Luchman and Rouleau reported that merlin expression can decrease mitosis in a dose-dependent manner. In the same cell line, but now transformed with the Ras oncogene, merlin has the ability to rescue the Ras phenotype of anchorage independent growth. This anchorage independent growth, serving as a model for metastasis, is the epitome of what happens when a tumour suppressor protein is lost. It should be noted that in the tissue culture studies the phenotype was dependent on the expression of both domains of merlin, either in cis or in trans, again supporting the notion that the function of this protein is affected by homophilic interactions.

CONCLUSION

Several studies suggest that the careful regulation of merlin plays an important role in controlling cell cycle. Given merlin's structural homology to ERM proteins it is tempting to speculate that loss of merlin expression alters the link between the cytoskeleton and the plasma membrane-extracellular matrix. The loss of structural integrity has dramatic consequences on cell shape, due in part to the inability of merlin-deficient cells to adhere to each other or to a substrate. The loss in a cell's ability to adhere to a target may be the first step in tumour progression, but many questions remain. In any event, what one needs to find is an Excalibur to watch over our cells whilst Merlin sleeps in Camelot!

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ENDOCRINE THERAPIES OF ADVANCED BREAST CANCER IN POSTMENOPAUSAL WOMEN

By Michelle Suga, MEDS 2000

Since the initial therapeutic use of ovarian ablation by Beatson in 1896, hormonal manipulation has been the mainstay of the palliative management of metastatic breast cancer, and is the oldest form of systemic breast cancer treatment. Since estrogens play an important role in the development and promotion of human breast carcinomas, the inhibition of estrogen in estrogen dependent breast carcinomas (estrogen ablation) has become an important form of therapy. Treating breast cancer by decreasing estrogen support has fewer side-effects than cytotoxic drugs, and is more effective in most situations. Estrogen ablation consists of either (a) blocking the synthesis of estrogens, or (b) blocking estrogen receptors in the tumour. Blocking the synthesis of estrogens is accomplished through oophorectomy (via radiation or surgery) or the use of compounds that inhibit aromatase, the enzyme involved in the conversion of the adrenal androgens, androstenedione and testosterone, to estrone and estradiol, respectively, the major source of estrogen in postmenopausal women. This other major form of therapy, antiestrogens, are compounds which bind to estrogen receptors and competitively exclude estrogen. Other endocrine therapies that are less frequently used include estrogens, androgens, progestins and antiprogestins, and gonadotropin-releasing hormone (GnRH) agonists.

ANTIESTROGENS

Antiestrogens act through the estrogen receptor to regulate gene transcription. When an antiestrogen binds to the estrogen receptor, the receptor is no longer available to bind estrogen, and thus fails to effectively stimulate gene expression and DNA synthesis. The antiestrogen-receptor complex does, however, enhance production of some growth inhibitory factors, including transforming growth factor β (TGF-β), thereby preventing breast cancer growth and metastasis. Because antiestrogens act via binding to the estrogen receptor, the presence of estrogen receptor in the breast cancer cells has proven to be very important in predicting response to antiestrogen therapy.

Tamoxifen, a non-steroidal competitive estrogen antagonist, has been in use for over 20 years, and is the most commonly prescribed drug for the treatment of breast cancer. It is considered the ‘gold standard’ for antiestrogen treatment of metastatic breast cancer in postmenopausal women. Approximately 40% of breast cancer patients benefit substantially from tamoxifen treatment, and treatment has been shown to reduce the risk of development of contralateral breast cancer by almost one-half. Tamoxifen binding to the estrogen receptor inhibits cell proliferation by a mechanism partly due to the antagonistic effect on estradiol regulated proteins with growth regulatory functions. Studies have shown the following effects of tamoxifen: increased sex hormone-binding globulin, increased number of natural killer cells, decreased levels of tumour-stimulating autocrine growth factors (transforming growth factor-a and insulin-derived growth factor), and increased TGF-β (a tumour-suppressive growth factor).

Despite the effectiveness of tamoxifen, many women eventually suffer relapse, because some breast cancer tumours invariably develop resistance to tamoxifen, which leads to tumour progression and death. Although tamoxifen is predominantly an estrogen antagonist in breast cancer cells, acquisition of increasingly dominant agonist activity over time may result in clinical resistance because of the acquired ability of the drug to stimulate, rather than inhibit, tumour growth. In addition, although tamoxifen is mostly inhibitory in its function as an estrogen antagonist in breast cancer cells, it has some estrogen-like activity in other cells of the body. Stimulatory effects of the agent on the uterus and liver may underlie the increased incidence of endometrial hyperplasia, and alterations in liver function seen in women on prolonged therapy. Tamoxifen use has also been associated with discomforts such as hot flashes, vaginal discharge, thinning of the hair, brittleness of the nails, dryness of the skin, dizziness, nausea, depression, and thromboembolic phenomena. On the other hand, the estrogen-like activity of tamoxifen is beneficial in terms of enhanced bone mineral density in postmenopausal women, enhanced bone maintenance, and reductions in serum cholesterol level, with an associated decreased risk of coronary problems.

A new antiestrogen, toremifene, was recently approved for the treatment of postmenopausal women with metastatic breast cancer. Toremifene is a chlorinated structural analogue of tamoxifen and pharmacologically related to it. Toremifene causes growth inhibition in breast cancer cells by suppressing mitosis and inducing apoptosis, possibly via induction of TGF-β and inhibition of insulin-like growth factor-111. Although primarily an antiestrogen, it also has some estrogen agonist properties in postmenopausal women. Most of the adverse effects of toremifene are related to this estrogenic effect, and include hot flashes, vaginal discharge, and nausea.

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clinical trials, toremifene has demonstrated an efficacy against metastatic breast cancer that is comparable to that of tamoxifen. However, toremifene is potentially safer than tamoxifen, in relation to carcinogenic effects. In contrast to tamoxifen, in pre-clinical trials, high-dose toremifene was not found to be hepatocarcinogenic in rats and, thus far, no carcinogenic effects of toremifene have been noted in humans.

More recently, newly developed "pure" steroidal antiestrogens, such as ICI 164,384 and ICI 182,780, have been found to be complete estrogen antagonists, by binding and inactivating the estrogen receptor, and exhibiting no estrogen agonistic activity. It has been suggested that "pure [steroidal] antiestrogens may have a therapeutic advantage over tamoxifen in reducing the probability of treatment failure due to regrowth of tumours from resistant cells". The pure antiestrogenic activity and the high potency of steroidal antiestrogens suggests that these compounds are superior to tamoxifen both with respect to complete initial responses and long-lasting responses. However, they are not effective in preventing bone loss and may have detrimental effects on the cardiovascular system.

ICI 182,780 is a 7α-alkylsulfinyl analogue of estradiol that possesses a greater ability to suppress estrogen-sensitive gene expression and greater anti-tumour activity than the partial estrogen antagonist tamoxifen. However, as with tamoxifen, most tumours eventually became resistant to ICI 182,780 and grew independantly of estrogen.

ICl 164,384 is more effective than tamoxifen in inhibiting estrogen because tamoxifen binds to the estrogen receptor with an affinity of less than 5% of the binding affinity of ICI 164,384.

AROMATASE INHIBITORS

In premenopausal women, the main source of estrogen is the ovary, where it is synthesized from androgens under pituitary control. In postmenopausal women, estrogen is produced mainly by peripheral aromatization of androstenedione and testosterone, and is mediated by the enzyme aromatase. About two-thirds of human breast carcinomas contain detectable levels of aromatase. Since aromatase catalyses the final, rate-limiting step in estrogen production, it therefore has been the principle target of inhibition of estrogen synthesis. In postmenopausal women, the aromatase enzyme complex is not regulated by a feedback mechanism, and so its inhibition ultimately causes an appreciable decrease in tissue estrogen levels, which has therapeutic effect. Therefore, estrogen deprivation through aromatase inhibition provides effective therapeutic treatment of advanced, hormone-dependent breast cancer in postmenopausal women.

There are two main groups of aromatase inhibitors: suicide inhibitors (exclusively steroidal) and competitive inhibitors (either steroidal or nonsteroidal). Suicide inhibitors seem to be a better choice than competitive inhibitors, since they are highly specific, and the continued presence of the drug is unnecessary to maintain inhibition. With both types of inhibitors the inactivation of aromatase can be prevented by the presence of high concentrations of substrate relative to the inhibitor during the reaction.

Aminoglutethimide was the first aromatase inhibitor to be used in breast cancer therapy. It is a competitive nonsteroidal aromatase inhibitor. Unfortunately, aminoglutethimide lacks specificity, and also inhibits adrenal cortisol production and interacts with synthetic glucocorticoids, accelerating their metabolic clearance. This therefore necessitates hydrocortisone supplementation. Important side-effects of aminoglutethimide appear at the level of the central nervous system, the major symptoms being lethargy, vertigo, ataxia, mental depression, and insomnia.

Formestane (4-Hydroxyandrostenedione) is the first steroidal compound to be structurally designed as an aromatase inhibitor. It is an analogue of androstenedione, and it is a steroidal, irreversible inhibitor of aromatase. It has been shown to be 30- to 60-fold more potent than aminoglutethimide, and to significantly reduce plasma levels of estrogen. Formestane is very specific and requires no glucocorticoid replacement. It must be administered via intramuscular injection, and is well tolerated in patients, the major complaint being local pain at the injection site.

Anastrozole and letrozole are the first selective, oral, non-steroidal competitive aromatase inhibitors. Anastrozole reduces circulating estrogen levels by more than 80%, letrozole by 79%. Anastrozole has a low side-effect profile (low occurrence of hypertension, thromboembolic events, weight gain, dyspnea, vaginal hemorrhage, sweating and diarrhea). It is currently used to treat women as second-line treatment after tamoxifen and as first-line treatment after tamoxifen has been used as an adjuvant therapy. It may also be used when tamoxifen is not tolerated. Letrozole is a potent, highly selective competitive inhibitor of aromatase. The high selectivity has been demonstrated by the lack of compromise of glucocorticoid and mineralocorticoid production or thyroid function. Letrozole is able to achieve total estrogen deprivation in animals, similar to that produced by surgical oophorectomy. While it has a similar side-effect profile to anastrozole, it is less likely to cause thromboembolic events. Both anastrozole and letrozole are contraindicated in women who are pregnant, breast-feeding or premenopausal, and in patients with severe liver disease. Anastrozole is also contraindicated in patients with moderate liver disease or severe renal impairment.

OTHER ENDOCRINE THERAPIES

Surgical and Radiation-Induced Endocrine Ablation Therapies

The main therapy in this category is oophorectomy. Beatson first used surgical oophorectomy in 1896, and described dramatic post-surgical tumour shrinkage in three women with locally advanced breast disease. Radiation-induced ovarian ablation was introduced in 1922. Oophorectomy works by eliminating the ovarian estrogens, the main source of estrogen in premenopausal women, and is therefore of therapeutic value mainly in
Estrogens are generally well tolerated, although some patients may experience side effects such as hot flashes, nausea, and bloating. The most widely used androgen has been shown to be effective in treating advanced breast cancer, but less effective in postmenopausal women. The use of estrogen, however, has potential for inducing harmful effects, including increased risk of thromboembolic complications, fluid retention, stress incontinence, and withdrawal bleeding. Use of estrogens must be reserved for a last attempt at hormonal therapy in postmenopausal women.

Antiestrogens are used to treat breast cancer patients with estrogen-sensitive breast cancer. Two other surgical therapies used are adrenalectomy and hypophysectomy. Adrenalectomy eliminates adrenal stimulation of the ovaries, but requires a period of glucocorticoid, mineralocorticoid, and thyroid replacement for the first few months. GnRH analogues are currently recommended as the first line of treatment for postmenopausal women with advanced breast cancer. They are currently recommended as the first line of treatment for advanced breast cancer in postmenopausal women, although their mechanism of action is still unclear. In recent years, the use of estrogen has been shown to be successful in treating advanced breast cancer in postmenopausal women, and it has been found that different metastatic sites vary in their response to endocrine treatment.

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DYSPHASIC NEVI - A CLUE TO INCREASED CUTANEOUS MELANOMA RISK

By Noreen Galaria, George F. Murphy, M.D.

The characterization of the clinical and pathologic features of dysplastic nevi (heritable melanocytic lesions) by Wallace Clark et al. in 1978 allowed the recognition of these lesions as markers of melanoma risk in a specific subset of patients. Dysplastic nevi are now known to occur in two major epidemiological contexts. They were first described in the setting of melanoma prone families where the presence of a single dysplastic nevus was shown to be a sensitive phenotypic marker of a strong genetic tendency to develop melanoma. It was later discovered that even outside of this familial setting, these nevi were important markers of a smaller but as yet incompletely defined risk for developing melanoma. The dramatic rise in the incidence of melanoma, coupled with the clustering of other risk factors that is often seen in this population, implies that there are enormous public health benefits to the early recognition of dysplastic nevi.

CLINICAL FEATURES OF DYSPHASIC NEVI

Dysplastic nevi (DN) are clinically atypical nevi that may be important markers for the development of malignant melanoma. Clinically, they may have a macular component, irregular and indistinct borders that fade into the surrounding skin, variable color (tan, brown, pink), and a diameter greater than 5 mm and often greater than 10 mm. Dysplastic nevi occur more typically on sun-exposed areas (e.g. the back and chest) but they can appear on normally protected areas such as, the scalp, buttocks, groin, and breasts, where common acquired nevi occur less often. Patients with the dysplastic nevus syndrome will often have from twenty to over a hundred lesions, which are often larger than usual nevi and may occur singly or clustered together in groups. Also, typically, the dysplastic nevi are not present at birth in those with the syndrome. Instead, they begin to appear in mid-childhood years when they may resemble common moles. These patients usually develop melanoma at a younger age and tumors may be multiple and are often of the superficial spreading type.

HISTOPATHOLOGIC FEATURES OF DYSPHASIC NEVI

Benign nevi are divided into three subtypes - junctional, compound and dermal nevi. This classification is based on the location of nevus cells in the epidermal and dermal layers of the skin. The three types represent sequential developmental stages in the life cycle of a nevus. Flat junctional nevi, with nevus cells located at the dermal-epidermal junction, are the first to be seen. These evolve into compound nevi when some of the nevus cells begin to percolate into the papillary dermis. Continued migration of all of the nevus cells into the dermis with disappearance of the intraepidermal component results in the dermal nevus. The majority of DN, close to 80%, are compound in nature. There are many slightly varying criteria in use for the histologic characterization of a DN. Generally speaking, the epidermis shows elongated rete ridges that are often club-shaped, with increased melanocytes at the basal layer. Spindle shaped and epithelioid melanocytes often form horizontal bridges between nests at the dermal-epidermal junction and nests may also form in the interrete spaces or at the edges of the rete ridges instead of from the rete tips, as is normally seen in benign nevi. The nests, in comparison to those seen in typical nevi, will often vary in size, shape and spacing (they are not at equidistant intervals). At the edge of the lesion, a shoulder of exclusively intraepidermal growth often shows more pronounced architectural atypia and this lateral extension can be useful in identifying DN particularly at scanning magnification. In the papillary dermis, both lamellar and concentric eosinophilic fibroplasia can be seen. There may also be an increased number of blood vessels, pigment incontinence, and a spotty lymphocytic infiltrate. At higher magnification, cytologic dysplasia is seen when the individual nevus cells randomly display enlarged nuclei, hyperchromasia, and contour angulation, forming rectangular or rhomboidal shapes. Cells with these characteristics will often show coarsely granulated (muddy) cytoplasmic melanization. Histologically, severely dysplastic nevi may be difficult to distinguish from in-situ or even invasive melanoma, unless detailed histologic criteria are rigorously applied.

GENETICS AND EPIDEMIOLOGY

The full development of malignant melanoma seems to result from multiple genetic alterations, occurring in sequence, in the neoplastic cells. Many of these alterations are recognizable as chromosomal alterations. In the context of acquired melanocytic nevi, a focal proliferation of structurally normal cells may progresses to a DN, with abnormal hyperplasia of melanocytes and
atypia. Alternatively, DN may appear de novo as in the dysplastic nevus syndrome. Following this step comes primary melanoma, first as the radial growth phase, which spreads centrifugally within the epidermal layer and does not have the capacity to metastasize, and then as the vertical growth phase, which invades perpendicular to the epidermal surface and is capable of progressing to metastatic disease. Dysplastic nevi in the setting of the dysplastic nevus syndrome and melanoma appear to be pleiotropic effects of a single autosomal dominant gene with high penetrance, that may be situated on chromosome band 1p36. However, non-random karyotypic changes involving chromosomes 6, 7, 9, and 10 have also been identified by several groups. Interestingly, the well-known oncogenes p53 and K-ras have also been identified by molecular studies to be involved in melanocytic transformation. There is evidence that RAS gene mutations may be important in the progression of the radial growth phase melanoma to the vertical growth phase melanoma.

In addition to genetic studies, the risk of melanoma in those with dysplastic nevi has been evaluated. Isolated dysplastic nevi are found in 2-5% of the population, whereas the incidence of the dysplastic nevus syndrome is probably less than 1%. The lifetime risk of developing cutaneous melanoma among the Caucasian population in the United States is about 0.6% (1 in 150). Persons who have a DN and no family history have a 6% risk of developing melanoma. Persons who have DN and a history of melanoma have a 10% risk of developing a second melanoma; persons who have DN and a family member with melanoma have a 15% risk. The lifetime risk of melanoma approaches 100% for individuals with DN from families with two or more first-degree relatives having cutaneous melanoma.

Halpern et al. found that those with dysplastic nevi often had a clustering of other risk factors as well. Considering a number of risk factors (i.e. freckling, greater than 50 nevi, blond or red hair, a tendency to burn severely, little ability to tan, and a history of multiple painful or blistering sunburns) their group found that 46% of those with dysplastic nevi had at least three or more of these additional risk factors. This finding suggests that "the identification of people with DN translates into the identification of people likely to possess multiple independent risk factors for melanoma."

MANAGEMENT

There is still some controversy regarding the management of dysplastic nevi. In 1983, the National Institute of Health recommended classifying the patients into one of two groups after an accurate family history and evaluation of parents, siblings, offspring, aunts and uncles and grandparents: individuals with DN and a family history of melanoma or those with DN and no history of melanoma.

A thorough history and physical which includes examination of the scalp, intertriginous regions, mucosal surfaces and eyes is necessary for initial detection of melanocytic dysplasia. In patients with the dysplastic nevus syndrome it is recommended that the physical be repeated twice a year or more often depending on the patients ability to monitor their own lesions and the stability of the lesions. In these individuals, it is advantageous to take clinical photographs or computer scans of larger or more clinically atypical nevi to monitor change. Biopsy of at least one or more dysplastic nevi is generally performed to establish the diagnosis. Nevi undergoing sudden change, as well as lesions that are otherwise suspicious should be removed. There is no place for the wholesale surgical excision of all DN, however. Prophylactic excision of DN of the scalp or other potentially hidden areas is often recommended since these lesions are difficult to monitor. It is prudent for these patients to avoid sun exposure as there is evidence that this will increase the number of nevi and their activity, as well as the general risks for development of melanoma and other skin cancers.

In the setting of isolated dysplastic nevi (non-familial), excisional biopsy is often performed if a) the lesion is perceived as changing in size, shape, or color either by the patient or the physician; b) the lesion has become symptomatic (i.e. itching); or c) the lesion has clinical ambiguity with early melanoma.

The incidence of malignant melanoma is rising at an alarming rate, as is the mortality associated with this disease. The increased melanoma risk in those patients with dysplastic nevi supports the need for targeted education in this high-risk group. Early recognition and surgical cure are two ways in which we can hope to better control the morbidity and mortality associated with disease.

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INTRODUCTION

Sir William Osler stated that it is “in the student spirit you can best fulfil the high mission of our noble calling.” He goes on to define the components of the student’s spirit: humility, confidence, pride and hope. It is this enthusiasm and dedication that incoming medical students bring with them as they embark on their medical training. Somewhere along this path, students will face unique stresses: enormous volumes of material to master, call-schedules not conducive to adequate sleep, as well as challenging and potentially abusive interpersonal experiences with faculty, house staff, residents and patients. Recognizing the reality of many of these stresses and providing strategies to promote stress management early in a student’s career may translate into better coping skills as a resident and ultimately as a practicing physician.

Evidence indicates that these stressors impact on the attitudes of students toward their educational experience and their futures as physicians. Furthermore, the effects of mistreatment and abuse have been identified as stressors influencing medical student health, both psychologically and emotionally. There is also evidence that experiences with mistreatment in undergraduate training have even impacted on the wellness of physicians in a post-graduate setting. In fact, parallels have been made between the abuse experienced by medical students and the abuse experienced by children in dysfunctional families. It has been hypothesized that the cynicism and lack of caring that an abusive medical school environment can create translates into potentially adverse interactions with patients later in life. Hence, the abused may demonstrate abusive behaviour and this may begin as early as clerkship. This disturbing theory obviates the need for further research into the area of stress, mistreatment and the evolution of student attitudes toward their profession as they progress through the many levels of training.

Ultimately, preventative measures must be taken to minimize stress and maximize student wellness and health. That is, medical school should aim to be a safe learning environment that is conducive to student well being. Described as a culture unto itself, educators and curriculum developers must realize the unique experience of the medical student. Many students enter their program in their early 20s and require an adjustment period to acculturate themselves with the demands of medical school. By directing strategies to ensure, promote and maintain student health and a positive attitude students can benefit from programs and supports immediately.

Presented here is a brief account of the literature concerning medical student stress and mistreatment. There will be a discussion of potential strategies to improve health and treatment of students with an introduction to the WHIMS (Wellness and Health Impairment in Medical Students) pilot project to be implemented at the University of Western Ontario Medical School in addition to the other medical schools in Ontario.

MEDICAL STUDENT STRESS AND MISTREATMENT

Unquestionably, medical students are faced with stresses unique to their curriculum. For example, the expectation to master large volumes of information, dealing with the challenges that patients experience with their illness, attempting to meet the diverse needs of the public, and ultimately choosing a field to train and practice in upon graduation are all part of the medical students’ realm. A University of British Columbia (UBC) appointed advisory group determined the following stressors that medical students face over the course of four years (Table 1). By examining the unique features of each year, an adequate needs assessment can be performed and the appropriate support offered.

The stresses listed in Table 1 may be unique to UBC, but would presumably be reflective of the issues concerning students at most Canadian medical schools. However, with each school boasting a different cultural flavour, this type of assessment would need to be performed at each institution in order to tailor workshops and offer appropriate supports to students.

Currently counselors, both academic and personal, are available to medical students at the University of Western Ontario (UWO). Students are aware that they can speak freely with these individuals about any personal issue of concern; however no formal student wellness program is in place. As well, extracurricular groups interested in educating peers about attaining a balanced lifestyle have taken the initiative to give students a chance to ask questions and express feelings of stress.

A study of 318 British medical students employed a General Health Questionnaire to assess medical student stress levels and to further identify which areas of stress students found to be most difficult. Compared to employed individuals, graduated non-medical students and non-medical students still enrolled in school, medical students were identified to have a higher mean score indicating a higher ranking of stressful experiences. Relationships with academic staff and consultants as well as talking to terminally ill patients were identified to be

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the most stressful experiences. In contrast, Lloyd et al. determined that the most stressful aspect of medical school was the volume of material students were expected to master. Demands of academic excellence and lack of leisure time were also considered stressful.

Lloyd et al. also demonstrated the evolution of stress throughout the four years of medical school, with women scoring higher total stress scores than men. The mean total stress score increased year to year, but decrease in the fourth year. Stress attributed to lack of leisure time was consistent throughout the four years although the volume of material to learn became a less stressful issue by the senior year. In contrast, the most prominent concern of practicing physicians in UBC was remaining current with medical education. Whereas students move away from a theory based learning approach toward the end of their undergraduate studies, as a practicing physician, the learning process is critical to remaining aware of the latest trends in medicine as are essential to the practice of medicine.

Although an assessment of student stress has not been performed at UWO, it would be interesting to determine what students find particularly stressful about the new curriculum versus the old curriculum. Have the stresses increased or decreased? Does a more integrated approach organize material in such a way that the volume of material does not seem as overwhelming? Is a patient centred approach more conducive to successful patient interaction sooner? If the University of Western Ontario Faculty of Medicine is to champion the movement toward addressing the issue of student wellness, an accurate assessment of the unique needs of our students would be important in developing stress management and health promotion programs.

Throughout the non-Canadian literature, the uncertainty of postgraduate training and choosing a specialty were not identified as sources of stress. However, in a recent issue of MediScan, stress related to the Canadian Resident Matching Service (CaRMS) process experienced by students were identified. Seventy-eight per cent of the 2500 students surveyed found choosing a future discipline in medicine to be extremely difficult. A similar number confirmed that it was an inadequate exposure to the various specialties that made the CaRMS experience particularly stressful. Furthermore the lack of opportunity to change fields of training was identified as a flaw in the system. Sixty-eight per cent indicated that there was a great deal of stress related to making their career choice. The fact that this choice is virtually inflexible makes the process all the more stressful. The new curriculum at Western has modified the clerkship program in third year to allow students more elective time and therefore more time to gain exposure to the specialties of interest. Students training in the old curriculum have applauded this modification.

Recently, students from the Manitoba Medical Students’ Association responded to the three suicides of medical students and residents in the Faculty of Medicine at the University of Manitoba. They wrote:

What do third-year students know about what sort of specialty they would be interested in? Once accepted in a particular program, residents are locked into this field for the rest of their lives. What if they hate it? What if they want to change fields? Unfortunately this is impossible the way things stand.

Dr. Jacyk, coordinator of the Manitoba Medical Association Physicians at Risk Program commented on the perceptions of residents once placed in their respective program, stating that they “don’t want to be perceived as being vulnerable...[and] residents are too afraid to access [help] for fear of reprisal.” These hindrances must be explored and viable options to seek help must be provided through an employee assistance program run through the hospital.

It is important to understand what services are available to residents and medical students. The CFMS (Canadian Federation of Medical Students) has made a series of recommendations to address the issue of student stress. A “comprehensive mental health care plan” has been suggested which would include multiple entry points for students and be visible, accessible as well as confidential. Proactive programs including stress and career management in clerkship was also suggested, and that support should be available at all points in a student’s education, not exclusively to those in their first year. It is, however, in this first year of medical school that a student’s attitude and health can begin to be influenced adversely. Wolf et al. determined that medical students reported a decrease in self-esteem, and increased expression of cynical attitudes after their first year compared to their feelings upon entry in to medical school. By employing a number of psychological assessment scales, this group looked at lifestyle, nutritional, physical, and emotional changes among first-year students before school began and then at the end of their first year. In an analysis of the adjustment of students to a medical school environment, it was found that psychosocial functioning and self-esteem decreased while depression and hostility, a so-called negative mood, increased. Understandably, a student’s ability to cope

Table 1.

<table>
<thead>
<tr>
<th>Year</th>
<th>Issues</th>
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<tbody>
<tr>
<td>First Year</td>
<td>gender issues, performance expectations, &quot;keener envy&quot;, emphasis on facts</td>
</tr>
<tr>
<td>Second Year</td>
<td>emphasis on hard facts, lack of intimacy of small groups, little emphasis on attitude/human issues</td>
</tr>
<tr>
<td>Third Year:</td>
<td>anxiety, depression, academic anxiety, lack of academic support</td>
</tr>
<tr>
<td>Fourth Year:</td>
<td>burn out, overworked, phase of apathy, overwhelmed on rotations, inadequately prepared for career decisions</td>
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U.W.O. Medical Journal 69(2) 1999
within medical school is influenced by their prior level of function, but knowledge of the deterioration in attitude and feeling of the medical school can have implications for prevention. Wolf suggests that stress management and the establishment of realistic expectations in medical school are possible ways of promoting health in the medical student. Improving mentoring programs with more emphasis on role modeling and lifestyle management may also be beneficial.

Wolf et al. also determined that mistreatment was positively associated with an increase in cynicism and hence a negative evolution of student attitudes. In fact, a number of studies identified abuse (verbal, physical or sexual) to be a significant source of stress. The study reported that of 87 graduating medical students, 98.9% experienced some type of mistreatment during their four years as a medical student. Ninety-two per cent of these students were yelled at with the greatest source of mistreatment coming from residents and interns. In this particular study, the term mistreatment was defined to include: shouting, belittling, being assigned punitive tasks, physical harm, sexual harassment or exploitation.

Similar results were found by Baldwin et al. who surveyed third and fourth year students across the United States and determined that mistreatment was most commonly manifested in the form of humiliation. Sixty-five per cent reported having received negative or disparaging comments about their choice of medical career or the practice of medicine. The majority of students implicated residents in these cases. Seventy percent of students felt these comments were bothersome. In determining the degree of effect that such mistreatment had, being threatened with an unfair grade was the most concerning form of abuse with humiliation being second.

**WHIMS**

The Wellness, Health and Impairment in Medical Students (WHIMS) project was created to address the issues of “loneliness and helplessness which can facilitate the development of dysfunctional behaviour.” By recognizing the unique demands of medical school and the various opportunities to offer prevention strategies, it is felt that cultivating positive attitudes early in medical school can steer students away from substance abuse, depression and despair. The learning module designed to be implemented into the curricula across all five Ontario medical schools focuses on substance misuse amongst physicians. The overall goals, however, include increasing awareness of illnesses in medical students, the importance of maintaining wellness personally and professionally and offering education about the resources available to students in need of support. By incorporating addiction medicine issues into the LMCC exam, medical schools will be compelled to educate students about impairment issues.

The evidence presented by Richman et al. provides an example of how mistreatment can lead to depression and substance abuse. Informing students about the warning signs of the impaired colleague and how to inform the appropriate authorities is part of ensuring quality of care and maintaining the integrity of the profession, a responsibility belonging to all health care professionals. Taking advantage of certain teachable moments: entry to medical school, preclerkship and during clerkship, students are empowered with the knowledge and resources that will hopefully lead to a heightened awareness of addiction that will extend into the postgraduate years.

When considering ways to address student stress and mistreatment, it is important to think of strategies that implement measures for prevention versus rescue. Enhancing student wellness and offering an outlet for students’ stresses and concerns can be both therapeutic and beneficial to the maturation of a medical student. Most schools have a mentor program where students are paired or grouped with a community physician, usually for social interaction. Having an academic faculty advisor allows students to address issues of scholastic nature, be it exams, career choices or CaRMS. A predominantly socially oriented mentor group may not be conducive to discussing a student’s concerns. Perhaps if students have an option to address concerns early, faculty advisors can discover where they falter and offer support. Finally, mentors should ideally be role models. Physicians that reach out to students, sharing their personal experiences and coping mechanisms further enforce the reality of juggling personal stresses in a highly demanding professional environment. Positive role models that demonstrate enthusiasm for the profession as well as balanced lifestyles may influence medical students to seek and maintain similar goals.

Clinical vignettes have already been designed to address boundary issues in medicine between patients, medical students, and clinicians. Demonstrating typical medical student stressors and boundaries may be equally beneficial. Because the stresses medical students experience are dynamic, different scenarios for each year can be used to generate discussion and help introduce support programs available to students at each phase of their career. It is important that any strategies to improve student wellness be met with enthusiasm from faculty. Strong, well-established programs that allow for student involvement will create an environment where students’ needs are met.

Medical school can be a challenging and rewarding experience. The learning environment must be a safe and healthy one in order to preserve positive attitudes about self and others. Furthermore, maintaining respect for the profession and the values students will take with them into their professional careers should be considered an essential element of the medical school experience. Ideally medical schools should boast a zero-tolerance policy regarding student intimidation and mistreatment. However, with the complexities of interpersonal communication, this is clearly impractical. It is important for all schools to have a code of conduct, which should be included in student handbooks as well as resident training/teaching manuals. Educating students and faculty about the existence of policy on mistreatment, its enforcement and the available resources, however informal, that students can use should be a priority if progress in this field is to be made.
PREVACID 30 MG
LANSOPRAZOLE

PRESCRIBING INFORMATION
NAME OF DRUG: PREVACID 15 and 30 mg (lansoprazole delayed-release capsules)

THERAPEUTIC CLASSIFICATION: H+ K+-ATPase Inhibitor

NOTES: 1) When used in combination with antimicrobials for the ERADICATION OF H. PYLORI INFECTION, the PRODUCT MONOGRAPH for THOSE AGENTS SHOULD BE CONSULTED.

INDICATIONS AND USAGE: PREVACID (lansoprazole delayed-release capsules) is indicated in the treatment of conditions where a reduction of gastric acid secretion is required, such as:
1) duodenal ulcer;
2) gastric ulcer;
3) non-ulcer dyspepsia including patients with Barrett's esophagus, and patients poorly responsive to an adequate course of therapy with ranitidine HCl or metronidazole;
4) pathological hypersecretory conditions including Zollinger-Ellison Syndrome (see DOSAGE AND ADMINISTRATION);
5) eradication of Helicobacter pylori infection in combination with antimicrobials

Triple Therapy: PREVACID (lansoprazole delayed-release capsules), in combination with clarithromycin and amoxicillin or tetracycline, is indicated in the treatment of patients with H. pylori infection and active duodenal ulcer disease. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence.

(For additional information on triple therapy for the treatment of H. pylori infection and active duodenal ulcer recurrence, refer to the IP-PAC Product Monograph.)

Dual Therapy: PREVACID (lansoprazole delayed-release capsules), in combination with tetracycline as dual therapy, is indicated for the treatment of patients with H. pylori infection and active duodenal ulcer disease who are either allergic or intolerant to clarithromycin or in whom resistance is known or suspected. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence.

(See DOSAGE AND ADMINISTRATION). In patients with a recent history of duodenal ulcer whose H. pylori-positive, endoscopic ulceration is the site of recurrence of duodenal ulcer disease.

The optimal timing for eradication therapy for such patients remains to be determined. However, there is little information on how therapy combination containing tetracycline, clarithromycin, or ciprofloxacin should be tested. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, an alternative combination therapy is recommended.


TABLE 1

| Study | Eradication Rates (%)
|-------|---------------------|
| Triple Therapy | Eradication Rates (%)
| Evaluable Patients | 92 (44.8)
| Total (M01-131) | 88 (40.8)
| Total (M01-125) | 86 (39.6)
| Combined T1 (01111) | 81 (36.3)
| Combined T1 (01111) | 79 (34.8)
| ITT (All Available Data) | 94 (42.0)
| T01 (M01-131) | 87 (39.1)
| T01 (M01-125) | 85 (38.3)
| Combined | 83 (37.4)
| Dual Therapy | Eradication Rates (%)
| Evaluable Patients | 76 (35.9)
| Total (M01-131) | 72 (34.1)
| Total (M01-125) | 73 (34.1)
| Combined | 73 (34.1)
| ITT (All Available Data) | 74 (35.2)
| T01 (M01-131) | 70 (32.3)
| T01 (M01-125) | 72 (34.1)
| Combined | 71 (34.1)
| Dual Therapy | Eradication Rates (%)
| Evaluable Patients | 55 (25.1)
| Total (M01-131) | 53 (25.1)
| Total (M01-125) | 50 (24.1)
| Combined | 51 (25.5)
| ITT (All Available Data) | 54 (25.9)
| T01 (M01-131) | 56 (26.5)
| T01 (M01-125) | 56 (26.5)
| Combined | 56 (26.5)

REFERENCE:

Nisker JA. The yellow brick road of medical education. CMAJ 1997;156:688-691.


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WARNING:
Clarithromycin should not be used in pregnancy except where no alternative therapy is appropriate, particularly during the first trimester of pregnancy. If pregnancy occurs while taking the drug, the patient should be apprised of the potential hazard to the fetus. Clarithromycin has demonstrated adverse effects on pregnancy outcome and/or embryo-fetal development in nonhuman primates, rats and rabbits at doses that produced plasma levels 2 to 10 times the serum levels obtained in humans treated with the recommended doses. (See Warning section in the Clarithromycin Product Monograph.)

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range from severity of mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin pro-duced by Clostridium difficile is a primary cause of "antibiotic-associated" colitis. After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug effective against Clostridium difficile. Allergic reactions (including anaphylaxis) have been reported in patients receiving clarithromycin orally. Serious and occasionally fatal sensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are not necessarily limited to patients with a history of penicillin sensitivity and/or a history of sensitivity to multiple allergens. There have been well-documented cases of individuals with serious or fatal anaphylactic reactions who have experienced severe hypersensitivity reactions when treated with cephalosporins. Before initiating therapy with any penicillin, careful inquiry should be made regarding previous penicillin allergy and the presence of systemic reactions. If an allergic reaction occurs, amoxicillin should be discontinued and the patient should be treated with an alternative drug. Penicillin-sensitive patients have been treated with a one-year course of amoxicillin for the treatment of Campylobacter jejuni infection, without evidence of recurrence.

In general, therapy with amoxicillin should be discontinued and the patient treated with an alternative drug if an allergy reaction occurs. If an allergic reaction occurs, amoxicillin should be discontinued and the patient should be treated with an alternative drug. Penicillin-sensitive patients can be treated with a one-year course of amoxicillin for the treatment of Campylobacter jejuni infection, without evidence of recurrence.

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There were no frequently reported (>2% incidence) adverse events in the treatment-emergent or the possibly/probably treatment-related event categories with onset at any point from the start of maintenance treatment to the time of first recurrence of disease in 20% of the patients treated with Placebo.

**Treatment Group** | **Placebo** | **Mean Exposure (Days)**
---|---|---
**CUM** | **(N = 236)** | **(N = 236)**
**Mean Exposure (Days)** | 105.4 | 205.7

**Musculoskeletal System** | 1.32 (1.3F) | 4.4 (1.17)
**Respiratory System** | 3.12 (1.9) | 2.18 (1.9)
**Nervous System** | 0.41 (1.1) | 0.4 (1.1)
**Digestive System** | 1.33 (1.2) | 3.12 (1.2)
**Cardiovascular System** | 0.7 (1.3) | 0.5 (1.6)
**Skin and Appendages** | 2.07 (1.7) | 4.1 (1.6)

**Urogenital System**

**Table 2** Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-Term, Placebo-Controlled Studies in TAP Safety Database

**Table 3** Incidence of Possibly or Probably Treatment-Related Adverse Events in Short-Term, Placebo-Controlled Studies in TAP Safety Database

**Table 4** Treatment-Emergent Adverse Events Reported by >2% of the Placebo and Lansoprazole Patients to the Time of First Recurrence of Disease in the Maintenance Treatment Studies

**Table 5** Treatment-Emergent Adverse Events Reported by >2% of Patients Treated with Placebo in Placebo-Controlled, Double-Blind, Phase III, 60-Week Controlled European Studies

**Table 6** Treatment-Emergent Adverse Events Reported by >2% of Patients Treated with Placebo in the Short-Term Placebo-Controlled Studies
Successful outcomes begin with careful listening. That's why, for over 25 years, more health care providers have counted on the reliability and superior acoustics of 3M™ Littmann® stethoscopes than any other brand. To hear more, call 3M Health Care at 1-800-3M HELPS (364-3577), or visit our website at http://www.3M.com/Littmann.
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But unlike them,
we already have 150 years of practice

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During the Second World War, our scientists were the first to develop a way to mass-produce the world’s first wonder drug, penicillin. Since then, Pfizer medicines have contributed significantly to the revolution in healthcare of our modern age.

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And, perhaps, some of today’s graduates will help us find the way.

Pfizer

Life is our life’s work

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