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Physicians and Peace: Promoting Peace By Pursuing Health

Adnan Pirbhai, Meds 2005

The modern definition of health is widely regarded as not simply an absence of disease, but rather a state of physical, mental, social and ecological well-being. If one interprets the effects of war and violence as they apply to each of these components, a sobering picture develops, one that should be of particular concern for health professionals. The physical effects of war are devastatingly obvious, with the increasing numbers of civilian deaths particularly concerning. The mental effects are reflected in a very high number of war related mental illnesses in victims and combatants.[1] War and violence also carries a high cost to social cohesion and infrastructure, which consequently adversely affect health by destroying the networks and physical infrastructures that support healthy societies. Some of these examples include water systems, food distribution systems, sanitation and primary health care.[2] Ecologically, there are many examples from the last decade that corroborate the destructive capacities of war on the environment.[3] With such widespread effects of war on health, combined with a current world climate that puts war almost on par with infectious disease as a global cause of morbidity and mortality[4], it should hardly come as a surprise that physicians stand to play very important roles in the effort to delegitimize war and promote peace.

That war and violence negatively impact health is stating the all too obvious. However, what is needed in order to pragmatically outline the role the physician can play in promoting peace amidst conflict is a simultaneous understanding of how health promoting initiatives can lead to peace. In recent years, there has been a considerable amount of interest and attention paid to examining the basis of health to peace mechanisms.[5] Health-peace initiatives refer to "any initiative that is intended to improve the health of a population and to simultaneously heighten that population's level of peace and security."[6] Enlisting Hippocratic ideals that guide everyday practice, such as extended altruism, a commitment to impartiality and scientific rigor, and the overriding goal of improving health, physicians are highly capable of initiating and maintaining peace by remaining committed to health. Pursuing the 'superordinate goal of health' has proven to promote peace in part by creating "an opportunity to build a negotiating framework, to counter dehumanization of the enemy, and sometimes to demonstrate the possibility of stopping the violence."[5]

There are several well established examples of health-peace initiatives that underscore this point. During the civil war in El Salvador, nearly twenty thousand health workers collaborated with each other and guerilla fighters to negotiate three days of truces each year for the purposes of immunizing children against polio and other diseases.[7] This initiative is widely regarded as spurring peaceful resolution of the conflict. The lessons learned through these "days of tranquility" were also enlisted to vaccinate endemic (of both disease and conflict) areas such the Democratic Republic of Congo and Afghanistan, among others. Another creative example of a health-peace initiative is the Canadian International Scientific Exchange Program (CISEPO), a voluntary organization that is implementing an infant screening program for hearing loss between Jordan, Israel and the Palestinian Authority. As Dr. Arnold Noyek, the chairman of CISEPO states, "We are launching this program not only for the benefit of the children, but to build and grow working relationships and promote regional cooperation between health care and scientific professionals. The problem of hearing loss in this region is not confined by political boundaries." Thus, health initiatives are increasingly and convincingly being equated with peace initiatives.

What is important to ascertain from these and other health-peace initiative examples, however, is that the nature of the work of physicians, epidemiologists and other health workers was not centred around using expertise developed in a medical context and extending it into the realms of conflict management and politics. Rather, it should be duly noted that implementing programs wholly focused on the overriding goal of health was able to achieve peace as a result. However, there is indeed considerable opportunity and cause for physicians to become politically outspoken in a context of war and violence.

Physicians have a public perception of being objective, caring, educated and altruistic. In fact, in recent years, physicians have been given higher public ranking than politicians in matters

of honesty and ethics.[8] This perception lends itself to a considerable amount of legitimacy and influence in public debates. The altruistic pursuit of health, a commitment to truth and objectivity and the legitimacy and status afforded by society, provide physicians with a great deal of moral and technical expertise that enables physicians to effectively influence public policy and be political motivators.

Traditionally, in the political arena in times of war, physicians were relied on primarily as scientific experts, for example as they testified against the actions of the United States in Vietnam from a medical perspective.[6] More recently, Medact, a UK charity of health professionals, published *Collateral Damage*, a report that suggests death tolls could potentially be in the hundred of thousands as a result of the present conflict in Iraq.[9] By interpreting political decisions in their potential for death and destruction, physicians are able to redefine war as a health issue. The best example of this is the work done by International Physicians for the Prevention of Nuclear War (IPPNW) as they redefined nuclear war as primarily a public health issue. Pursuing scientific evidence in a public forum allows physicians to effectively expand their role of expertise from strictly a scientific realm and become spokespeople of a political nature as well.

In the case of the current situation in Iraq, thousands of physicians have chosen to become politically outspoken as they united in outlining the disastrous potential health effects of military action in Iraq. They also cited, among others, their commitment to truth and objectivity in contending that American and British leaders failed to supply convincing evidence supporting reasons to go to war.[10] One of many specific examples includes the work of Physicians for Global Survival, the Canadian arm of IPPNW, who lobbied Prime Minister Jean Chretien to reject war and pursue peace.[11] While purists may contend that physicians may be overstepping their bounds by entering moral and political debates, others can argue that it is the nature of the political decisions in the context of war and their impact on health that make physicians as good candidates as any to be political spokespeople.

One other very important role for physicians amidst world conflict is through the concept of public health. In matters of health, most physicians will agree with the notion that prevention is preferable to treatment. The same idea naturally applies to war. Development indicators and health are positively related, so the worse off a country and the members of that society are developmentally, the greater the incidence of ill-health.[12] Therefore, if too few financial resources are committed to health care and other health producing aspects of the society (including education, poverty, and equitable distribution of wealth, to name a very few), mortality and morbidity are likely to increase.[13] This analysis can at least partially justify the proven association of high levels of military expenditure with unemployment, poverty, starvation and ill health.[14] Similar associations also outline a list of identifiable public health parameters that can be considered risk factors for the development of war and violence. These parameters include infectious diseases, mental health disorders, vulnerability of population groups, disparities in health status within and among countries, and weakening of human rights.[15] Since countries with the lowest developmental scores (based on many of the public health parameters outlined above) are also most often involved in,

or may soon be involved in violent conflict of some kind, a fair conclusion follows: ill-health and war are connected, or conversely, effective public health can promote peace and prevent war.

Some inroads have already been laid down this path that have curtailed the overall destructiveness of war. In addition to the 1984 Nobel Prize winning achievements of IPPNW in redefining nuclear war, the 'rules of war' no longer allow the use of many other types of weapons and ban the production of others. This was due to the work by the International Committee of the Red Cross in defining and outlining the effects of weapons based on health effects.[6] These two examples chronicle work done by specific groups regarding specific aspects of armed conflict. Consider a future where the lay person acknowledges and interprets all aspects of a war by their effects on the health of those populations involved. With the grim prediction of war as one of the top ten causes of disability-adjusted life years lost by the year 2020[4], generating and implementing effective public health strategies, including raising the awareness of war as a public health issue, represents yet another avenue physicians can pursue in promoting peace.

Physicians, in various ways, can contribute to a more peaceful world community. Increasingly, research is uncovering scenarios where health initiatives can bring health, and consequently peace, to a region of conflict. An argument also exists for the appropriate and effective involvement of physicians as agents for peace in the political arena, while pursuing the superordinate goal of health. Finally, public health issues, evidenced as both a cause and consequence of war, offer physicians what may be the most effective avenue to pursue in order to prevent war and achieve peace. The foundation for a new academic discipline entitled *Peace Through Health* is being developed at McMaster University in Hamilton in light of this growing body of evidence. The case for continuing to develop this discipline is strong in that many believe it is important to apply what is already known in the field, outline future areas of research and ultimately disseminate the findings and lessons to all health professionals.[5, 16] Others, however, contend that rather than creating a new discipline and unnecessarily committing more resources to such initiatives, what is needed is to mainstream the interaction between health, peace and conflict resolution in existing institutions concerned with public health, interstate and intersocietal conflict.[17] Although there is some debate regarding *how* work that needs to be done in the field of peace and health should progress, there is no denying that the work *will* and *should* continue and the connection between health and peace will only grow stronger. Physicians must recognize that while remaining committed to the principles on which health care and the profession are based, they are uniquely capable of positively affecting war prevention and peace promotion. The imperative to enlist this capacity, given the current world climate and future outlook, has never been stronger.

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Magnetic Resonance Imaging: Opportunities for early diagnosis of rheumatoid arthritis

Nina Ghosh, Meds 2005

RA is a progressive arthropathy, without appropriate treatment, can result in irreversible joint damage.[1] Early diagnosis presents the challenge of often vague symptoms and signs that progress relatively slowly. Radiographs, although able to find structural joint involvement in patients where disease is established, have not been sufficiently sensitive in finding early RA joint and soft tissue changes.[1] MRI has thus been looked upon as an imaging modality for the detection of early RA pathology due to its more sensitive data and better predictive value[1] In RA, due to its superior contrast resolution and tomographic nature, MRI can demonstrate soft tissue and joint involvement better than plain radiography.[8] Specifically, active synovitis and pannus are markedly enhanced by intravenous gadolinium chelate injection. Fat-suppressed T1-weighted imaging with gadolinium enhancement is the most sensitive technique to demonstrate these tissues.[8] Moreover, semiautomated methods have been developed to measure the volume of bone erosion with MRI.[8] This article will review the current evidence demonstrating the use of MRI in the early detection of RA.

INTRODUCTION

RA is a progressive arthropathy, without appropriate treatment, can result in irreversible joint damage.[1] Early diagnosis presents the challenge of often vague symptoms and signs that progress relatively slowly. Furthermore, the early months of RA are critical in that irreversible joint damage can occur. Thus, an early clinical diagnosis may be key in preventing the long-term disability that challenges many RA patients. Radiographs, although able to find structural joint involvement in patients where disease is established, have not been sufficiently sensitive in finding early RA joint and soft tissue changes.[1] MRI has thus been looked upon as an imaging modality for the detection of early RA pathology due to its more sensitive data and better predictive value[1] According to Emery, MRI could detect abnormalities in 70% of patients at presentation, whereas radiographs were able to detect characteristic or pathognomonic joint erosion in 15% of patients with RA[2]

In RA, due to its superior contrast resolution and tomographic nature, MRI can demonstrate soft tissue and joint involvement better than plain radiography.[8] Specifically, active synovitis and pannus are markedly enhanced by intravenous gadolinium chelate injection. Fat-suppressed T1-weighted imaging with gadolinium enhancement is the most sensitive technique to demonstrate these tissues.[8] Although there has been little validation on how to score bone erosion using MRI, when strict criteria for defining bone erosions are applied to scoring, there is a 97% consistency in the recording of such lesions by MRI.[1] Moreover, semiautomated methods have been developed to measure the volume of bone erosion with MRI.[8] This article will review the current evidence demonstrating the use of MRI in the early detection of RA.

EVALUATION OF THE HANDS AND WRISTS IN EARLY RA

MRI of the hand and wrist joint can demonstrate joint erosions earlier than plain radiographs and can detect more erosions,[6] specifically, common sites detected through MRI include the capitate, lunate and scaphoid. Bone marrow signal changes frequently occur and are most frequent in the capitate, lunate and triquetrum. MRI also shows synovial thickening and enhancement, most commonly in the radiocarpal joint. More than half of patients who present with RA also show tenosynovitis, most commonly involving the extensor carpi ulnaris tendon. On MRI it is seen as sheath fluid, thickening and enhancement.[6]

Jorgenssen also showed that MRI demonstrated abnormality of the soft tissue in 13 of 15 patients with early RA, compared to none using standard radiography.[7] On coronal MRI, sites of synovitis included the recess of the distal ulnar, the distal radioulnar joint and the radiocarpal joint.[7] Furthermore, on axial MRI, tendon sheath effusion of the digital flexor was demonstrated in 3 patients.[7] These data suggest that MRI is a sensitive mode of detection of synovitis involving the wrist in early RA.

EVALUATION OF SYNOVITIS

A recent study in which patients were randomized to receive treatments with disease modifying antirheumatic drugs, bone damage and synovitis were measured by MRI. The MRI data suggested that the level of synovial thickness was vital in determining the extent of bone damage.[1] Since no damage occurred in joints without synuvitis, the presence of synovitis suggests that it is prognostic for bone damage.[4] Unlike plain film or CT radiography, MRI can be used to image the synovium including synovium volume and level of inflammation.[4] The use of gadolinium-enhancing imaging properties in the synovium correlated well with the microscopic appearances on arthroscopic biopsies. MRI has also been shown to be more sensitive than clinical examination for the identification of synuvitis.[4] For instance, Sugimoto et al correctly diagnosed 25 out of 26 patients at the onset of RA using MRI criteria, 23% more patients than diagnosed using ACR criteria.[5]

EVALUATION OF THE HUMERAL HEAD

The early development of joint damage in peripheral joints is well known and occurs in approximately 75% of patients during the first two years of the disease.[3] However, data on the shoulder joints are scarce. Radiographic damage to the shoulder has been found within six years of disease in more than fifty percent of RA patients. By 12 years of RA, MRI can detect erosions in 96% of shoulders, compared to 73% by plain films and 77% by CT.[3] Thus, although MRI examination of the shoulder may not diagnose the overall disease process, it is useful in early detection of shoulder joint involvement. Erosive changes tend to occur most often on the superolateral aspect of the head of the humerus. According to Takalo, MRI images of subcortical areas of high signal intensity in T2-weighted images and low signal intensity on T1 weighted fulfill criteria for erosions. Using this criteria, MRI detected more erosive lesions than other imaging modalities such as U/S and CT, particularly in the postero-lateral region of the humerus.[3]

MRI IN THE DIAGNOSIS OF JUVENILE ARTHRITIS

MRI of the knee in early JRA depicts the synovium and its effects on joint structures in children. Using the criteria of maximal synovial thickness of 3 mm or a synovial volume of 3 ml, Graham et al. Synovial hypertrophy and joint effusions are the most frequent MRI findings in the knees in early JRA, however occult cartilage and bone erosions may also be identified.[9]

LIMITATIONS OF MRI

Although evidence suggests that MRI is a sensitive, accurate, non-invasive modality to assess components of the rheumatoid arthritic joint, several practical and diagnostic limitations arise. In Canada, the limited availability and expense of MRI preclude its use on a routine basis for diagnosis.

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An Interdisciplinary Approach to Patient Care

Maryanne Rockx, Meds 2004

This article will explore the interactions between two internal medicine subspecialties, endocrinology and cardiology. After completing three years of internal medicine in London, in July 2002 the residents profiled here began subspecialty training, Dr. Wael Haddara in endocrinology/intensive care and Dr. James White in cardiology. One of the main concerns of an endocrinologist is the management of patients with diabetes mellitus (DM). An ever increasing number of Canadians have Type 2 DM, in which atherosclerosis is the primary factor for morbidity and mortality. An interdisciplinary approach is required to treat them effectively.

Dr. Haddara graduated in 1991 with a B.Sc. Pharm. from Memorial University of Newfoundland and completed the MD degree at Queen's University in 1999. How did you discover your interest in endocrinology?

WH: I first became interested in endocrinology during my undergrad years. It struck me that profs kept talking about "master glands" that control the body's metabolism but in reality we knew very little about the details of how that worked.

What part of endocrinology appeals to you and why combine it with intensive care?

WH: Endocrinology is very heavily physiology-based and pharmacology-based. Given my background, I find that appealing. In addition, although it is a very old specialty, in some respects it is very young in that there are so many unanswered questions. That's a stimulating thing.

I first became interested in ICU after first year of medical school. I had taken a year off from Medicine because of personal reasons and landed a job as a critical care pharmacist at the Hamilton General Hospital. It was a great experience and my interest in ICU was reaffirmed during my residency. I had always been interested in endocrinology and strangely enough my research interests lie at the intersection of the two fields.

Most intensivists in the past were either anesthesiologists or respirologists. Metabolism and hormonal regulation, despite their importance, have not figured prominently in the clinical practice of ICU and I hope to change that.

What is your favourite book and why?

WH: The theme of *The Count of Monte Cristo* is that no human being, regardless of power, wealth or influence, is perfect. The novel is the story of a man who had every reason to believe otherwise but discovers that only God is without fault.

Dr. Haddara was the chief medical resident at LHSC-UC from July to December 2001.

What was the most challenging part of this role?

WH: Certainly the most challenging part of being Chief Resident at Western is balancing all of the different responsibilities. We continue to carry a significant clinical load during the months of being Chief and added to the clinical work are the various other duties. Another kind of balance that is sometimes hard to strike is the balance between being part of administration and being an advocate for residents.

Dr. White was the chief medical resident at LHSC-UC from January to June 2002?

What do you consider the most challenging part of this role?

JW: This should really be divided into two distinct areas, that of education and of administration. The educational challenge was how to convey knowledge in an interesting and exciting fashion. The administrative challenge, for me, was the realization that my role was to look out for others and the "greater good" while everyone else's role was to let me know their demands, regardless of what everyone else wanted. Believe me, these roles are not synergistic!

How did you discover your interest in cardiology?

JW: One day in Grade 13 biology, my teacher was discussing the cardiovascular system. I found it so interesting that I called the Chief of Cardiology at UH to see if I could come and do some research ... he said yes. I worked in the Cardiac Investigation Unit from Grade 13 up until, well, now. The generous mentorship and encouragement of the staff cardiologists is what led to my interest in cardiology.

What do you find appealing about the practice of cardiology?

JW: Cardiology is a specialty that is both challenging and gratifying. The challenge is found in the acuity and severity of the illness as well as the constant appreciation and manipulation of cardiovascular physiology. The gratification is both immediate and delayed, from the patient finding relief from pain during a myocardial infarction to that of a patient coming back for follow-up visits with chronic congestive heart failure.

Did a particular cardiologist act as your mentor and what did you learn from him?

JW: The physicians that I have done research with for over eight years have had a substantial effect on my decision to go into cardiology. Both Dr. Peter Pflugfelder and Dr. Bill Kostuk deserve much of the credit for this. Dr. Pflugfelder especially has conveyed to me how rewarding a career in cardiology can be if one takes time to understand how the patients' disease effects their lives rather than simply their test values.

The CBC movie *Glory Enough For All* details the life of Sir Frederick Banting, who won a Nobel Prize in 1923 for his discovery of insulin. It is said that Banting's ideas were conceived in London where, besides having a general practice, Banting taught orthopaedics at U.W.O. The house where he lived and practiced is now Banting House, a national historic site with an eternal flame, lit in 1989 to be extinguished when a cure for DM is found.

Have you seen the movie or been to Banting House and has either of these encouraged you to be involved in research or to attend medical school?

WH: I have seen both the movie and visited Banting House. The story of insulin is one of the most inspiring stories of contemporary medicine. As with many other stories of discovery it is the number of nay-sayers and doubters that I find most fascinating.

Would you use Banting House as a community resource for a newly diagnosed diabetic?

JW: Absolutely! The more people know about their condition and the research that has taken place and is underway, the more they will take part in the treatment.

What is the impact of DM on today's health care system?

WH: I think it is unfortunate that Type 2 DM is on the rise when we could probably prevent a significant number of people from developing this disease through weight loss and weight control.

JW: A profound impact! Type 2 DM is an epidemic in North America and the impact, both on the patients themselves and on the health care system, has been a crescendo of financial burden. As most cases are preventable, we should focus on education in order to protect patients at risk and our future health care system.

What are the implications for the future?

WH: I think more money in health care should be spent on prevention than we are doing presently. However, research into the mechanisms of insulin resistance and beta cell destruction is likely going to yield very important information on the basic metabolic function of the body. I think this is a very exciting time in endocrinology.

JW: What concerns me the most is if we can sustain the present level of care for a population that is aging, and with that age getting more disease such as diabetes. As many already know, we struggle to provide that care now. What will be the situation in ten or twenty years when the portion of the population with significant illness expands?

Many important trials have examined the association of heart disease with DM. In the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial, heart failure accounted for 66% of total mortality following acute myocardial infarction[1].

In the Heart Outcomes Prevention Evaluation (HOPE) trial, compared with controls, ramipril-treated diabetic patients experienced a 25% relative-risk reduction of the primary composite endpoint (myocardial infarction, stroke, or cardiovascular death), a 22% relative-risk reduction in developing myocardial infarction, a 20% relative-risk reduction in developing any heart failure, a 33% relative-risk reduction in developing stroke, a 24% relative-risk reduction in total mortality, and a 37% relative-risk reduction in cardiovascular deaths.[2]

Most recently, researchers are studying a newer oral hypoglycemic agent of the thiazolidinedione class, rosiglitazone. Since Type 2 diabetics are at a particularly high risk for heart failure and have a poor prognosis once they develop it, it is important to prevent the onset of DM. A large, prospective trial, the Diabetes Reduction Assessment with Ramipril and Rosiglitizone Medication (DREAM) trial, with a target enrollment of 4000 people with no diabetes at baseline, will evaluate the effects of ramipril and/or rosiglitizone in people with impaired glucose tolerance.

Any thoughts on these trials?

WH: I think this is a good example of prevention. It would be nice to know that we can do something for people to keep them healthy rather than treat them once heart disease has already struck.

JW: Our appreciation of how both traditional and novel treatments can retard or even prevent illness is only in its infancy. If one looks at how much we have learnt in the last ten years, it is exponentially more than in the last one hundred years. What is important is to embrace and utilize this knowledge but also to

critically appraise the data and apply it to the individual, rather than a generic population. That being said, these trials are encouraging and are changing clinical practice.

What interaction do you see between endocrinologists and cardiologists?

WH: As you have alluded to, diabetics are at a significant risk of developing heart disease. So far the interaction between cardiologists and endocrinologists has not been the closest. As we get more results from clinical trials, however, I think there will be much more cooperation. One of the endocrinology fellows here at Western conducted a survey of cardiologists and their adherence to the DIGAMI protocol and found that very few did. On the other hand, some of the cardiologists here are undertaking a study on glucose control post-MI…so I think closer cooperation is going to evolve soon.

JW: Although traditionally there has not been a strong association between these two departments, over the last several years the emphasis has shifted to primary and secondary prevention. This has united the cardiologists with the skills of the endocrinologists to assess and alter cardiovascular risk, such as management of lipids and diabetes as well as certain conditions such as hyperhomocysteinemia and morbid obesity. I feel this trend will continue with further emphasis on preventative medicine.

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Arthrocentesis

Elizabeth Au-Yeung, Meds 2004

Arthrocentesis or joint aspiration is a procedure that drains fluid from a joint using a sterile needle and syringe. Aspirating a joint can be both therapeutic by relieving painful joint swelling as well as helpful in determining the cause of a joint effusion such as arthritis, infection, trauma, or gout. This relatively simple technique can be performed in an office setting and can provide a quick diagnosis for the cause of a joint effusion. Complications of arthrocentesis include introduction of infection into a joint space (0.072%)[1], trauma to surrounding structures (i.e. articular cartilage, nerves, blood vessels, and soft tissue), bleeding, hematoma formation, joint injury, and pain.[1, 2, 3] Contraindications to arthrocentesis include cellulitis or broken skin over the entry site, anticoagulant therapy that is not well controlled, severe primary coagulopathy, suspected bacteremia (unless joint is the suspected source of the bacteremia).[1] Additionally, drugs can be injected into the joint after joint aspiration for a variety of purposes. Some commonly used drugs include local anesthetics, corticosteroids, and hyaluronic acid derivatives.[2]

GENERAL APPROACH TO ARTHROCENTESIS

The equipment required for arthrocentesis is listed in Table 1.

Table 1. Equipment [1,2]

Antiseptic solution for skin preparation (i.e. povidone-iodine or alcohol)
Sterile gloves
Sterile drapes
Local anesthetics (i.e. lidocaine HCl or bupivicaine HCl)
Syringes (one or more 5- to 60-mL syringes depending on joint and amount of fluid)
Needles (18- to 25-gauge)
Hemostat
Culture and laboratory supplies
Bandages and compression dressing

The technique for arthrocentesis can vary depending on the site that is being targeted, however a general approach which can be applied to all sites is as follows: [1,2,3]

Before aspiration, the process of joint aspiration should be explained to the patient and the patient should be placed in a comfortable position that will provide access to the site. Maintain sterility by using drapes, gloves, and careful technique.

1. Mark the site of entry on the skin.
2. Clean the area of skin with antiseptic.
3. Inject the appropriate amount of local anesthetic into the area around the joint.
4. Insert needle carefully taking care not to move the needle from side to side.
5. After insertion, pull back on the plunger to ensure that vascular structures have been avoided. If blood is drawn, withdraw needle and reposition it. Normal synovial fluid will appear clear or pale-yellow. It is possible that blood can be drawn from the joint space or that the needle has entered a hematoma.
6. As the needle enters a joint, a "pop" may be felt or heard. As the needle is positioned within the joint space, very little pain should be felt.
7. Slowly drain some of the fluid into the syringe.
8. Withdraw the needle slowly and cover the entry site with a dressing and bandage. Bandage should be left on for at least 8 to 12 hours.
9. After aspiration or injection, the affected area should be rested. In particular, weight-bearing joints will require a longer period of rest.

SITE-SPECIFIC APPROACHES

Listed below are approaches to joints that commonly require either aspiration or injection of medication.[1, 4]

1. Shoulder: Subacromial Space
   Use: 1.5-in., 25-gauge needle with 5- to 10-mL syringe
   Insert needle between the posterior tip of the acromion and the head of the humerus. Aim the needle anteriorly towards the coracoid process.

2. Shoulder: Long Head of Biceps Tendon
   Use: 1.5-in., 25-gauge needle with 5-mL syringe
   Flex patient's elbow to a 90° angle and rotate the patient's arm (internally and externally) to palpate the tendon lying within the bicipital groove. Insert needle at the point of maximal tenderness.

3. Knee: Pes Anserine Bursa
   Use: 1.5-in., 25-gauge needle with 5-mL syringe
   Patient should be seated or supine. This bursa is located 2 cm below the medial joint line at the insertion of the sartorius, gracilis, and semitendinous muscles. Insert needle at the point of maximal tenderness.

4. Knee: Prepatellar Bursa
   Use: 1.5-in., 25-gauge needle with 3-mL syringe for anesthesia
   10- to 60-mL syringe with 18-gauge needle for aspiration
   Patient should be supine. This bursa is located between the skin and the patella. While stabilizing the patella with one hand, use the other hand to insert the needle at a 45° angle to the bursa.

5. Knee: Intra-articular
   Use: 1.5-in., 25-gauge needle with 3-mL syringe for anesthesia
   10- to 60-mL syringe with 18-gauge needle for aspiration
   Patient should be seated or supine with the knee slightly flexed. Palpate the superior lateral aspect of the patella and insert the needle into the space between the patella and femur parallel to the inferior border of the patella. Angle the needle to the centre of the patella.

6. Hand: Thumb Abductor or Extensor Tendon Sheath
   Use: 3- to 5-mL syringe with 1- to 1.5in., 25-gauge needle
   Abduct the patient's thumb and palpate along the abductor or extensor tendon for the point of maximal tenderness. Insert needle into the point of maximal tenderness at a 45° angle, aiming away from the hand. Bending the needle at the hub may facilitate insertion of the needle along the course of the tendon.

7. Elbow: Lateral Epicondyle
   Use: 1- to 1.5-in. , 25-gauge needle on 5-mL syringe
   Flex the elbow at a 90° angle. Palpate the lateral epicondyle for the point of maximal tenderness. Insert the needle 1 cm superior and 1 cm distal to this point aiming perpendicular to the skin's surface.

8. Elbow: Intra-articular
   Use: 10- to 60-mL syringe with 18- to 25-gauge needle for aspiration
   Flex the elbow at a 45° angle. Palpate the lateral epicondyle. Insert the needle into the joint space inferior to the lateral epicondyle and superior to the olecranon process of the ulna.

9. Hip: Greater Trochanteric Bursa
   Use: 10-mL syringe with 1.5- or 2-in., 22- to 25-gauge spinal needle
   Patient should be lying on unaffected side. Palpate over the posteroinferior edge of the greater trochanter for the point of maximal tenderness. Insert needle slowly until it gently contacts bone. Then withdraw the needle 0.5 cm to approximate the location of this bursa.

10. Foot: Plantar Fascia
    Use: 1.5-in, 25-gauge needle on 5-mL syringe
    Patient should place the foot with the medial (tibial) side upward. Palpate the area between the calcaneus and the fascia and insert the needle into this space.

SYNOVIAL FLUID ANALYSIS

The aspirated fluid can be analysed for cell count, glucose levels, protein levels, gram stain, bacterial culture, and other tests such as microscopy for crystals if indicated. Blood aspirated from a joint (hemarthrosis) can be a result of both traumatic and non-traumatic causes. Non-traumatic causes include hemophilia, synovioma, pigmented villonodular synovitis, and oral anticoagulant therapy.[3] Table 2 lists some of the key differences between normal and abnormal synovial fluid.

Table 2. Synovial Fluid Analysis 3,5

Findings	Normal	Inflammatory	Septic
Colour	Clear	Yellow to Green	Yellow
Clarity	Transparent	Opaque	Opaque
Viscosity	High	Low	Variable
WBC per mm³	<200	2,000 to 150,000	15,000 to 200,000
PMNs	<25%	>50%	>75%
Mucin clot	Good	Good to poor	Poor

WBC = white blood cells; PMNs = polymorphonuclear cells

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The Assisted Human Reproduction Act:
Regulation of reproductive therapeutics and technology

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The advent of cloning and stem cell technology created much excitement within the scientific community with respect to reproductive research. These new technologies provided promise to infertile couples and reached beyond reproductive issues to offer new opportunities for the cure of such debilitating diseases as cancer, Alzheimer's and Parkinson's.[1] Cloning and stem cell research, however, involves the use of human embryonic tissues and this leads to complex ethical questions. Public fears of the misuse of these technologies and other more longstanding reproductive issues, such as, surrogacy demand the presence of legislation to regulate these activities. In response to such concerns, the federal government introduced Bill-C13 to parliament on May 9, 2002. The bill entitled, the *Assisted Human Reproduction Act*[2] aims at protecting reproductive rights and promoting scientific advances, while remaining within the ethical limits set by current public opinion.

CIHR GUIDELINES FOR STEM CELL RESEARCH:

When Bill-C13 was introduced to parliament many felt that it was long overdue. According to Dr. Patricia Baird (head of the federal Royal Commission on Reproductive Technologies): "Unless we have a proper management system to reassure people that what is being done is ethical, balanced and accountable, I think we could end up not, in fact, using the potentially promising avenues of research that are presenting themselves now." It was evident that regulations were needed and in response, the CIHR (Canadian Institute for Health Research) released a report in June 2001, *Human Stem Cell Research: Opportunities for Health and Ethical Perspectives*.[3] The report provides guidelines that were developed by the Working Group on Stem Cell research chaired by Dr.Janet Rossant, co-head of the department of Development and Fetal Health at Toronto Mount Sinai Hospital. These guidelines must be met in order for researchers working with human stem cells to qualify for CIHR grants. According to the guidelines, it is permitted to use or derive stem cells from embryos, human fetal tissue, amniotic fluid, umbilical cords and placentas, provided that the embryos were created for the purpose of reproduction and are no longer required. The guidelines disallow the creation of human embryos via somatic cell nuclear transfer (cloning), as it was felt that cloning is an inefficient process that leads to abnormalities and is complicated by ethical concerns[4]. The creation of embryos strictly for research purposes and research in which non-human stem cells are combined with a human embryo is also disallowed. In order to ensure that these guidelines are met, a national oversight body was created consisting of experts in stem cell biology and therapeutics, ethics and law, as well as members of the public[3]. Although, these guidelines aim to establish an ethical code for stem cell research, they are not legally binding and legislation is needed to prevent the misuse of this new technology.

THE ASSISTED HUMAN REPRODUCTION ACT:

Introduction:

The preparation of legislation dealing with reproductive therapeutics and technology involved a lengthy process beginning in 1989 with the creation of the Royal Commission on New Reproductive Technologies. In 1996, Bill C-475 (the *Human Reproductive and Genetic Technologies Act*) was introduced to parliament. The bill was highly criticized for including only prohibited actions and for being difficult to amend, an important concern considering the numerous scientific developments expected to occur in the coming years[6]. Bill C-47 was never passed and it was not until 2002, that the federal government presented a new bill, Bill C-13 (the *Assisted Human Reproduction Act*). It is apparent that the guidelines for stem cell research developed by the CIHR significantly influenced this act; sections relating to stem cell research closely reflect the aims of the CIHR. However, Bill-C13 addresses a wider range of reproductive health issues. The Bill [section 2] stresses that the rights of children born through the application of reproductive technology is paramount. Also emphasized is that the principle of free and informed consent must be promoted and applied as a fundamental condition for the use of human reproductive technologies. The legislation aims to

protect Canadians from the commercial exploitation of women's and men's reproductive capabilities and to preserve human individuality, diversity and the integrity of the genome.

Prohibited activities:

As expected, the Bill bans the creation of human clones for any reason. Also prohibited is the *in vitro* creation of an embryo for any purpose other than creating a human being. It also prohibits the introduction into human embryos of germ-line mutations capable of being transmitted to descendants. Research involving the production of human hybrids (human ovum combined with non-human sperm or vice versa [section 3(1)]) and human chimeras (an embryo into which a cell of any non-human life form has been introduced; or an embryo that consists of cells of more than one embryo, fetus or human being [section 3(1)]) is banned [section 5(1)].

Although the above measures are generally widely supported, the stiffling of the commercialiazation of assisted reproductive technology is more controversial. The act makes it illegal to offer payment to surrogate mothers or to counsel or induce someone to be a surrogate mother[section 6]. It is also illegal to purchase, sell or provide goods and services in return for ova, sperm, *in vitro* embryos and human cells or genes [Section 7]. Section 5(1(e)), which prohibits both the identification of the sex of an *in vitro* embryo (except for the purpose of identifying a sex-linked disorder) and any procedure that ensures or increases the probability that an embryo will be of a given sex, is felt by some to infringe on a person's freedom of choice.

Controlled Activities and Privacy Issues:

The act states that a license must be obtained for a person to undertake a controlled activity. The controlled activities include the alteration, manipulation or treatment of any reproductive material [section 10(1)] or *in vitro* embryo [section 10(2)]; the obtaining, storage, transfer and destruction of gametes and embryos [section 10(3)] and the participation in research involving human transgenics [section 11(1)]. The law would, therefore, allow for embryonic and adult stem cell research and for surplus embryos created for *in vitro* fertilization to be used for medical research.. However, licensees may only make use of reproductive material or *in vitro* embryos after obtaining the fully informed written consent of the donor of these materials and embryos [section 8(1)]. Once consent is given, a licensee must collect a donor's medical information [section 14(1)] and give the children born through the donated reproductive material access to this material [section 18(3)]. This information may also be disclosed to an individual or organization for scientific research or statistical purposes [section 15(5)]. The identity of the donor must never be disclosed unless this person has given explicit written consent [section 15(4)]. A licensee is allowed to reimburse surrogate mothers and donors of sperm, ovum or *in vitro* embryos of expenditures incurred in the course of a controlled activity[section 12(1)].

Assisted Human Reproduction Agency of Canada:

To regulate reproductive technologies and therapeutics, Bill C-13 states that an Assisted Human Reproduction Agency (AHRA) is to be created as an entity separate from Health Canada. According to the bill, the AHRA is responsible for reporting to the Ministry of Health and consists of up to 13 members of the Board of Directors reflecting a range of backgrounds and disciplines [section 26(2)]. It would be given numerous responsibilities including the issuance of licenses for controlled activities; designating inspectors and analysts to enforce the Act; monitoring and evaluating developments in assisted human reproduction (AHR); collecting, analyzing and managing health reporting information relating to controlled activities and reporting any risk factors associated with infertility or AHR [section 24(1)]. The AHRA would also maintain a donor and offspring registry, and set the parameters for stem cell and other reproductive research.

Conclusion:

When Bill-C13 was introduced, it was well received by the scientific community. A majority of scientists, including Dr. Barbara Beckett (of the Stem Cell Network, representing university-based scientists across the country), feel that the act allows for the progress of science in a responsible and ethical way. However, pro-life groups, supported by the Canadian Alliance party, are strongly opposed to the use of embryos for research purposes. The Campaign Life Coalition is concerned that the *Assisted Human Reproduction Act* reflects the CIHR guidelines rather than the views of MPs. It insists that stem cell research should only be conducted with stem cells isolated from adult tissues. Scientists argue that adult stem cells are harder to work with and that it is unclear whether adult stem cells have the same potential as embryonic stem cells to form cells from every tissue in the body. Controversy also surrounds the banning of commercialized AHR. Doctors and lawyers who deal with infertile couples desperate to conceive fear that there will be a resulting decrease in the availability of ova, sperm and surrogate mothers, subsequently promoting illegal AHR activities[6,7].

Like Canada, the U.S. permits federal funding of stem cell research using embryos discarded from fertility centres. Currently, the George Bush administration wants the Senate to pass laws banning human cloning for any purposes. The United Kingdom, however, has taken a different stance. Although the House of Lords has passed a bill making reproductive cloning illegal, therapeutic cloning to cure illness was not disallowed[6]. Has Canada chosen the right approach to deal with the often controversial issues surrounding reproductive health? Numerous questions have arisen since the *Assisted Human Reproduction Act* was introduced to parliament: does the Act accurately reflect public opinion? Will scientists comply with the regulations? Will it ensure that there are no financial incentives or coercion? How will donors feel about the Act? Will there be enough donors to meet the demands? If not, how should the government respond? As the bill undergoes revision, these concerns are hopefully being addressed. Nevertheless, with the potentially dangerous consequences of the misuse of reproductive technologies, an imperfect law may be better than no law at all.

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Risk Factors in Osteoarthritis

Anna Labuda, Meds 2005

Osteoarthritis affects a vast segment of our population and is associated with significant disability. While some risk factors have been clearly established, others receive less support. Recognized risk factors are usually classified as local or systemic. Naturally however, one may predispose to, result from, or interact with the other. It is important to keep in my mind that ultimately, the goal of risk factor studies is to assist with the development of strategies against potentially preventable risk factors. Prospective preventable local and systemic risk factors reviewed in this article include occupational factors, sports injuries, past acute joint injury, obesity and nutritional factors. Additionally, this article provides a brief overview of other risk factors, which are less likely to become targets of intervention. Some of these include the role of muscle weakness, proprioception problems, estrogen and ethnicity in the development of osteoarthritis.

Arthritis, which refers to more than 100 different conditions, is the leading debilitating disease in the United States.[1,2] Osteoarthritis (OA) is the most common form of arthritis, affecting 21 million people.[1] As it is primarily a disease of aging, OA will become increasingly more prevalent in the near future, due to maturation of the baby boomers. OA is responsible for more difficulty walking and climbing stairs than any other disease, and it is the primary reason for total hip and knee replacements.[3] Over the age of 50, females are more affected with knee, foot and hand osteoarthritis than males; conversely most studies show OA of the hip to be more frequent in men.[3] The impact of arthritis on patients' lives is tremendous. It includes decreased health-related quality of life, activity limitations, work disability, role limitations, economic consequences, as well as psychological consequences, social consequences and life strain.[2] The aim of primary OA prevention is to reduce these negative outcomes, however, for this to be feasible and successful, the risk factors for OA must be well-identified. To date, a large number of risk factors have been identified, which generally fall into one of two classes, local or systemic.[3-5]

LOCAL RISK FACTORS

Physical activity, including occupational factors and sports participation, has been linked to OA development via non-physiologic joint loading or injury.[2,4] It has been found that occupations in which workers do certain physical activities repetitively increase the risk for OA in those joints.[3,4] At least one study showed that a job involving medium physical demands and knee bending doubled the risk of knee OA, in comparison to a job with minimal (i.e. sedentary) physical demand and no knee bending.[6] Other studies have found correlations between incidence of knee OA and duration of knee bending activities in various professions, such as carpenters and painters; squatting has also been identified as a risk factor for knee OA in males.[4,7] Other occupational activities, such as stair and ladder climbing, standing, and lifting heavy objects, have been inconsistently associated with increased OA incidence.[7] Similarly, participation in certain sports may increase the risk for osteoarthritis. These include high intensity activities, with direct impact of the joint via contact with other players, playing surfaces, or equipment.[3] Football and soccer are but two examples of such sports. On the other hand, moderate, regular running has a low to non-existent associated risk of osteoarthritis.[3]

Many studies have shown an association between knee injuries and the development of knee OA.[4] In a recent longitudinal study, it was found that both knee and hip OA were more likely to occur in those individuals who had suffered a joint injury in young adulthood.[8] Even though the exact nature of the relationship between joint injuries and OA is unclear, it is apparent that articular surface fractures, joint dislocations, ligament and meniscal tears do increase the risk for post-traumatic OA.[3] It has been hypothesized that possible risk factors for post-injury OA devel-

opment may include residual joint instability or misalignment, articular surface discrepancy, increased body weight, and high level of activity.[3]

SYSTEMIC FACTORS

One of the best described risk factors for OA is obesity.[5] Overweight individuals have an increased risk for knee OA, and in most studies, this association is more marked in women than men.[3,5] It has been shown that weight increase in women, in the mid to later years, definitely affects the risk of onset of osteoarthritis.[10] The association of hip OA and obesity is less marked than that for knee OA; unilateral hip OA is not clearly associated with obesity, while bilateral hip OA is.[3] It is thought that weight could possibly act in several ways to predispose an individual to OA. Most of the increased risk for OA is likely explained by the overloading of the joints, which can lead to cartilage breakdown, failure of ligaments and other supports.[3,5] Furthermore, adipose tissue could predispose underlying bone and cartilage to OA via production of atypical concentrations of certain growth factors an hormones.[5] It is of no surprise than that in obese individuals, weight loss had been associated with reduced risk for osteoarthritis.[10]

Though it has been shown that nutritional factors can increase the risk of established knee OA, no evidence has been found that these factors influence the risk of development of new onset OA.[12] In fact, there are very few clinical trials examining the association between diet and OA; the existing trials have primarily focused on vitamins C, D and E.[5] Evidence does exist however that indicates prolonged exposure to oxidants contributes to development of several "aging" diseases, such as osteoarthritis.[3] As oxygen radicals are recognized for destruction of cartilage and connective tissue, research directed at OA prevention has focused on the use of anti-oxidant vitamins A, C and E; vitamin D may also play an important role, via bone mineralization and cell differentiation.[5,13]

In addition to the above discussed potentially preventable risk factors of OA, several other local and systemic factors have been linked to osteoarthritis development. Locally, knee laxity, which is the displacement of the tibia with respect to the femur, may precede OA development and predispose to the disease.[3,4] Problems of proprioception, which is the conscious and unconscious perception of joint position and movement, may also precede OA development.[3,4] Congenital dislocations and acetabular dysplasia have been definitely linked to premature osteoarthritis of the hip.[3] Some have also proposed that quadriceps weakness may increase the risk of knee OA.[3,4] Finally, a recent study implicated past surgery as a risk factor for OA, by showing an increased risk of knee osteoarthritis 21 years after open menisectomy as compared to controls.[9] In terms of systemic risk factors, the increase in incidence of OA among post-menopausal women has suggested estradiol deficiency as a risk factor for OA.[3,11] However, there is currently no consensus on this, as estradiol has been implicated as both increasing and decreasing the risk for OA.[11] It is evident that heritability plays a crucial role in development of OA, at least in some subgroups.[5] In fact, genetics are responsible for over 50% of OA cases in the hips and hands.[14] Finally, ethnic differences in the incidence of hip and knee

osteoarthritis have also been studied, and the results are conflicting.[3] Above all, age is the most powerful, and the least preventable, risk factor for the development of OA.[1]

Osteoarthritis affects a large percentage of the population and leads to significant disability. In some cases, joint replacement may be the only hope for an improved quality of life. Following the models of OA pathogenesis, risk factors are usually classified as local or systemic. Naturally however, one may predispose to, result from, or interact with the other. Some risk factors, such as increasing age, obesity, past joint injury, occupational factors and developmental abnormalities have been extensively studied and well established. Other risk factors, such as muscle weakness, role of estrogen and ethnicity have received less support. Furthermore, knowledge is lacking regarding the specific influence of many of the risk factors on the key events in OA: the onset of OA, progression of the disease, and disability in those with OA. Ultimately however, the goal of risk factor studies is to assist with the development of strategies against potentially preventable risk factors.

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Forensic Medicine in China

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The Chinese tradition of forensic medicine developed separately from both the Western tradition and medical practice within China. Unique philosophical and societal factors contributed to the early rise and meticulous practices. Beginning with early writings over two thousand years ago, the practice of forensic medical investigation has been highly scientific and played a key role in the investigation of deaths. The Chinese are credited with developing the first systematic treatise on forensic medicine in the world. Only after European practices of autopsy did the practice of forensic medicine in China become fully integrated into the medical system.

INTRODUCTION

Forensic medicine has been gaining prominence in recent times with the rise of molecular techniques. In Western tradition, the autopsy has formed a major component of the post-mortem investigation and is a central skill in a pathologist's armamentarium. However, an entirely different practice arose in China long before parallel activities in Western medicine. Rather than developing alongside medicine as a whole, forensic medicine and investigation in China evolved outside the domain of medical practitioners and was only integrated at the beginning of the twentieth century.

INFLUENCES ON CHINESE FORENSIC MEDICINE

Several factors influenced the early rise and structure of Chinese forensic medicine. From the beginning, forensic investigations were essentially separate from the medical profession.[3] Chinese physicians were of a low class and not usually called upon to give a medical opinion - they dealt with the living and not the dead.[3] Furthermore, the wu tso (a sort of slave-class undertaker) and the tso pho (a woman, usually the midwife, who examined female corpses) had no medical training.[3]

In contrast to the West, Chinese philosophy was not based in religious considerations, and therefore the idea of a higher form of justice was not prominent. One school in particular is associated with the development of forensics. The legist school, originating over 2000 years ago, held that the population at large was stupid, predisposed to evil,[8] and acted from largely selfish motives such that all laws had to be clearly stated and not subject to interpretation.[3] Included was a moral imperative to clear the names of the innocent.[3] The legist school had become the official policy of the Qin state (221 BC). It is not hard to see how such a belief system would promote detailed investigation to ensure that the correct person was punished to the full extent of the law.

Another factor was the highly organized political structure of Chinese government. Each county had a sub-magistrate who was in charge of the victim, living or dead.[5] His function also included searching and arresting the accused.[5] Slaves (wu tso) were brought in to do the drudge work, and doctors were consulted in cases of disease.[5] As the system evolved, careful documentation had to be made for every case and signed off by the presiding official as being factually correct.[3,5]

An important feature of Chinese forensic medicine is the exclusion of dissection and the lack of internal examination. The Chinese view of the body and its disorders was built on an elemental theory, and like other cultures of the time, rejected the idea that dissection was necessary for an understanding of the body.[6] There was also the belief that mutilation continued after death, which impaired the development of surgery and may have also contributed to the lack of internal examination.[1] In any event, the energies of the investigators were focused on detailed external observations.

EARLY DEVELOPMENTS AND WRITINGS

The first writings on forensic investigation date back to the time of the Warring States (475-21 BC) with "The Book of Rites" and "Lü Shi Chunqiu" which urged officials to view injuries, analyze findings, and judge cases.[5] The next key period was the Qin State (252-21 BC) with "Dialogue to Law" and "Feng Zhen Shi." These works were concerned with criminalistics and forensic.[5] Although findings such as the tell-tale neck marks made by hanging were known,[5] other investigations were clearly hampered by a lack of medical knowledge.[3]

Forensic investigation in this period followed a highly scientific approach, as demonstrated by story of Zhang Ju and the pigs.[5] Zhang Ju was a magistrate (sometime between 27-97 AD) who used two pigs to demonstrate the difference between pre and post-mortem burning. It was found that the living pig had powder and debris in the mouth and nose. By this demonstration, he was able to show that the accused was lying.[5]

THE SONG DYNASTY

The most significant period in the development of forensic medicine in China was the period of the Song Dynasty (960-1287 AD). By 1000 AD, all suspicious deaths were examined, with violent deaths reported and re-examined. By 1174 AD, a standard form to be filed in triplicate including such information as the name of the prosecution, presiding official at the inquest, the assistant, the warrant, time of arrival at the scene, number of wounds on the deceased, and the cause of death.[5] At this point, the wu tso removed the body, anointed it with wine or vinegar to discover the injuries, and marked the wounds under supervision.[3,5] Doctors were brought in for examinations of the living.[5] Anterior and posterior diagrams were introduced in 1204 so that the coroner could mark wounds accurately.[3]

SUNG TZ'U AND "THE WASHING AWAY OF WRONGS"

It was during the Song Dynasty that the definitive work of forensic medicine was written. Sung Tz'u was a public official who consolidated all previous learning and practice in the area into a single systematic treatise on the subject in 1247 AD. The work devotes a section to nearly every type of death with case studies and approaches to the investigation of each.[2] From the very beginning of the work, a meticulous attitude is stressed.

If death has just taken place, first examine the top of the head, and the back, the ears, the nostrils, the throat, &c., and all places where anything might be inserted... Moreover, deaths from self-strangulation, throat-cutting, taking poison, burning, drowning, and the like, produce very different results, and only the most minute investigation of every little detail will ensure a complete and reliable verdict.[2]

Among the included theory and techniques are two noteworthy examples. The first concerns the concept of "vital spots," places on the body where it is particularly susceptible to internal injury and death without obvious external signs. There were 16 anteriorly and 6 posteriorly. Modern medicine has confirmed many of these, which include the fontanelles of the skull, occipital or cervical regions, just superior to the sternum, the perineal region, and the scrotum.[3]

Numerous techniques are described, including the technique of making wounds, severe contusions and bruises appear on the surface of the body. Bones were prepared by burning off the flesh and then viewed on a bright day under a red-coloured umbrella. Bone bruises would show red traces, and fracture edges would have a red halo. This method also distinguished pre and post-mortem fractures because there would be no red on post-mortem fractures. The principle seems to be similar to modern infra-red lighting.[3]

MORE RECENT TRENDS

After the publication of Sun Tz'u's work, it was recopied many times. Together with a later work "The Cancelling of Wrongs" written in 1308, translations appeared in Japan and Korea, forming the basis of forensic medicine there.[3] China preferred Sung Tz'u's work and it was the definitive manual up until 1927.[6] The work was so comprehensive that it basically shut down further experimentation in the field, much like Galen's work did for Western medicine in the Middle Ages.[6] In fact, new findings could not be accepted if they contradicted the text.[5]

The Xin Hai Revolution of 1911 changed the situation significantly. The Criminal Procedure Law of 1912 permitted internal examination (heretofore banned).[5] It was at this point that the medical profession became involved in examinations of the dead. While either the coroner or doctor could perform the external examination, only the doctor could perform the autopsy.[5] The demand for such investigation became so great that the first department devoted to instruction of autopsy techniques was founded in 1930 by Lin Ji, a physician who studied in Germany.[5] At the peak of the period, every physician with one year of hospital experience was trained to be a senior pathologist for serving the judicial system.[5] Others from senior middle schools were tapped to become technicians for the courts. Coroners received 6 months of intensive training.[5]

The founding of the Republic in 1949 ushered in a period where the use of forensic medicine waxed and waned repeatedly, and is currently not as prominent as it was in the first half of the twentieth century.[5]

COMPARISON WITH EUROPEAN FORENSIC MEDICINE

Forensic medicine was largely unknown in the practice of Greece and Rome, and had a limited use in Hellenistic Egypt. The Justinian Code (529-64 AD) urged the cooperation of medical experts in various legal problems such as pregnancy, sterility, impotence, legitimacy, rape, poisoning, and mental disease.[3] This is regarded as the highest point in forensic medicine prior to the Middle Ages, but no systematic treatise existed.[3]

Similar to the sub-magistrate of early Chinese investigation, England had a "crowner" in each county investigating suspicious deaths by 1194. Bologna was the first city to use expert medical investigation in all criminal offences against persons in 1252. However, the role of the physician was limited to determining whether a wound was mortal or whether they were caused pre or post-mortem.

There is a lack of any reference to medico-legal doctors through the Middle Ages, and no developments are recorded until

1507. In the Germanic territories, expert medical testimony was used to guide verdicts in murder, wounding, poisoning, hanging, drowning and other such crimes. As with the rest of medicine, Vesalius' "De fabrica humani corporis (1543)" revolutionized the situation and put the tools of dissection into the physicians' hands rather than the prosecutors. The first comprehensive text on forensic medicine was printed in 1602 by Fedele followed by "Quaestiones medico-legales" by Zacchia (1621-35) which marked the beginning of forensic medicine in Europe.[3] It has been theorized that the lack of a comprehensive text on forensic medicine in Europe spurred the development of the field as doctors sought to explain the mechanics of crime.[6]

CONCLUSION

The Chinese tradition of forensic medicine is a rich one beginning much earlier than the tradition in Western medicine. From very early on, it was a highly scientific practice driven by the desire to ensure that only the guilty were punished for crimes. In contrast to Western practices, which included physicians early on, the Chinese tradition only included doctors in post-mortem examinations once Western practices were introduced into the Chinese system. Indeed, the emphasis placed on external examination of the body and the scene of the crime is very similar to the approach used in this country today.

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Assessment of glenohumeral instability and indications for surgical repair

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The shoulder is an extremely common joint to injure despite the stabilization it receives from both static and dynamic structures. Shoulder instability can be identified with a complete physical exam with careful attention to specific tests for instability. The most severe form of shoulder instability is dislocation. A dislocation commonly occurs in young males, especially athletes, when a traumatic force is applied to the shoulder while it is abducted and externally rotated. Once the joint is reduced, several factors such as the person's age and the number of times the shoulder has been dislocated must considered in the determination of whether conservative or surgical treatment should be attempted. If surgical stabilization is indicated, serious consideration should be given to arthroscopic stabilization due to its increasing reliability and decreased morbidity compared to an open procedure.

INTRODUCTION

The shoulder represents a ball and socket synovial joint, formed by the articulation of the head of the humerus with the glenoid cavity of the scapula. The shoulder is the most commonly dislocated joint of the body[1] due to the lack of restraint placed on the shoulder joint, and the high potential for injury with an active lifestyle.

The glenohumeral joint is stabilized by static and dynamic forces. Static forces include the labrum, joint capsule, rotator interval, and glenohumeral ligaments. The fibrocartilagenous labrum attaches to the glenoid rim and serves to increase the glenoid's depth and act as a shock absorber[2]. It is important to note that the humeral head has a much larger diameter and surface area compared to that of the glenoid[2]. This is responsible for the increased range of motion possible in the shoulder joint. The fibrous joint capsule attaches medially to the glenoid cavity and laterally to the anatomic neck of the humerus[3]. The rotator interval is composed of the leading edge of the supraspinatus and the superior edge of the subscapularis muscles[4]. Finally, the glenohumeral ligaments act to stabilize the shoulder joint. These include the superior, medial and inferior glenohumeral ligaments, and the coracohumeral ligament[3].

Dynamic forces include the rotator cuff (the "SITS" muscles, consisting of supraspinatus, infraspinatus, teres minor, and subscapularis) and the scapular stabilizers (serratus anterior, the pectoralis and latissimus dorsi)[2].

The term shoulder instability encompasses laxity, subluxation, and dislocation. Shoulder laxity describes an inherent looseness in the static forces stabilizing the shoulder. Shoulder subluxation implies that the relationships between the bones of the shoulder have changed however there is still contact between the joint surfaces. Shoulder dislocation occurs when the humeral head is completely put out of joint.[5]

Many pathological lesions have been identified in traumatic and atraumatic shoulder instability. The classical traumatic one is the Bankart lesion, in which the anterior inferior labrum and the inferior glenohumeral ligament detach from the glenoid rim[6]. A Hill-Sacks lesion is a defect on the posterolateral aspect of the humeral head. This is due to compression of the humeral head against the anterior glenoid rim during dislocation[6].

NATURAL HISTORY

The exact prevalence of shoulder instability has been difficult to accurately determine in the general population. It is estimated that 4-8% of the injuries sustained by an active population are shoulder related[7]. Shoulder instability commonly presents in its most severe form as a shoulder dislocation.

The majority of shoulder dislocations occur in patients during their 20's, and are equally likely to occur in either arm independent of handedness[8]. These dislocations are generally classified by the direction of the dislocation (anterior, posterior, inferior or multidirectional). Approximately 85-90% of these patients

are male and 95% of these dislocations are anterior dislocations[8].

Anterior dislocations generally occur when a force is applied to the shoulder when it is abducted and externally rotated. Other possible mechanisms include a direct blow to the shoulder, falling with the arm outstretched, a seizure or electrocution[8]. The chance of a recurrent shoulder dislocation is extremely high in those younger than 20 years, and much less likely in those older than 40 years[2].

A patient with an anterior dislocation generally presents with their arm slightly abducted and internal rotated with pain present if the arm is moved[7]. The patient may report transient loss of sensation in the arm, with numbness and tingling.

PHYSICAL EXAM

A full physical exam of the shoulder should involve careful observation of the affected and normal shoulder, palpation of bony and muscular landmarks, passive and active ranges of motion, neurovascular exam (especially of the axillary nerve, which if damaged may cause loss of sensation over the lateral shoulder and weakness of the deltoid), and a screening exam of the elbow and cervical spine.

There are also specific tests that relate to shoulder instability. Although these tests are not necessary for the diagnosis of a shoulder dislocation, they provide important prognostic information for future dislocation, and may influence the management of a subluxation or dislocation once it has occurred[5]. Some of the most common tests include:

1. Load and Shift test

The patient is placed in the supine position so that their scapula is centered over the edge of the examining table. The arm is grasped with one hand near the humeral head and the other hand approximately half way down the humerus. The arm is positioned in 20 degrees of abduction and pulled with the distal hand while the proximal hand attempts to shift the humeral head. This is highly specific (100%) for shoulder instability, but not very sensitive (ranging from 8% for inferior instability to 50% for anterior stability)[5,9].

2. Sulcus sign

This test primarily analyses the superior glenohumeral ligament. The patient is seated with their arms relaxed by their sides. Their elbow is grasped and pulled inferiorly. A positive test is established by the appearance of a dimple in the subacromial region. A dimple greater than 1cm has a sensitivity of 72% and a specificity of 85% for shoulder instability[5].

3. Apprehension/Augmentation/Relocation test

The patient is supine with their scapula centered over the edge of the examining table. Their arm is positioned in 90 degrees abduction, 90 degrees of flexion at the elbow, and then externally rotated. If the patient reports a sensation of an impending dislocation then the Apprehension test is positive. If a sensation of dislocation is enhanced with the application of an anterior force on the humeral head, then the Augmentation test is positive, and if this sensation is relieved with a posterior force applied to the humeral head then the relocation test was positive. The augmentation and relocation test have a specificity of 100%; sensitivity for the augmentation test is 68% and for the relocation test is 57%[5].

Physical exam under anesthesia is considered the gold standard for assessing the degree of shoulder instability. Results of a physical exam of the shoulder joint under anesthesia demonstrated a sensitivity of 100% and a specificity of 93% in one trial of 55 shoulders clinically diagnosed with shoulder instability[10].

RADIOLOGY

Standard X-Ray views of a suspected dislocation include anteroposterior views of the shoulder internally and externally rotated, an axillary view (especially if posterior dislocation is suspected), a modified axillary view (especially if there is anterior instability) and the Stryker notch view (important for assessing for a Hill-Sachs lesion)[11]. More accurate labral imaging may be done with the use of MRI.

TREATMENT AND SURGICAL OPTIONS

There are two techniques for the reduction of an anterior dislocation. The modified Kocher method is carried out by placing the patient supine and applying traction on the humerus while the arm is in an adducted, externally rotated and flexed position[12]. If this does not spontaneous reduce, then the arm is internally rotated and further adducted. In the Stimson technique the patient is prone and a weight is placed on the dislocated arm[12]. Within 15 minutes the humerus returns to position with the aid of gravity.

Conservative treatment consists of rest and immobilization, the use of NSAID's and ice for symptomatic relief, followed by rehabilitation. Physiotherapy generally consists of range of motion exercises, isometric/isotonic strengthening, and finally activity/sport specific activities[7].

Indications for a surgical approach after the initial reduction include the following: the initial dislocation where a second occurrence would be dangerous (for example athletes, construction workers, and mountain climbers), a second dislocation after the initial one was managed conservatively, continued pain from glenohumeral subluxation after conservative treatment, a Hill-Sacks lesion, and a torn rotator cuff with a greater tuberosity fracture.[2,6,13] There is also some support for initial surgical stabilization of the shoulder if the person is young (less than 25), if the initial trauma causing the dislocation was minimal, or if general ligamentous laxity is present[14].

Once the decision has been made to surgically stabilize the shoulder, consideration should be given as to whether an open or arthroscopic procedure is appropriate. Arthroscopic repair is theoretically ideal due to less time in the operating room, less blood loss, a shorter hospital stay and fewer post-operative complications. However, initial studies found much higher dislocation recurrence rates of between 13 to 70% with arthroscopic repair versus 0 to 30% with open repairs[2]. This limited the use of arthroscopic repair and patient's willingness to undergo arthroscopic stabilization.

Arthroscopic repair has since become much more reliable. This is due to better techniques, instruments, surgical experience and post-operating room rehabilitation.[2,13] One study found that open versus arthroscopic stabilization had equivalent recurrent dislocations if the procedure was selected based on examination under anesthesia, and if diagnostic arthroscopy was used to ensure that no contraindications to arthroscopy existed[15]. Such

contraindications include glenoid bone loss, attenuated capsulo-labral tissue, engaging Hill Sachs lesion, rotator interval lesions, and the absence of a Bankart lesion[15].

CONCLUSION

Shoulder instability is a complex problem that plagues many young athletes, and is a common traumatic shoulder injury. A careful history and physical exam, with proper imaging will lead to an accurate diagnosis and assist in determining the appropriate treatment course. It is important to recognize the situations in which surgical stabilization may be appropriate. If a suitably experienced surgeon is available, arthroscopic glenohumeral stabilization may now be an appropriate intervention.

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Early and late cardiac involvement in rheumatic disorders

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This paper provides an overview of selected rheumatic conditions and their extraarticular features with a focus on cardiac involvement.

Both seropositive and seronegative arthropathies may present with clinically appreciable extraarticular features, but the symptoms are often overlooked as the much more dominant joint troubles tend to draw the clinician's attention. Extraarticular features including cardiac, pulmonary, neurologic, occular, and vasculitic disease can be a considerable source of morbidity, and should be excluded in the assessment of a pathologic joint.[1,2,3]

INFLAMMATORY ARTHROPATHIES:

Affecting approximately 0.3 - 0.5% of males and 1.5 - 1.8% of females, an inflammatory arthropathy may occur at any age but has a peak incidence in the fifth decade of life.[1,4] Patients with a polyinflammatory arthritis such as rheumatoid arthritis typically present with complaints of joint pain, swelling, deformity, and morning stiffness. Commonly affected joints include MTPs, subtalars, ankles, knees, shoulders, elbows, wrists, MCPs, and PIPs. Joint destruction occurs early; 70% show radiologic signs of damage within 3 years of onset.[4] On laboratory investigation, 70 - 80% will be IgM rheumatoid factor positive. Other markers of the disease include elevated ESR, CRP, immune complex assays, and platelet counts.[1]

Extraarticular features tend to be more prevalent in males and seropositives. Common constitutional features include fatigue, weight loss, and fever. Subcutaneous and intracutaneous nodules occur in 20 - 30% of patients; nodules may also develop in other tissues including the eye, pleura, pericardium, and parenchyma of the lungs and heart.[2] The latter may lead to dysfunction of the heart valves and conducting tissue. Evidence of pericarditis is often found in patients with rheumatoid arthritis but is rarely symptomatic; a pericardial rub can be heard in up to 30% of patients, and a pericardial effusion can be identified echocardiographically in 14 - 50%.[2,5] In extremis, pericarditis can lead to cardiac tamponade, requiring urgent surgical intervention.[5] Vasculitis is seen in 20% of patients, which may cause circulatory disturbances leading to renal dysfunction, neuropathies, and coronary ischemia.[1,2] Other extraarticular manifestations of inflammatory arthritis have been described in bone, renal, liver, lung, and lymph tissue.[1,2,4]

SERONEGATIVE ARTHROPATHIES:

The seronegative arthropathies are a group of diseases that can present with sacroiliitis, spondylitis, peripheral arthritides, uveitis, or other extraarticular manifestations. They are associated with the HLA-B27 allele, with a prevalence estimated at 7% in the North American Caucasian population.[1] Diseases in this category include ankylosing spondylitis, Reiter's syndrome, reactive arthritis, psoriatic arthritis, juvenile spondyloarthropathy, enteropathic arthritis (not B27 positive), and undifferentiated spondyloarthropathy.

Ankylosing spondylitis presents predominantly in males under the age of 40 with inflammatory joint symptoms of the low back progressing to nil ROM as the spine fuses. Up to 40% of these patients will have peripheral joint involvement and/or enthesopathy.[2] Cardiovascular disease develops in up to 50% of adult patients with ankylosing spondylitis.[7,8] Diastolic abnormalities apparent on echocardiogram are the most common early manifestation, most likely caused by increased connective tissue deposition in the myocardium.[6] Aortic regurgitation secondary to aortitis has been found in approximately 1 per cent of patients, usually in those with advanced severe disease. Atrioventricular block is also a recognized association.[7]

The remainder of the seronegative arthropathies (except adult Still's disease) are not commonly associated with cardiac involvement and will not be discussed further in this review.

PRESENTATION OF CARDIAC INVOLVEMENT:

It may be difficult to differentiate primary cardiac disease from that of rheumatic involvement, particularly when this extraarticular feature presents before the arthritic disease reveals itself. The clinical picture is identical in many cases. There are therefore a number of clinical situations that must be recognized in order to appropriately investigate and successfully treat the underlying disease:

- Cases of valvulopathy secondary to ankylosing spondylitis preceding the more characteristic symptoms of the disease have been reported.[8,9] Therefore, in any young male presenting with isolated aortic or mitral regurgitation, seronegative arthropathy must be in the differential diagnosis.
- 20% of rheumatoid arthritis patients will have vasculitis. A percentage of them will have coronary artery involvement, which can result in angina.[1] For these patients, a course of steroids and immunosuppressants may improve symptoms, providing an alternative to more invasive revascularization techniques.
- Similar consideration is necessary for late onset cardiac involvement. Up to 20% of rheumatoid arthritis patients with peripheral joint involvement for more than 30 years have significant aortic regurgitation.[1] These patients can be identified and treated before the onset of significant valvulopathy and cardiomyopathy to avoid potential complications and more invasive treatments (eg. beating-heart annuloplasty vs. valve replacement).
- Finally, when dealing with an arthropathy, one must rule out cardiac causes. Musculoskeletal involvement of bacterial endocarditis (BE) can mimic a rheumatic condition: one study reports that 74% of BE patients experienced myalgia and arthralgia, with the most common articular symptoms being polyarticular and symmetric, affecting both the large and small joints. 17% of the patients even had a positive test for rheumatoid factor.[10]

In the diagnosis and treatment of rheumatic conditions, a thorough investigation including a comprehensive review of systems and physical examination is essential for an accurate assessment and interpretation of the findings. Extraarticular features can assist or mislead the clinician, potentially creating unnecessary morbidity and mortality. Care must be taken to ensure that the entire picture is being seen.

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Arthropathy of Hemochromatosis

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Hemochromatosis (HC) is an inherited multisystem disorder produced by the excessive accumulation of iron in visceral organs and the musculoskeletal system, leading to cellular damage. Arthritic changes associated with HC often precede well recognized features such as diabetes, skin pigmentation and cirrhosis. Arthritis has been shown to affect up to 82% of patients with HC and is the single greatest cause of poor quality of life in these patients. The arthropathy of HC results from a non-inflammatory degenerative process that is often misdiagnosed as osteoarthritis, rheumatoid arthritis or calcium pyrophosphate deposition. However, the arthropathy can be differentiated based on its distinctive pattern of joint involvement, radiographic features and systemic manifestations. The mainstay of treatment for HC is therapeutic phlebotomy which is used to deplete the body of excess iron stores. Although this treatment is effective for visceral and cutaneous pathology, arthropathy does not respond to phlebotomy. On average, complaints of joint pain and stiffness precede the diagnosis of HC by 10 years. This represents a decade of missed opportunity for diagnosis and possible prevention of joint destruction and systemic disease. Therefore, screening of high risk populations for detection of HC and early initiation of treatment is the best strategy for delaying or preventing the complications of HC.

INTRODUCTION

Hemochromatosis (HC) is the most common inherited metabolic disorder in the Western world.[1] Although the triad of diabetes, cirrhosis and skin pigmentation classically was used to diagnose HC, these features actually may be late manifestations of the disease.[1,2] In reality, patients often present years sooner with complaints of fatigue, abdominal pain and joint tenderness.[3]

Iron homeostasis in the body is essential as cellular dysfunction can result from either excess or deficient iron stores.[4] Since there are no appreciable means of eliminating iron, regulating absorption to meet bodily requirements is essential to ensure adequate iron stores.[4] HC is a disorder in which iron absorption is in excess of the body's requirements. Overtime this leads to saturation of serum transferrin, deposition in parenchymal cells and cellular toxicity.[4] The organs that are primarily affected are the liver, pancreas, heart, gonads, skin and the joints; the latter of which will be the focus of this paper.[3]

Hereditary HC (HHC) is the most common genetic disorder, with a reported prevalence as high as 1 in 200, primarily in whites of northern European and Australian descent.[3,4,5] HHC is an autosomal recessive disorder, resulting from homozygosity of a mutated form of the HFE gene on chromosome 6.[4] HFE mutations have been shown to increase both intestinal iron absorption and uptake into tissues.[4] The C282Y mutation is the most common, with a frequency of 12%.[4,5]

CLINICAL PRESENTATION

With the advent of genetic screening and earlier detection in recent years, presentation with diabetes, skin pigmentation and cirrhosis has become less common.[3,6] Correspondingly, Adams et al[3] reported that abdominal discomfort, joint pain and weakness have become more prominent presenting complaints. Interestingly, it was also found that joint stiffness and pain persisted on average 10 years before a diagnosis of HC was made.[3] It is important to note that women tend to present later than men and are at a lower risk of developing severe iron overload, due to menstruation, child-birth and lactation.[4,5,6] The iron overload and associated pathology in HC occurs over many years, and thus the majority of patients present with symptoms after the age of 40.[7]

ARTHROPATHY OF HEMOCHROMATOSIS

Arthritis was first described as a feature of hemochromatosis in 1964[8] and has since been shown to affect 25 to 82% of patients.[1,7,9,10,11] Although arthropathy was initially thought to be a late consequence of HC, it is now recognized as an early mani-

festation that precedes visceral symptoms.[7] Patients are diagnosed as having arthritis if they are found to have stiffness, pain, and tenderness in at least one joint, with corresponding radiographic changes.[1,9] These radiographic changes may be evident prior to the onset of arthritic symptoms.[10]

Many complications of HC have the potential to decrease a patient's quality of life. Symptoms that may contribute to this decline include extreme fatigue, joint pain, impotence, decreased libido and headache.[2,9] Arthropathy has been shown to cause the greatest decline in overall quality of life and physical functioning.[3,9]

The pathogenesis is not completely understood although it is thought to be degenerative as opposed to inflammatory, as the erythrocyte sedimentation rate is typically normal.[1] Excess iron is reported to be present in synovial lining cells of the joints and calcium pyrophospate dihydrate crystals may be found embedded in synovial tissue.[10] The arthropathy can lead to extensive joint destruction with as many as one third of patients whose hips are affected requiring joint replacement surgery.[1] Calcium pyrophosphate deposition (CPPD) with chondrocalcinosis is found in many cases and commonly affects the wrists, knees, hips and symphysis pubis.[1]

The distribution of the arthropathy is distinctive, typically affecting the second and third metacarpophalangeal (MCP) joints of the hand and the intercarpal joints of the wrist.[1,10,11] It may progress to polyarthritis involving the larger joints (hip, knee, ankle, shoulder, and elbow) and the spine.[10] The first, fourth, and fifth MCP joints, and proximal interphalangeal joints are involved less frequently.[7] There may also be chondrocalcinosis of the wrists, knees, symphysis pubis, hips and the elbow, which often present as stiff and tender on examination.[1,10]

Common radiographic abnormalities in affected joints include the following: loss of articular cartilage with joint space narrowing, osteopenia, sclerosis, pseudocysts, osteophytes and chondrocalcinosis similar to CPPD.[7,10,11,12] Abnormalities specific to the MCP and intercarpal joints of the hand include: joint space loss, "hook-like" osteophytes, subchondral cysts, erosion of bone, and synovial calcification.[7,10,11,12] Based on the above features arthropathy can be confirmed radiographically in 81.3%, as reported by Sinigaglia et al.[12]

The arthropathy of HC is often misdiagnosed as rheumatoid arthritis (RA), OA or CPPD.[7] The polyarticular, symmetrical involvement of the hands and wrists may lead to a misdiagnosis of RA, although it can be differentiated based on the fact that the arthropathy of HC is not inflammatory.[1,7] Because the arthropathy is degenerative, it may resemble OA.1 However the pattern of joint involvement is different, as the arthropathy of HC preferentially affects the MCP joints and wrist, which is less common in OA.[7] Distinguishing between arthritis of HC and CPPD is very difficult as the clinical and radiographic manifestations are very similar.[7]

TREATMENT

Early detection and initiation of treatment is the best strategy for delaying or preventing the complications of HC. Numerous treatments have been developed for HC, such as iron chelation and erythrocytapheresis; however, therapeutic phlebotomy has proven to be the safest, most efficient, and most economical therapy.[6] On average 1 unit of blood (400-450mL) is removed per phlebotomy treatment, which corresponds to 200-250mg of iron.[6] Weekly phlebotomy is continued until mild hypoferritinemia is achieved (10-20µg/mL).[4,5] However, sustaining such levels would be detrimental to the patient and so the goal is to maintain a level of less than 50µg/mL.[6]

Phlebotomy is effective at reducing and reversing complications of HC such as malaise, weakness, fatigue, liver pathology, cardiomyopathy, hyperpigmentation and diabetes.[6] In fact, normal life-expectancy has been reported in HC patients with regular phlebotomy, in the absence of cirrhosis, diabetes, or cardiomyopathy.[6]

On the other hand, phlebotomy has been proven ineffective at treating gonadal failure, thyroid disorders, cirrhosis and arthropathy.[6,7,13] In fact, progression of arthritis has been described despite phlebotomy therapy.[6,13] Furthermore, features of the arthropathy often precede the other manifestations of HC.[7] Therefore, early detection of HC and initiation of phlebotomy is imperative in an effort to prevent the development of arthropathy.[3,6,13] In those patients with existing arthropathy potential management strategies include relative joint rest, NSAIDs, physical therapy, and surgical arthroplasty (usually the hip or knee).[6] Recognizing arthritis as a early manifestation of HC may help to reduce the time delay between presentation with arthritic pain and diagnosis of HC.

Diagnosing the arthropathy of HC is important for two reasons: (1) to avoid misdiagnosing another condition such as RA, which has different therapeutic implications; and (2) to recognize that the patient has HC, and thus phlebotomy can be used to prevent the progression of its complications.[7] The high prevalence of this disorder in Caucasian populations is justification for routine screening.[5] Numerous sources have reported that Transferrin-saturation (TfS) is the most effective screening method for HC and iron overload.[5,6,7] TfS of ≥60% in men and ≥50% in women on at least 2 occasions indicates HC in the absence of other known causes of elevated TfS.[6] Although TfS is more sensitive, some still recommend serum ferritin levels also be considered.[3] Alternatively, since the gene is inherited and thus present before the development of iron overload, genetic screening holds the most promise for early detection, treatment and prevention of complications.[3,5]

CONCLUSION

Arthritis has been shown to affect many patients with HC and is the single greatest cause of poor quality of life in these patients. Depletion of excess iron in the body via phlebotomy improves survival and decreases systemic complications, except for that of arthritis. This lack of correlation between arthropathy and degree of iron overload suggests that other still undefined factors influence the progression of arthropathy in HC. On average, arthritic complaints precede the diagnosis of HC by 10 years. This represents a decade of missed opportunity for diagnosis and possible prevention of joint destruction and systemic disease. Therefore early detection of HC and initiation of treatment is imperative to prevent the development of serious systemic complications as well as irreparable joint damage.

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The Injured Anterior Cruciate Ligament: A Review in Current Concepts

Alexander Wong, Meds 2005

The injured anterior cruciate ligament (ACL) is becoming more commonplace in competitive athletes and "weekend warriors", and advances in basic research and arthroscopic technology have made surgical reconstruction using either the quadruple hamstring tendon graft or the bone-patellar tendon-bone graft the current standard of care. Longitudinal studies indicate that the majority of patients electing to undergo ACL reconstruction report favourable results, with most successfully returning to preoperative activity levels. Controversy exists in choosing appropriate candidates for reconstruction, determining the superior graft material, and in pre-operative planning and post-operative rehabilitation protocols. Continual progress in molecular biology, tissue engineering, and computer-assisted surgery combine to make treatment of the injured ACL one of the most dynamic areas in orthopaedic surgery today.

INTRODUCTION

For two main reasons, there is no area in orthopaedic surgery which is currently receiving more attention and scrutiny than treatment of the injured anterior cruciate ligament (ACL). First, an increased emphasis on maintaining an active lifestyle has led to an increased incidence of ACL injuries. From skiing alone, it is estimated that there are anywhere from 100,000 to 150,000 acute ruptures in the United States per year.[1] Secondly, there is still a tremendous amount of controversy surrounding the ideal approach to treatment, because no single approach has completely solved the problem of ACL insufficiency. A significant amount of basic science and clinical research along with improved arthroscopic surgical technology has allowed management of these injuries to evolve from non-operative supportive therapy to primary repair to ACL reconstruction. Maintaining an emphasis on clinical relevance, this article provides a review of fundamental concepts required to understand how ACL injuries are currently managed.

ANATOMY AND FUNCTION OF THE NORMAL ACL

The ACL is a band of dense connective tissue containing many fascicular subunits which connects the femur and the tibia, and it is surrounded by a synovial lining which originates from the posterior intercondylar area of the knee.[2] It is attached to a fossa located on the posterior aspect of the medial surface of the lateral femoral condyle, and another fossa in front of and lateral to the anterior tibial spine. The ACL moves anteriorly, medially, and distally across the knee joint as it passes from the femur to the tibia. It also appears to "twist" in a mild lateral spiral, likely the result of the orientation of its bony attachments.[3]

The ACL consists of fibroblasts surrounded by an extracellular matrix which consists of two main components: a highly-organized arrangement of macromolecules (mostly Type I collagen) and water. The maintenance of the ligament tissue and its ability to respond to changes in load depend on the interactions between the cells within the ligament and the extracellular matrix. The femoral and tibial attachments occur through an incorporation of collagen fibers from the ligament within mineralized bone, and consist of a "transition zone" of fibrocartilage and mineralized fibrocartilage, allowing a gradual change in stiffness at the attachment site.[4] The ACL is supplied with blood mainly from soft tissue sites (the infrapatellar fat pad and synovial lining), and numerous nerve fibres and sensory receptors are located throughout its the entire length.

The ACL appears to have important proprioceptive and mechanical roles within the knee. Although its exact proprioceptive function remains undetermined, histological studies have demonstrated the presence of proprioceptive nerve endings within the ligament, and clinical studies have suggested that the ACL likely has a role in proprioceptive "feedback" to the knee joint.[5] The mechanical role of the ACL is well-defined, as it has been shown to carry loads through the entire range of knee motion, primarily resisting forces which would cause the tibia to translate anteriorly relative to the femur. During normal activity, the ACL carries only small loads (estimated to be no more than 20 percent

of its failure capacity), which indicates that the ACL probably only nears its failure capacity in atypical situations such as those encountered in sporting activities which involve start-stop and pivoting motions as well as rapid deceleration.[6]

THE NATURAL HISTORY OF THE INJURED ACL

A patient who presents with an acute rupture of the ACL will have increased tibial translation and swelling in the knee as a result of the formation of a local hematoma. When the thin synovial lining which surrounds the ACL is torn during a complete rupture, blood dissipates throughout the joint and does not form a localized fibrinous clot which would otherwise occur as part of the normal healing process in other damaged ligaments around the body. In partial ruptures of the ACL where the synovial lining remains intact, a hematoma can form in place and promote the inflammatory response which allows for some degree of healing to the ligament. However, in injuries where the synovial lining has been torn, no local healing response is present.[7] As a result, the natural history of untreated ACL ruptures is extremely poor. Chronic instability in the knee leads to recurrent injuries which can damage secondary structures such as menisci or articular cartilage, promoting the onset of osteoarthrosis in the knee.[8] Hence, surgical intervention now involves reconstruction of the ACL as opposed to repair.

Because it is currently difficult to predict which patients who have an ACL injury will experience significant instability and progression to osteoarthrosis, it is not possible to determine which patients would benefit most from an operation. As a result, it is currently accepted that not all such patients require reconstructive surgery. For example, some patients may engage in vigorous rehabilitation to strengthen compensatory musculature which surrounds the knee, and others may alter their physical activity in order to significantly lessen the risk of re-injury. However, numerous studies have shown that certain characteristics define "high-risk" patients who would benefit most from reconstruction. Such patients are young, highly-competitive in high-speed pivoting sports such as basketball or squash, and have a complete rupture of the ACL which may or may not be accompanied by injuries to other structures in the knee.[9] Other factors which may be considered in determining the suitability of a patient for reconstruction include the presence of an associated injury to the menisci (an associated meniscal injury increases the risk of osteoarthrosis significantly due to increased knee instability), and the patient's profession (certain occupations may involve extensive knee-loading). Ultimately, a surgeon must recommend reconstruction based on a total consideration of the patient's lifestyle expectations, motivation for recovery, and current health.

ACL RECONSTRUCTION

The topic of ACL reconstruction has spawned considerable debate, and this article will attempt to summarize only the main issues of contention rather than offer an extensive procedural review of various reconstructive procedures. Excellent resources exist for those interested in learning more about the techniques of reconstructive surgery for the ACL.[10]

The primary goals of ACL reconstruction are restoration of knee stability, preservation of the menisci and articular cartilage, maintenance of knee motion, and a timely return to normal activity including athletics. The main decision that a surgeon must make is with respect to graft material. Currently, the most common autogenous graft choices are the quadruple semitendinosus/gracilis tendon graft and the bone-tendon-bone graft.[11-12] The bone-tendon-bone graft is typically an 8- to 10-mm wide graft taken from the central one-third of the patellar tendon, along with its adjacent patellar and tibial bony ends. In the mid-1980's, studies indicated that a 14-mm bone-tendon-bone graft had about 170% of the strength of a normal ACL, while the strength of either the semitendinosus or gracilis alone were both less than that of the intact ligament.[13] Despite the same study indicating the bone-tendon-bone graft was considerably more stiff than a normal ACL and that either the gracilis or semitendinosus exhibited a stiffness far more comparable to that of an intact ligament, it was believed that choosing a graft with superior strength was more advantageous than choosing a graft with more reasonable stiffness properties. Hence, the bone-tendon-bone graft became the standard of care for a number of years.

Beginning in the early 1990's, surgeons began to realize that by using either a doubled gracilis tendon or a doubled semitendinosus tendon, or even combining the two together to form a quadruple hamstring graft, they could create higher failure loads while gaining the advantage of appropriate stiffness characteristics. Recent studies have estimated the strength of the quadruple hamstring graft to be as much as 250% stronger than that of a normal ACL, and this construct has a considerably higher cross-sectional area of collagen than a 10-mm bone-tendon-bone graft.[14] During the operation, the graft is harvested from the donor site and secondary injuries to the menisci and articular cartilage are addressed, after which the appropriate location for the tibial and femoral tunnels are determined. The tunnels are drilled carefully, and the graft is then fixated into place.

The most common complications of ACL reconstruction using hamstring tendons is potential post-operative donor site weakness due to the loss of the semitendinosus and gracilis muscle tendon units. A number of longitudinal studies have evaluated knee flexion strength in patients several years following surgery, concluding that it is possible to regain full knee flexion strength following the harvest of hamstring tendons.[15] When using the bone-patellar tendon-bone graft, the most common post-operative complaint is that of anterior knee pain, with rates in some studies as high as 58% of all patients.[16] The severity of the pain ranges from mild to severe, and suspected causes include damage during the harvesting procedure, excess scarring, and inadequate rehabilitation. Even with aggressive rehabilitation, permanent loss of some degree of knee extension is seen in at least 4% of all patients.[17] Other intraoperative complications common to both procedures will not be covered here, but have been reviewed extensively elsewhere.[17-18]

A number of prospective randomized studies comparing both procedures have been conducted, and the consensus appears to be that there is no significant difference in overall outcome,[19-21] although the incidence of patellofemoral pain appears to be less in patients with hamstring tendon grafts.[22] To conclude, it would appear that both the quadruple hamstring tendon graft and the bone-tendon-bone graft are adequate for ACL reconstruction, although the harvest of the hamstring tendons appears to be more

easily tolerated with a subsequent increased rate of recovery of function in these patients.

REHABILITATION FOLLOWING ACL RECONSTRUCTION

It is generally recognized that rehabilitation is crucial to the ultimate success of the reconstructed ACL, and although the efficacy of various rehabilitation protocols remains in debate, evidence points to an intensive rehabilitation program preventing the onset of early arthrofibrosis and restoring normal strength and function earlier. Specific post-operative goals include adequate control of pain and swelling in the knee, restoring full range of motion and strength, and moving through a gradual functional progression which concludes with a successful return to athletic activity while preserving knee stability. It has been demonstrated that an early range of knee motion is required to avoid postoperative difficulties.[23]

The limits to which an intensive rehabilitation protocol can induce damage to the healing knee also remains in question. Certain exercises involving extension of the knee against quadriceps resistance (termed "open-chain" exercises) have been shown to apply additional strain on the ACL, especially in the last few degrees of extension if the lower limb is non weight-bearing. In addition to exercises specifically designed to restore strength, most protocols now include some element of balance or proprioceptive training such as weight-shifting (early phase) or plyometrics (late phase), which help to restore gait control and increase the patient's confidence in the leg's ability to perform at a level equal to or greater than its preoperative condition.

FUTURE DIRECTIONS AND CONCLUSION

Orthopaedic surgeons now have a number of well-established techniques to treat the injured ACL, with clinical follow-up studies demonstrating favourable results in the majority of patients. Much effort is currently being focused on understanding the function of the ACL in vivo as well the biology of the healing ACL using biomechanical analysis, which ultimately will lead to the improvement of all stages of ACL treatment: pre-operative preparation, surgical approaches, and rehabilitation protocols. As well, advances in molecular biology and tissue engineering as well as the continual development of robotic technology and computer-assisted surgery may one day allow an even greater level of consistency in returning the ACL-injured knee to its preinjury state.

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Percutaneous Internal Fixation of Distal Tibia Fracture

Gerard March, Meds 2004

Distal tibia and ankle fractures offer a special challenge to orthopaedic trauma surgeons due to the potential long-term implication on a patient's functional gait.[1] The ankle joint itself offers specific anatomical features that add to its stability and must be considered with any reconstruction.[2] Fracture stabilization may take the form of closed reduction or operative treatment. Operative treatment may consist of external fixation, inter-medullary nailing, or screw and plate fixation.[3] A new procedure of limited exposure internal fixation, which composes of subfacial insertion of stabilization plates with percutaneous screw fixation, offers the promise of shorter hospital stays and quicker recovery times.[4] We describe a case in which a patient suffers a proximal fibular and distal inter-articular tibial fractures. The patient was treated with a limited exposure internal reduction technique.

CASE

A 38-year-old white male was seen in the emergency room with severe pain and an inability to weight-bear on the right leg. The patient reported falling from a standing position while tobogganing earlier in the day. The patient denied striking his head, had no loss of consciousness, and reported no other injuries. Upon examination the patient appeared generally healthy except for an obvious swelling and deformity in the distal right leg. The patient demonstrated normal movement and stability in his right knee, yet was exquisitely tender upon palpation from the proximal right tibia to the right ankle joint. The patient was neuro-vascularly intact and his skin remained closed. Emergency room x-rays of the right leg revealed a closed, comminuted, minimally displaced intra-articular distal tibia fracture as well as a closed, non-comminuted, minimally displaced proximal fibular fracture. The remainder of the patient's exam was unremarkable.

DISTAL TIBIA AND ANKLE FRACTURES

The ankle joint's shape specifically contributes to its stability and function as a principle weight-bearing joint. The fibula and tibia form a mortise into which the talus acts as a talon.[2] The distal articular surface of the tibia, which forms the medial and superior aspects of the mortise, is known as the tibia plafond.[5] Relative to the hip or knee joints, the ankle has a large area of contact due to the specific mirroring of the proximal and distal joint surfaces. The ankle joint is further stabilized by the presence of the joint capsule and strong ankle ligaments that can be divided into three distinct groups: the medial collateral, lateral collateral, and syndesmotic ligaments.[2] Tibial plafond fractures generally occur due to an impact force that is directed vertically through the talus into the tibia.[5] The severity of bone, cartilage, or soft tissue damage is directly proportional to the size of the offending impact force.[2,3]

TREATMENT OPTIONS

All treatment options for distal tibia and ankle fractures aim for an acceptable reduction of the fracture including adequate alignment, rotation, length, and position, as well as restoration of the patient's pre-existing activity level.[1,2] Low energy, minimally displaced, and isolated distal tibia fractures are commonly treated conservatively with closed reduction and progressive weight bearing.[1,3,6] The fracture is first reduced with traction along the long axis of the limb and then completed by reversing the mechanism of fracture. The reduction and alignment of the fragments are then maintained via constant traction or an immobilizing splint or cast.[2] Contraindications to closed reduction usually hinges on one's ability to adequately reduce the fracture and maintain the reduction in order to allow healing to occur.[3,7]

Operative treatment is necessary when closed reduction fails, the fracture pattern is inherently unstable, or the fracture itself is open.[6,8] Operative treatment may include both internal and external fixation techniques. External fixation generally allows for basic stabilization of a fracture with only minimal disruption of

soft tissues.[7,9] The use of external fixation for distal tibial and ankle fracture is generally indicated when acute stabilization of open fractures is needed, with fractures involving bone loss, or in management of concurrent soft tissue injuries including compartment syndrome and burns.[2,3,10] However, a drawback of this method is that the degree of fracture reduction and stabilization is inferior relative to other fixation methods. Ultimately, external fixation balances the loss of stability with the conservation of soft tissue structure.[7,10] Additionally, pin tract infection is a common problem with external fixators, which can lead to osteomyelitis.[1,3] Thus, the decision to incorporate external fixation into fracture management must include consideration of the severity of the fracture, the degree of soft tissue injury, and the patient's ability and willingness to manage the necessary upkeep of the fixator.[7]

Internal fixation may be classified into procedures that do not bring about compression across the fracture plane such as an inter-medullary rod or procedures that do bring about compression such as lag screws or buttress plating. (8) Inter-medullary nails are tightly wedged within the medullary canal leading to a high degree of endosteal contact. (11) Inter-medullary nailing techniques have relatively low risks of pseudoarthrosis and infection. Generally, patients enjoy shorter hospital stays with earlier full weight ambulation. (11) The inter-medullary technique becomes problematic however with severely comminuted fractures or fractures that are either proximal or distal to the shaft of the long bone. (3)

With lag screws, optimal compression forces will be attained if the screw is placed perpendicular to the plane of the fracture. However, this arrangement is unsatisfactory if there are physiological shear loads such as weight bearing upon an oblique fracture plane. In these cases, the shear and rotational forces are usually controlled with a buttressing plate or even an external fixator.[2,8,12] Dynamic Compression Plates (DCP) provide excellent stabilization of fracture planes through self compression, but may have a detrimental effect upon bone structure due to the fact that 100% of their under body lies in direct contact with the bone surface.[8] Limited Contact-Dynamic Compression Plates (LC-DCP) have been developed that only have 50% contact with the bone. This allows for the formation of callus bridges due to improved cortical circulation under the plate.[8] Furthermore, Point Contact Plates (PCP) have been developed where the internal plate does not physically contact the bone surface except though pins and screws.[8]

Conventional Open Reduction and Internal Fixation (ORIF) requires exposure of the fracture site. Disruption of soft tissues at the fracture site during surgery can adversely affect bone healing.[1] Further efforts to decrease soft tissue disruption have lead to the development of subfacial insertion of stabilization plates with percutaneous screw fixation.[4,8] The procedure starts with minimal skin incisions either proximal or distal to the fracture site. A pre-contoured plate is then inserted beneath the facial and muscle layers and positioned along the periosteum. Reduction is achieved indirectly and when deemed adequate under intra-operative fluoroscopy, percutaneously drilled screws lock the plate securely.[11]

Percutaneous osteosynthesis blends the advantages of conventional ORIF with the advantages of external fixation. Fracture reduction can be maintained via a strong and stable internal plate, while soft tissue integrity is preserved.[4] Maintenance of the soft tissue envelope allows for the preservation of the periosteal blood supply and any fracture hematomas leading to accelerated bone regeneration. Furthermore, a percutaneous approach requires shorter operating times, has lower operative blood losses, and leads to lower wound infection rates.[8] Percutaneous stabilization introduces many technical challenges and increases the need for careful pre-operative planning as well as accurate intra-operative radiographic imaging. Absolute contraindications for this method include poor bone quality or fractures where bone loss is significant.[4] This method has limited use with severely comminuted intra-articular fractures as it prevents the surgeon from exploring the articular surface for subtle deformities.[4] Additionally, both the patient and the surgeon have to be prepared for a rapid transition to an open technique if adequate reduction has not been achieved or maintained via the percutaneous approach.

THE CASE REVISITED

The patient was admitted to the orthopeadic ward and taken to the operating theatre under general anaesthesia. A percutaneous plating technique reduced and fixated the tibial fracture with a small-fragment 14-hole precontoured low-profile medial-malleolar periarticular plate. The plate was inserted submuscularly down the periosteum through a distal incision on the medial aspect of the tibia. The plate was secured with two distal fully threaded cortical small fragment screws parallel to the tibial plafond. The comminuted fracture was reduced via axial traction and slight external rotation. The reduction was secured with several proximal percutaneously drilled fully threaded cortical screws. Two percutaneously drilled cortical partially threaded or lag screws were then used to compress the fracture midway along the tibial plate. An anterior to posterior partially threaded cancellous screw was then percutaneously drilled in order to secure the reduction of the vertical intra-articular fracture line. The percutaneous incisions were copiously irrigated and then sutured. The patient was placed on post-operative antibiotics and was discharged on post-operative day one in a lower limb cast with a prescription for analgesics.

Two weeks post operatively, the patient was seen in fracture clinic for removal of sutures and cast change. At that time it was noted that the fracture was healing. The patient was subsequently moved to a lower limb walking cast and allowed to weight-bear with the aid of crutches. The patient was seen again in fracture clinic six weeks post operatively where fracture union was confirmed. Examination of the patient showed only a slight antalegic gait favoring the right side. Leg length was identical bilaterally and the patient exhibited only slight restriction of dorsi flexion of the right ankle with all other right knee, ankle, and foot movements normal. The patient remained neurvascularly intact and the surgical incisions had healed without complication. The patient was advised to weight bear without crutches using the lower limb walking cast and move to full activity as tolerated.

SUMMARY

This case shows the advantage of percutaneous stabilization technique over traditional open reduction and internal fixation. The patient enjoyed a shorter hospital stay and a quicker recovery

time as well as minimal soft tissue disruption at the fracture site. Presently, percutaneous stabilization is becoming more popular among orthopaedic trauma surgeons and new applications are constantly being found.[8,11] Further study needs to be conducted however to both explore possible uses and define the potential limitations in an effort to standardize and maximize patient care.

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Ocular Toxicity of Chloroquine and Hydroxychloroquine (Plaquenil) used in the Treatment of Rheumatological Diseases

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INTRODUCTION

Cases of rheumatoid arthritis (RA) and discoid and systemic lupus erythmatosus (SLE) in which NSAIDS do not provide adequate relief of symptoms and the systemic side effects of immunomodulating drugs are wished to be avoided, the patient is often started on chloroquine and hydroxychloroquine. These two drugs have been used in these rheumatological diseases since the early 1950s.[1] While they provided much needed relief to patients, chloroquine and hydroxychloroquine were not without side effects. It was less than a decade later that chloroquine-using patients started to emerge.[2] It was in 1959 that Hobbs presented three cases of retinopathy in patients with SLE and RA who were treated with chloroquine for 3 years at an average dose of 300 mg/day.[3]

Since the presentation of these initial cases, a great deal of research has been conducted into the ophthalmologic consequences of the use of these drugs. Guidelines have been released, screening procedures implemented, and dosages adjusted. Most of the literature regarding the ophthalmological toxicity of antimalarials relates to the use of chloroquine. Where studies have looked at hydroxychloroquine, the incidence of problems has been much lower. For this reason hydroxychloroquine is almost exclusively used today.

Recent review of all the published literature by the American Academy of Ophthalmology in 2002 states that well over 1,000,000 individuals have used chloroquine or hydroxychloroquine while there has only been less than 20 cases of toxicity reported in individuals using low dose levels of either of the drugs–and all of these had more than 5 years of usage.[4] Several other large studies have failed to document any significant ocular toxicity with doses less than 6.5mg/kg/day hydroxychloroquine, regardless of duration of treatment.[5, 6, 7] While the number of actual cases of retinal toxicity has been low, the severity of the pathology induced when such a case arises, prompts professionals to keep a close eye on all patients using either of the drugs on a long-term basis.

PHARMACOKINETICS AND MOLECULAR DIFFERENCES OF ANTIMALARIALS

Although the exact mechanism of action of the antimalarials in the treatment of RA and SLE remains uncertain, the pharmacokinetics of these drugs have been studied in great depth.[3] Both chloroquine and hydroxychloroquine exhibit extensive uptake in a variety of tissues and also have extremely long half-lives. Three-4 months of treatment is required before a steady state is attained in the blood stream. Once this level has been reached, 99.9% of the drug is distributed to various tissues where it is slowly released. Levels can be detected in urine, red blood cells, and plasma up to 5 years after the medication has been discontinued.[8, 9] High accumulations are seen in the spleen, lung, and liver, where concentrations may reach several 100 times of that found in serum. Still higher concentrations are found in pigmented structures.[10]

On the molecular level there is only one difference in the structure of chloroquine and hydroxychloroquine: a hydroxyl group. This hydroxyl group limits hydroxychloroquine's ability to cross the blood-retinal barrier. Chloroquine on the other hand has been hypothesized to cross this barrier. This may partly explain the lower incidence of retinopathy caused by hydroxychloroquine in comparision to it's sister drug, chloroquine.[5]

PATHOPHYSIOLOGY

Studies have shown that use of chloroquine has resulted in the accumulation of large amounts of the drug in all organs of the body which are proportional to both the dose and duration of treatment.[11, 12, 13] The drug has also been found to have a high affinity for melanin granules which are in uveal tissue, retinal pigment epithelium, choroids, and in the ciliary body.[14, 15] Once bound to melanin granules, there is minimal turnover and long term retention of the drug.[16] Build up of the drug results in the disturbance of function of the retinal pigment epithelial cell with secondary photoreceptor degeneration.[17, 18] Chloroquine has been hypothesized to arrest retinal pigment epithelial cellular function by the mechanisms of inhibition of protein synthesis or by block-

ing DNA metabolism and repair.[15, 16] Although hydroxychloroquine has not been studied in the same detail as chloroquine, many postulate that its mechanism of pathogenesis is similar to that of chloroquine.

There are both reversible and irreversible side effects of hydroxychloroquine. Reversible side effects include: corneal deposits, loss of foveal reflex and impairment of accommodation. Corneal deposits are the most common side effect and are dose related. Often they are asymptomatic. As they are not related to retinal problems, they are not usually considered a contraindication to continuing treatment.[20]

Loss of foveal reflex is also considered as early reversible maculopathy or premaculopathy. It is important to note that it has been emphasized by Bernstein, a prominent researcher on this topic, that premaculopathy is not a precursor of retinopathy.[21] Impairment of accommodation is very rare and only requires a temporary reduction in dose.[20]

Retinopathy is the major and potentially most serious irreversible side-effect of chloroquine toxicity. Initially, patients may present with visual loss to a red target and mild stippling or mottling othe macular pigmented epithelium. Progressive pigment migration can eventually lead to the classic 'bull's eye' maculopathy (figure 1)[31], central scotoma and reduced acuity.[20] The 'bull's eye' consists of granular hyperpigmentation of the central macula which is surrounded, first by a zone of depigmentation,
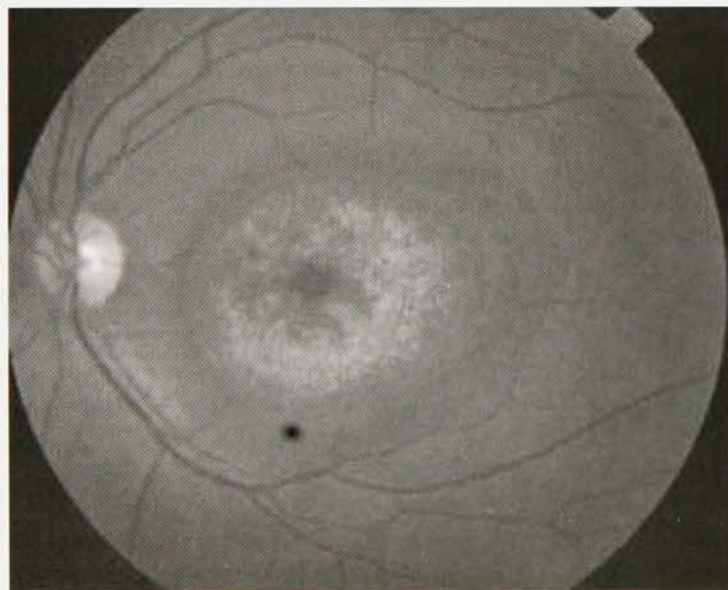

Figure 1. Bull's Eye Maculopathy. There is an area of granular hyperpigmentation of the central macula which is surrounded, first by a zone of depigmentation, and then by a second ring of hyperpigmentation.

and then by a second ring of hyperpigmentation. The greatest retinal damage occurs in a ring stretching from approximately 2 to 10 degrees about fixation. The fovea is basically spared, and for that reason 20/20 acuity often persists in the presence of advanced retinopathy. This condition is almost always bilateral, however, asymmetry is not uncommon.[3]

Subjective symptoms of maculopathy may include blured vision, difficulty reading, central or peripheral scotomas, as well as, photophobia, photopsias, ad othe entopic phenomena. Many patients will be asymptomatic however, as visual acuity is frequently unaffected.[10]

RISK FACTORS AND DOSE

Studies have found that risk factors for retinopathy may include: high daily doses of chloroquine (>250 mg) and hydroxychloroquine (> 400 mg or > 6.5 mg/kg/day), increased cumulative drug doses (use greater than 10 years), and decreased drug clearance (60% of HCQ is excreted by the kidney).[22]

As a result of these studies, patients typically receive 250 mg/d of chloroquine or 200-400 mg/day of hydroxychloroquine. More accurate dose calculations take into consideration the patient's 'lean or ideal' body weight by taking into account age, sex, and height if the patient is overweight.[3, 23] This is important as hydroxychloroquine is retained in the highly cellular muscle, liver, and retinal tissues to a much greater extent than in adipose tissue.[24] The recommended maximum daily doses are 4.0 mg/kg for chloroquine and 6.5 mg/kg for hydroxychloroquine.[25]

OPHTHALMOLOGIC FOLLOW UP

Manufacturers of Plaquenil (hydroxychloroquine) have recommended that an initial baseline ophthalmologic exam should be performed and then repeated every 3 months.[26]

Although a recommendation of the manufacturers of the drug, such a follow-up is not currently the standard of care, or has it been in the past. This is due to a number of factors including patient non-compliance and differing opinions of health care professionals. In addition, a consistent plan for follow-up has yet to be implemented, although many studies and papers have been written to suggest a schedule for follow-up.[27, 28, 20, 23]

In an effort to standardize the care and follow-up of these patients and to provide them with adequate care, the American Academy of Ophthalmology published retinopathy screening recommendations for patients using chloroquine or hydroxychloroquine in 2002. These recommendations are outlined below.

SCREENING RECOMMENDATIONS: AMERICAN ACADEMY OF OPHTHALMOLOGY 2002[29]

1. Baseline

Baseline testing should consist of a complete ophthalmologic examination including best-corrected visual acuity and dilated examination of the cornea and retina. Visual fields should also be examined with an Amsler grid or with Humphrey 10-2 fields. Color testing should be optional depending on whether the ophthalmologist intends to use it for future testing. Fundus photography, fluoroscein angiography or multifocal ERG are also optional.

2. Low risk Patients

Low risk patients are ones that have used the drug for less than five years; are taking the recommended dose or lower; and have no complicating medical conditions. These patients should receive an examination of their corneas and retina after papillary dilation. Visual fields should also be tested with an Amsler grid or Humphrey 10-2 fields. Other tests are optional. They should be instructed to return if they notice any change in visual acuity, Amsler grid appearance (tested at home), color sensations, or adjustment to the dark. Frequency of their visits should be determined by their age (table 1).

Table 1. Comprehensive Eye Evaluation for Patients with No Risk Factors[29]

Age	Frequency of Examination
20-29	At least once during period
30-39	At least twice during period
40-64	Every 2-4 years
65 or older	Every 1-2 years

3. High risk patients

These patients are those who have used the drug for more than 5 years; or are using doses greater than those recommended; or have a complicating medical problem (age-related macular degeneration, retinal dystrophy, renal/hepatic disease). These patients should receive an annual exam with testing as outlined for the low risk patient. Optional tests should be used if needed. Patients should also be instructed in the use of a Amsler grid and given grids to use at home for monthly self testing.

Although a screening procedure has been recently outlined, it is important to note that no gold standard exists for the detection of retinopathy at an early stage. Amsler charts are insensitive and non-specific with abnormalities in colour testing and scotomas being found in 6% of the normal population.[20] It is also important to note that after age 65, 1% of patients develop symptomatic age-related macular degeneration and that 25% of this population will have some asymptomatic macular changes.[21] There is also no evidence that screening tests will pick up retinopathy at a reversible stage or that stopping the drug will prevent progression.[20, 30]

MANAGEMENT OF TOXICITY

No medical therapy has been proven effective in chloroquine or hydroxychloroquine toxicity other than cessation of the drug. In practice, the management of suspected or recognized toxicity depends not only on the presence of retinal damage, but also on the medical status of the patient. These drugs are often the safest way to control a serious systemic disease and cessation could lead to worsening of the underlying disease or necessitate the use of other drugs with serious systemic side-effects. Therefore the decision to discontinue the use of the drug in a patient with recognized toxicity must be made in conjunction with the patient and the specialist managing the patient's underlying condition.[29]

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Bacterial Septic Arthritis: A Medical Emergency

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A priority in the management of acute onset monoarticular arthritis is to rule out a septic joint. Septic arthritis is a medical emergency, and can lead to extensive joint damage, long-term disability, systemic sepsis and possibly death. Early diagnosis and proper treatment is essential in preventing morbidity and mortality. This article reviews the epidemiology, risk factors, and common causative organisms of septic arthritis. Current approaches to diagnosis and management are discussed, and possible complications are outlined. The goal is to aid the reader in rapid recognition and treatment of this important, yet easily overlooked infection, in order to prevent the undesirable sequelae of septic arthritis.

INTRODUCTION

Septic arthritis is the invasion of a joint space by bacteria, viruses, fungi or protozoa. The majority of joint infections are caused by bacteria, which will be the focus of this review. The incidence of bacterial arthritis is between 2-10 cases per 100,000 in the general population1, with a bimodal age distribution. Peaks in incidence occur in children less than 5 years of age, and in adults over age 65.[1]

Bacterial joint infections are classically divided into two groups, gonococcal and non-gonococcal. Non-gonococcal septic arthritis is caused by several organisms:[2,3,4,5,6]

1. *Staphylococcus* species (40-60% of infections): Mostly *S. aureus*, although *S. epidermidis* is occasionally implicated, especially in prosthetic joints.
2. *Streptococcus* species (10-20%): Groups A, B, G, or *S. pneumonia*.
3. Gram negatives (10-15%): Include *Escherichia coli*, *Klebsiella species*, *Haemophilus influenza*, and *Pseudomonas aeruginosa*. The latter requires special consideration due to its antibiotic resistance.
4. Anaerobes (2%): Tend to be associated with wounds, bites, or surgery.
5. Other gram positives (very rare): caused by *Listeria* or *Corynebacterium species*.

Non-gonococcal septic arthritis is usually monoarticular (80-90% of cases)[7]. Although any joint can become infected, the knee and hip are most commonly involved; shoulder and ankle infec-tions are less common[7]. Intravenous drug users may present with atypical joint infections, affecting the sternoclavicular, sacroiliac, or costochondral joints.

Gonococcal septic arthritis usually presents as a polyarthritis, and affects more women than men (4:1 ratio)[8]. It is caused by two organisms, *Neisseria gonorrhea* and *Neisseria meningitides*. *N. gonorrhea* is the most common cause of septic arthritis in adolescents and young adults. A patient with mucosal gonorrheal infection (i.e. urethral, cervical, rectal or pharyngeal) has a 0.5% to 3% risk of developing a disseminated gonococcal infection (DGI). Approximately 40% of patients with DGI go on to develop septic arthritis[1].

Most septic joint infections arise from hematogenous seeding of the synovial membrane[7]. In some cases, infection can be introduced via penetrating trauma, joint aspiration, corticosteroid injection, or surgery. Contiguous spread from nearby osteomyelitis can also cause joint infection.

The development of septic arthritis depends on the interaction of the invading pathogen with the host immune response. Factors that diminish host immune response or promote joint seeding result in an increased risk of septic arthritis. Immunity-related risk factors include diabetes mellitus, corticosteroid therapy, cirrhosis, hypogammaglobulinemia, leukemia, and extremes of age. Factors promoting joint seeding include intravenous substance abuse and prior joint pathology (e.g. rheumatoid arthritis).[7] Risk factors unique for gonococcal septic arthritis include delayed diagnosis of a genitourinary gonococcal infection, promiscuity, homosexuality, and low socioeconomic status.[7]

DIAGNOSIS

Non-gonococcal septic arthritis

Timely recognition and treatment of non-gonococcal septic arthritis is crucial in preventing morbidity and mortality. Classically, the patient presents with abrupt onset of joint pain, with local warmth, swelling, effusion, and decreased range of motion. The joint is often maintained in slight flexion, which is the position of greatest comfort. Palpation of a septic joint is painful, as are attempts at flexion and extension. Children with septic arthritis will often avoid using the affected limb altogether.

Fever is present in at least 80% of children and 40% of adults[9]. Other constitutional symptoms may include general weakness, malaise, and anorexia. The presence of tachycardia and hypotension may indicate generalized sepsis.

The most important diagnostic tool is synovial fluid culture and analysis. Aspiration of the knee joint is relatively easy, whereas other joints (such as the hip) are more difficult to aspirate and may require surgical consultation and/or radiographic guidance. Synovial fluid culture is negative in approximately 20% to 25% of clinically suspected septic arthritis.[10] Gram stain, leukocyte count, glucose concentration, and lactate levels are also used to diagnose infection. In septic arthritis, the synovial fluid usually contains more than 50,000 leukocytes/mm^{3}, and the glucose concentration is less than half the serum glucose concentration. High lactate levels in synovial fluid also indicate bacterial arthritis. In appropriate age groups, (young to elderly adult males, and postmenopausal females) synovial fluid should also be examined by polarized light microscopy to rule out crystalline joint disease, although concurrent bacterial arthritis and crystalline joint disease have been reported.[11]

Blood tests are not often helpful in diagnosing septic arthritis. Peripheral white blood cell counts are often within normal limits in adults, but are usually elevated in children[7]. Blood cultures are positive in 25% to 50% of cases[9]. C-reactive protein levels and erythrocyte sedimentation rates are elevated in most patients with septic arthritis, but are of little utility in differentiating among acute inflammatory joint diseases[7].

Gonococcal septic arthritis

Most patients with DGI manifest symptoms of their local genital or oral infection. DGI can present as a clinical triad of migratory oligo- or polyarthritis, tenosynovitis and dermatitis. The arthritis is often asymmetrical, frequently involving the elbow, wrist, knee and ankle joints. Tenosynovitis and dermatitis are each found in about two-thirds of patients with DGI. The tenosynovitis is usually asymmetrical, often occurring in the fingers and hands[9]; at times, the skin overlying the affected tenosynovium is warm and erythematous. Dermatitis typically manifests as erythematous papules on the trunk and extremities[9] (Figure 1), but a large variety of skin lesions have been reported.

Joint fluid composition in gonococcal septic arthritis differs from that of non-gonococcal septic arthritis.[9] In gonococcal septic arthritis, leukocyte counts are usually below 50,000 cells/mm^{3}, and the joint fluid glucose concentration is normal. Gram stains and joint fluid cultures are often negative. When clinical suspicion for gonococcal arthritis is high, it is important that mucosal
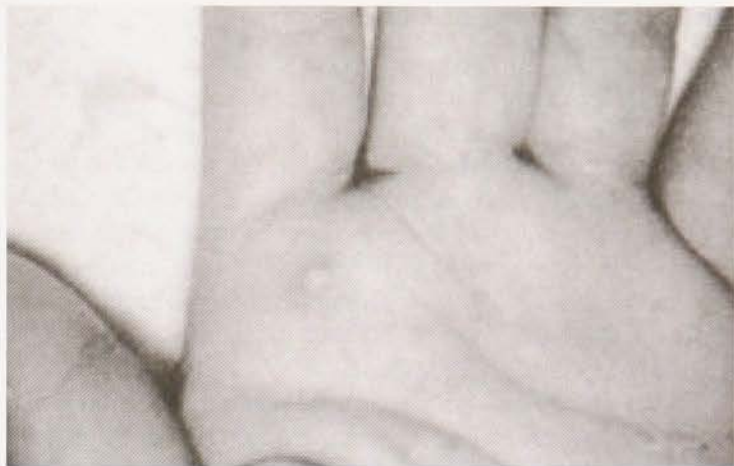
Figure 1. Papular skin lesion characteristic of disseminated gonococcal infection (DSI). Lesions are often found on the trunk and extremities. [Source: Kelley's Textbook of Rheumatology, 6th edition. ©2001 W.B. Saunders Co. Figure 96-5. Used with permission].

surfaces are cultured, as such cultures are positive in 80% of cases of gonococcal arthritis.[9]

Imaging is usually unnecessary in the diagnosis of septic arthritis, regardless of pathogen. Radiographs may show swelling, fat pad displacement, joint space widening, or cartilage destruction (Figure 2), but usually reveal little in the first days of infection. However, preexisting conditions, such as osteoarthritis, may be detected. Ultrasound can be used to locate small fluid effusions and to subsequently guide aspiration. MRI, CT and radionuclide scans are used only in ambiguous cases of possible septic arthritis, or to ascertain the extent of soft tissue or bone infections[7].

Figure 2. An anteroposterior view of a septic hip shows loss of cartilage and most of the subchondral bone of the femoral head and acetabulum. [Source: Kelley's Textbook of Rheumatology, 6th edition. ©2001 W.B. Saunders Co. Figure 43-24. Used with permission].

DIFFERENTIAL DIAGNOSIS

A number of disease processes cause a clinical picture similar to acute septic arthritis.

In children, osteomyelitis may cause an effusion in a neighboring joint and can therefore mimic septic arthritis, although the two infections can exist concurrently. Juvenile rheumatoid arthritis occasionally presents as a monoarticular arthritis that can be mistaken for septic arthritis; however, it is most often polyarticular. Transient synovitis, a self-limiting inflammatory process often affecting the hip may be mistaken for an infection, although patients do not appear ill or febrile.[12]

In the adult, osteoarthritis, rheumatoid arthritis, seronegative spondyloarthropathies, and crystalline joint diseases should be considered when evaluating a painful joint.[12] Pre-existing joint disease increases the likelihood of a joint becoming infected, due to increased risk of joint seeding and, in the case of inflammatory joint diseases, immunosuppression caused both by the inflammatory arthritis itself and immunosuppressive drugs used to treat it. Hence, prior joint disease is not an acceptable reason to delay aspiration of an acutely swollen, painful joint, especially if it is hot and/or erythematous.

MANAGEMENT

Not surprisingly, antibiotics are the foundation of therapy for septic arthritis. While awaiting culture results, it is crucial to begin administration of empiric antibiotics based results of the Gram stain and clinical data.[13,14,15] Most commonly, gram-positive cocci are the cause, and a penicillinase-resistant penicillin is the appropriate empirical treatment. In the case of suspected methicillin-resistant S. aureus (MRSA), vancomycin should be substituted.

In otherwise healthy younger adults with a stain indicating Gram-negative organisms, penicillin or ceftriaxone are often used empirically. Older or immunocompromised hosts may be treated with an aminoglycoside in combination with an anti-pseudomonal penicillin or a third-generation cephalosporin.[13,14,15] In children less than two years of age, antibiotics should cover S. aureus, Group B streptococcus, and H. influenzae.

Once culture results are available, it is important to institute specific therapy based on organism (Table 1).[16] Antibiotics are usually given for a three week IV treatment course, often followed by two to three weeks of oral therapy.[16] This can be extended for immunocompromised hosts. Intra-articular antibiotic administration is rarely used, as it may introduce further infection or provoke an inflammatory response.[16]

In addition to antibiotics, needle aspiration or surgical decompression of purulent synovial effusion is necessary. Needle aspiration is generally sufficient, but surgical drainage may be required for joints inaccessible to aspiration. An infected prosthetic joint usually has to be surgically removed.

Physiotherapy, exercise and rehabilitation are adjuncts to medical and surgical treatment, preventing adhesions, deformities and muscle atrophy.

COMPLICATIONS

Septic arthritis can lead to both local and systemic complications. Twenty-five to fifty percent of non-gonococcal septic arthritis result in long-term joint damage, and 10-15% result in mortality.[1] Limb amputation is not infrequent in patients with infected prosthetic joints. The prognosis for patients with gonococcal septic arthritis is favorable, and only 1-3% experience complications[7].

Unfavorable local sequelae of septic arthritis include soft tissue destruction, ankylosis, adhesions, flexion contractures, and avascular necrosis[1]. In children, the infection may extend into the bone, resulting in growth plate damage and eventual limb length discrepancy. Systemic sepsis can occur in patients who are immunocompromised, elderly, or very young, and leads to significant morbidity and mortality.

Risk factors for a poor outcome include delay in instituting treatment, underlying joint disease, advanced age, lack of physiotherapy, and infection of more than one joint[7].

CONCLUSION

Joint infections pose a diagnostic challenge for physicians. Septic arthritis must be suspected in any patient with joint pain, and early diagnosis and treatment can have a profound effect on morbidity and mortality. Following joint aspiration, immediate empiric treatment is instituted, and subsequently tailored based on culture results. Purulent effusions must be removed by needle aspiration or surgical drainage. Physiotherapy and rehabilitation helps to prevent long-term sequelae. Prompt treatment of septic arthritis can prevent permanent joint or soft tissue damage, systemic sepsis, and mortality.

ACKNOWLEDGMENT

Table 1: Specific treatment for septic arthritis based on organism isolated.

Micro-organism Cultured	Antimicrobial Treatment	Alternative Treatment
Staphylococci	Cloxacillin ± rifampicin	1st gen. cephalosporin
MRSA	Vancomycin ± rifampicin	Teicoplanin ± rifampicin
Streptococci	Penicillin ± clindamycin	Macrolides
H. influenza	Amoxicillin ± clavulanic acid	Fluoroquinolones
Enterobacteriaceae	Amoxicillin ± clavulanic acid	3rd gen. cephalosporin
Pseudomonas	Ceftazidime ± aminoglycosides	Piperacillin ± aminoglycosides
Gonococcus	Ceftriaxone	Spectinomycin

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Necrobiosis Lipoidica and Diabetes

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Necrobiosis lipoidica is a cutaneous disorder of degenerative collagen that is considered a marker of diabetes. It is important that primary care providers recognize the signs of necrobiosis lipoidica to aid in efficient diagnosis and treatment. Necrobiosis lipoidica may precede the presentation of diabetic disease by years and the careful follow up of nondiabetic NL patients may assist in the early detection of diabetes.

Diabetes mellitus (DM) is the most common endocrine disorder in the world1 and is characterized by impaired glucose utilization resulting in hyperglycemia and long term systemic complications. There are also many cutaneous manifestations of DM. It is estimated that between 30% and 71% of diabetic patients will develop a cutaneous disorder associated with their diabetes.[1,2]

Necrobiosis lipoidica, although uncommon, is the best known cutaneous marker of DM.[3] This condition, which has a distinctive clinical and histopathological appearance but unknown pathogenesis, was first described by Oppenheim in 1929.[4] It was named necrobiosis lipoidica diabeticorum by Urbach in 1932[4] but because of the occurrence of the condition in nondiabetic patients, many now choose to simply call it necrobiosis lipoidica (NL).[5]

CLINICAL PRESENTATION

The characteristic lesion of NL begins as a well circumscribed erythematous papule or plaque. The slowly enlarging lesion becomes indurated and develops an elevated reddish border and atrophic yellow center. Telangiectasiae are often visible in later stages.[3,5,6] The most common site for NL lesions is the pretibial and medial malleolar areas, with 85% of lesions occurring here.[3] Although other sites such as the face or scalp are sometimes affected, these are more common in nondiabetics, and only 2% of NL cases have no leg involvement.[5] The lesions are usually multiple and bilateral and approximately one third of them ulcerate. Areas of NL lesions may have decreased or absent sensation to pinprick and fine touch[1,3] and at least half of NL patients have associated neuropathy.[1,6] Although extremely rare, squamous cell carcinoma can also arise in NL lesions.[7]

EPIDEMIOLOGY

NL is rare, occurring in 0.3% to 1.6% of the diabetic population.[1,2,8] Of the population that has NL, however, the majority also have DM. In their now frequently cited studies, Muller and Winkelmann showed that 65% of their 171 NL patients had DM. Of the remaining NL patients, 42% had abnormal oral glucose tolerance test (OGTT), and of those with normal OGTT, 55% had a family history of diabetes.[4] Using these statistics, one could infer that approximately 90% of patients with NL will either develop DM, have abnormal glucose tolerance, or report a history of DM in at least one parent. The strength of this association has recently been challenged by O'Toole et al. who claim that only a minority of NL patients have DM.[9] NL affects females three times more often than males and typically appears in the third to fourth decades of life.[6] NL is associated with both insulin dependent and non-insulin dependent diabetes and it may precede the onset of DM, appear concomitantly with DM or after the diagnosis of DM.[2]

LINK WITH DIABETES

The association of DM with NL has lead to theories of the effects of glycemic control on NL. Most authors report the absence of a correlation between diabetic control and the pres-

ence of NL[5,9] based on research done by Dandona and colleagues examining the gycosylated hemoglobin levels of patients with NL.[10] Dandona et al. measured the HbA1 levels in 22 NL patients, 9 with DM and 13 without DM. They found that all 9 of the NL diabetic patients had elevated HbA_1 versus all 13 NL non-diabetic patients who had HbA_1 levels that were normal. These researchers concluded that the microangiopathic changes in NL occur independently of elevated glucose concentration. Other researchers have challenged this conclusion however. Cohen et al. interpreted the results of this study differently, suggesting that NL can occur in diabetic and nondiabetic patients, and patients with NL and DM are in poor glycemic control.[4] Furthermore, there is evidence that the histology of NL lesions from patients with DM differs from that of nondiabetic patients[4,9] suggesting that the pathogenesis of NL may differ in these two groups.

HISTOLOGY

Two major histological patterns of NL have been identified: the necrobiotic which is usually present in DM and the granulomatous which is more common in nondiabetic patients. The major histological changes are found in the dermis. In the necrobiotic reaction, large areas of necrobiotic collagen (young collagen fibers seen adjacent to degenerating collagen) are present in the lower two thirds of the dermis. A cellular infiltrate consisting of histiocytes, fibroblasts, and lymphoid cells surrounds the necrobiotic areas, and fat deposits may be scattered between degenerating fibers. Elastin fibers are absent and significant vascular changes occur.[5,6] The granulomatous reaction differs in that there is little or no necrobiotic material, a moderate to severe inflammatory infiltrate is present near hyalinized collagen, and vascular changes are rare.[5]

ETIOLOGY

Although it is well established that NL is a disorder of degenerative collagen, little is known of its pathogenesis. It has been suggested that diabetic microangiopathy may contribute to the collagen damage seen in NL.[6,7] Microangiopathy and thickened basement membrane are commonly seen microvascular changes in NL, present in two thirds of biopsy specimens.[5] Binazzi and Simonetti suggest that the presence of diabetic microangiopathy in NL favors a connection with diabetic disease and suggest that these changes sometimes precede diabetic disease and should be added to the diagnostic methods of DM.[11]

Other popular theories of NL etiology include abnormal platelet aggregation[3,5] which may be caused by elevated levels of factor VIII – related antigen or poor glycemic control. Since abnormal collagen is found in NL, some have looked to this as a cause. There is a marked decrease in the collagen concentration in NL patients. This deficiency of collagen is limited to lesional areas and when compared to normal fibroblasts, the fibroblasts from affected areas have a reduced collagen synthesizing ability in vitro. Although the reason for this is unknown, one possibility is that this defect is due to inflammatory cell mediators.[12] Increased collagen crosslinking or overhydrated collagen have also been suggested as causative factors.[5]

Immune mechanisms are another possible cause of NL. Dahl and Ullman used direct immunofluorescence microscopy to show that C3, fibrinogen, and immunoglobulins (IgM and IgA) were deposited around dermal blood vessels in lesional areas but not in normal skin of NL patients. They suggested an antibody mediated vasculitis as the cause of necrobiosis.[5] A delayed hypersensitivity reaction has also been suggested because of the presence of fibrin in lesions associated with palasading histiocytes.[6] Other theories include sweat gland dysfunction, decreased number of cutaneous nerves, decreased plasma lipoproteins, and abnormal leukocyte function.[5]

TREATMENT

When there are few subjective symptoms and ulceration is absent, treatment of NL is usually not required. Protection from injury is important because the lesions are prone to ulcerate and bleed.[1] If the lesions are painful, there is ulceration present or the appearance of the lesions is particularly distressing to the patient, treatment may be indicated.[3] A consistently efficacious treatment for NL has yet to be identified. Various topical, oral, and surgical treatments have been tried with variable success. Among the more common treatments are nonspecific anti-inflammatory agents such as topical, intralesional, and systemic corticosteroids; fibrinolytics based on the assumption that angiopathy is associated with poor fibrinolysis; antiplatelet agents such as aspirin and dipyridamole based on the theory that platelet aggregation and prostaglandin secretion cause NL; physical techniques such as excision / grafting and laser surgery; and immunomodulatory drugs such as cyclosporin. Other methods that have been used to treat NL include the use of anti-malarial drugs, nicotinamide, topical tretinoin, and PUVA.[5,7,13,14] The lack of controlled studies in this area make it difficult to assess the effectiveness of the different therapies.

CONCLUSION

Much has yet to be learned about necrobiosis lipoidica. What causes NL, what is the most effective treatment for NL, and what is the nature of the relationship between NL and diabetes are all areas that need further investigation. Primary care physicians need to be able to recognize the signs of NL and should be aware of the association of necrobiosis lipoidica and diabetes. Although NL is easy to recognize in patients already diagnosed with DM, NL is often not considered without a previous diagnosis of diabetes. NL can exist with prolonged asymptomatic hyperglycemia and its recognition may result in the early detection of diabetes.[15] Prolonged follow-up and screening for diabetes is indicated for nondiabetic patients with NL as NL can precede the onset of diabetes by years.[1,15]

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Cost-Effectiveness to Evaluate HIV/AIDS Interventions in Developing Countries: Limitations and Ethics

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Millions of Africans continue to be reeped of their lives and livelihoods by this devastating disease. HIV/AIDS is responsible for nearly 20% of all deaths and disability-adjusted life years lost in Africa. What should be done, how resources should be allocated and how programs and policies should be implemented remain debated. To ensure that new resources have the maximal possible effect on the pandemic, cost effectiveness can be considered in the design of strategies for prevention and treatment. unless cost-effectiveness studies are done in a manner that accounts for the fallibility of non-trial situations, the sociocultural barriers to seeking treatment and care, political influences and the value of "intangible" costs and outcomes, they provide a limited scope for extrapolation and implementation.

As AIDS emerged insidiously into the medical and social landscape of the early 1980s, North Americans were drawn into an atmosphere of empathy, horror and compassion. Hollywood and the media bombarded us with images. The ravages of AIDS were everywhere – from the fiery lesions of Kaposi's sarcoma on Tom Hanks' wasting arms in the film "Philadelphia" to Ryan White's heart wrenching campaign against AIDS discrimination. AIDS was to be a battle more daunting than any disease we had encountered before.

Slowly, as AIDS transformed from a relentlessly efficient terminal illness to a chronic disease that could be controlled by the right drug "cocktail", interest began to wane. No longer could you discern a person with HIV walking down the street from a diabetic person or a completely healthy person. Out of site, out of mind.

But as North Americans and Europeans sighed with relief about the improved and less devastating nature of AIDS, millions of Africans continue to be reeped of their lives and livelihoods by this devastating disease. HIV/AIDS is responsible for nearly 20% of all deaths and disability-adjusted life years lost in Africa.[5] Indeed, the epidemic has reduced life expectancy by more than 10 years in the worst affected countries.[5]

Yet what should be done, how resources should be allocated and how programs and policies should be implemented remain debated.

One school of thought purports that it is imperative to treat those already infected with AIDS. The recent reduction in HIV drug prices and development of the Global Fund has resulted in a renewed push to provide widespread antiretroviral (ARV) treatment to people living with HIV/AIDS in low-income (and some middle-income) countries. Pharmaceutical companies have reduced the prices of some ARV drugs for developing countries by up to 90%.[8]

There is also a school of thought that points to prevention of HIV/AIDS as a more urgent and feasible approach in resource- and infrastructurally- scarce contexts. Programs such as education, condom distribution, and STD control for instance, may act synergistically, and more cost-effectively to address the AIDS epidemic.

A rational approach to the problem of prevention versus treatment requires attention be paid to both the economic and ethical facets of the different strategies available. Indeed, there needs to be a cognizance that economics and ethics, in this situation, go hand-in-hand. Several research and evidence-based approaches are available to the policy-maker to address the question of prevention versus treatment. For example, to ensure that new resources have the maximal possible effect on the pandemic, cost effectiveness can be considered in the design of strategies for prevention and treatment.[1] On the other hand, efforts must be made to ensure that seemingly cost-effective approaches, once implemented, will succeed at the level of the individual. Health-related quality of life tools are perhaps the most available and objective tools to assess the impact of disease and treatment at the level of the individual. In this paper, I will examine the utility and limitations of cost-effectiveness studies in developing policy combatting HIV/AIDS in Africa.

COST EFFECTIVENESS ANALYSIS AND HIV/AIDS IN AFRICA: GUIDELINES AND UTILITY

UNAIDS defines cost effectiveness as "a tool which enables programme managers to make informed decisions about resource allocation by measuring and comparing the consequences of various interventions"[2]

UNAIDS has proposed a standard framework within which to carry out cost effectivness analysis of AIDS/HIV interventions in developing countries.[2] Standardization of cost effectiveness studies improves the utility of studies by making them more comparable.

COST EFFECTIVENESS ANALYSIS AND HIV/AIDS IN AFRICA: LIMITATIONS

There are limitations to cost-effectiveness studies, both generally and in ways that are specific to studies pertaining to HIV/AIDS interventions in developing countries.

General problems encountered in cost-effectiveness studies include how to quantitatively measure the true "value" of intangible costs and consequences. How can monetary values be assigned to the pain and anxiety related to new and foreign medications or conversely to the feelings of self-worth related to returning to work after symptoms have improved? Cost-effectiveness as a determinant in policy-making is also limited in that costs and outcomes often have a different impact on different individuals or groups.[7] It is possible that an intervention that is cost-beneficial to the public health system is not beneficial for certain individuals. For example, although a centre offering Voluntary Counselling and Treatment theoretically increases access to HIV diagnosis and treatment, the stigma associated with the diagnosis may be, to the individual, a cost too high to bear, despite better care and treatment.

In the context of HIV/AIDS in developing countries, cost effectiveness analysis presents specific challenges depending on the intervention being measured.[2] The primary outcome measurement used in prevention programs is number of infections averted. However, it is rarely feasible to measure infections averted in a randomized, controlled manner.[2] Finally, prevention strategies are rarely implemented in isolation to others. Thus, it may be difficult to accurately attribute infections averted to the most effective intervention or to estimate the synergestic effects of multiple preventative strategies being run concurrently.[3]

Measuring consequences in cost-effectiveness studies of treatment poses several challenges. In studies of cure and treatment, life years gained or disability adjusted life years (DALY) is the ideal outcome.[2] However, it is often impossible to measure these outcomes due to constraints of time and budgets. UNAIDS suggests that an alternate outcome is number of infections treated and cured for those studies that evaluate programs aiming to treat a particular AIDS-related infection.

Studies looking at the cost-effectiveness of highly active anti-retroviral therapy may overestimate its effectiveness in several ways. First, studies may not account for increased rates HIV transmission since risky behaviour by HIV-positive people with improved life expectancy could increase. Some studies indicate that the availability of treatment has been positively correlated with an increase in risky behavior among homosexual men in some developed countries.[8] Second, since antiretroviral therapy has side effects, the value of one year of life is likely to be less than the 1 DALY assumed in most studies.

On the other hand, cost-effectiveness studies examining HAART interventions in Africa may underestimate positive consequences which cannot be easily measured. First, treatment availability may provide incentive to get HIV testing by reducing the stigma against people living with HIV/AIDS and improving the prospects of life with HIV/AIDS.[8] Second, since HAART decreases the viral load in HIV positive individuals, the probability of transmitting HIV to others even if they do engage in risky behaviours is reduced compared to no treatment.[8] Finally, cost-effectiveness studies may not account for the impact of treatment on reducing the economic and social burden of the disease, which prevention alone cannot do in the short run.

Another challenge for HIV/AIDS interventions and their evaluation is the influence of the context and prevalence in which the intervention is implemented. For instance, questions have arisen as to whether the cost-effectiveness of interventions change as the prevalence rises. A study by Wawer et al. on the failure of the Rakai mass STD treatment trial in Uganda shows that at later stages of the epidemic, STD management may have less impact as one tries to expand in higher prevalence settings.[11] This has been one of the explanations for the contrast between the success of the Mwanza trial, where overall HIV prevalence was four percent, in contrast to the failure of the Rakai where the HIV prevalence was 16 percent. Thus, it may be difficult to extrapolate cost-effectiveness studies between different prevalence settings.

It is thus apparent that unless cost-effectiveness studies are done in a manner that accounts for the fallibility of non-trial situations, the sociocultural barriers to seeking treatment and care, political influences and the value of "intangible" costs and outcomes, they provide a limited scope for extrapolation and implementation. Many would argue that the most unacceptable facet of cost-effectiveness analysis of AIDS/HIV interventions in Africa is the implicit commoditization of millions of lives in poor countries in the face of state-of-the-art treatments being used by those countries who own the lion's share of global wealth.

CONCLUSION

In my opinion, the dichotomy of the cost-effectiveness of prevention versus the cost-effectiveness of treatment is false. The ideal approach is to address both prevention and treatment. Ethically, it is imperative to control the epidemic as effectively as possible while providing all the needed care and support for people with the disease.[11] This combined approach may indeed be more cost-effective than focusing on one or the other. Reynolds et. al show that efforts to provide access to HAART that do not incorporate other cost-effective interventions such as access to preventative care and treatment of opportunistic infections, could have a limited effect on morbidity and mortality among HIV-infected patients.[10] However, a definitive conclusion as to the cost-effectiveness of a diversified portfolio of interventions against HIV/AIDS requires more research. To date, there has been no study that has systematically documented the cost-effectiveness of a combined preventative/treatment approach in a single setting.

In the mean time, the human rights perspective cannot be ignored. It should be used to incite a solid effort from the international community to fund a comprehensive response against HIV/AIDS that incorporates treatment.[8]

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The Effects of Exercise on the Prevention of Heart Disease

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Heart disease is the leading cause of death in Canada. It is for this reason that much emphasis has been placed on incorporating more physical activity into one's lifestyle. The beneficial effects of exercise are substantial, from improved blood pressure to lower cholesterol levels. Some of these effects are mediated by alterations in hormones, namely changes in epinephrine, insulin, and atrial natriuretic factor (ANF). ANF has effects on blood volume while ANF, epinephrine, and insulin have effects on attenuating the sympathetic nervous system.

The preventative effects of physical activity on heart disease have been known ever since the 1950s when Morris et al. reported in the Lancet in 1953 that sedentary London bus drivers had significantly higher rates of coronary disease than their bus conductor colleagues, who had to repeatedly climb the stairs between the upper and lower decks of London buses[1]. In a more recent study at the Lipid Research Clinic, 4276 middle-aged men were divided into four groups based on their physical fitness and followed for an average of 8.5 years. Coronary heart disease (CHD) mortality was six times greater in the least fit group compared to the most fit group[1]. The main mechanisms through which exercise prevents CHD are altered autonomic activity, structural and functional adaptations to the vasculature, increased cardiac blood supply, a reduction in the intrinsic heart rate, altered lipid profiles, increased insulin sensitivity, reduced body fat, changes to blood coagulation, improved myocardial and skeletal muscle function and a reduced blood pressure.

Although there is conflicting information on the effects of exercise on sympathetic activity, there is at least some data to indicate that endurance training induces a reduction in the activity of the sympathetic nervous system and an increase in the activity of the parasympathetic nervous system[2]. Physical activity decreases norepinephrine activity at rest as well as in response to emotional stress and exercise[3]. There is also a down-regulation of endorphin receptors in the heart. Endorphins facilitates epinephrine release and so decreased levels of endorphin receptors reduces the sympathetic system[3]. Cardiopulmonary baroreflex-mediated increases in blood pressure, renal and mesenteric sympatheitic nerve activity, and total peripheral resistance are all attenuated in response to exercise. At the same time splanchnic and skin blood flow are increased[3]. All of these responses help to reduce blood pressure. Fewer beta-adrenoceptors (stimulated by catecholamines) are found in the heart after exercise training due to down-regulation. One study if male swimmers who underwent a 2-month training program shows a drop in mean beta-adrenoceptor density from 1074 ± 52 per cell before training to 458 ± 78 per cell after training[4]. Those with the largest change in VO_2max also had the largest drop in beta-adrenoceptor density.

The larger stroke volume observed after exercise training helps stimulate the cardiopulmonary baroreceptors by increasing the stimulation of stretch receptors in the heart[3]. In response to stretch receptor stimulation, the cardiopulmonary baroreflex attenuates the sympathetic nervous system and thereby inhibits vasoconstriction. Elevated parasympathetic activity is a result of and raised circulating dopamine levels and dopamine receptors on neurons[3]. Stimulation of dopamine D_2 receptors in the nucleus ambiguous induces bradycardia by exciting vagal preganglionic cordioinhibitory neurons to the heart.

Endurance training promotes arterial compliance, which results in larger resting and maximally dilated arterial diameters. When the four coronary arteries of trained runners was stimulated with nitroglycerine, it was found that the total cross-sectional area of these arteries was double that of controls stimulated with nitroglycerine, indicating better vasodilatory reserver[3].

Furthermore, the nitric oxide (NO) synthase gene expression and NO release are increased in response to exercise[3]. NO is a potent vasodilator. A general increase in blood vessel responsiveness to vasoactive substances is seen with exercise training. Arterioles show an enhanced response to acetylcholine and terminal feed arteries exhibit an increased sensitivity to nitroprusside. Chronic exercise increases the total surface area of myocardial capillaries for perfusion and transport and, in the presence of coronary stenosis, stimulates coronary collateral growth[5]. The larger the increase in VO_2max attained through exercise, the larger the arterial compliance and the larger the drop in total peripheral resistance achieved[3]. The structural and functional changes seen in blood vessels helps to increase maximal perfusion, oxygen delivery, and oxygen uptake so as to increase the efficiency of the cardiovascular system and reduce the workload on the heart.

The bradycardia seen in endurance training is accounted initially by the altered sympathetic and parasympathetic activity seen in response to the training. More long term reductions in heart rate are attributed to a lower intrinsic heart rate[3]. This adaptation is a result of a prolonged atrial action potential, suggesting metabolic changes to the pacemaker cells[2]. Desensitization of cardiac ß receptors to catecholamines also reduces the intrinsic heart rate. Pacemaker firing rates increases with atrial stretch. Exercise is known to increase atrial and ventricular volume and compliance. This will lead to a reduction in stretch induced stimulation of the pacemaker and will therefore lower the firing rate[3].

Exercise training increases HDL cholesterol and lowers LDL cholesterol levels so as to increase the HDL/LDL ratio. More specifically, the HDL_2 subfraction of HDL is also increased which is thought to have a protective effect against CHD[6]. Exercise increases lipoprotein lipase (LPL) activity, and this helps LPL's action of inhibiting HDL_2 breakdown and metabolizing triglycerides. In terms of LDL cholesterol, it is the small dense LDL subfraction of LDLs that is reduced with exercise, and it is the small dense LDL that is associated with a more rapid development of atherosclerosis[6]. LDL receptors are up-regulated in exercise and this helps to lower LDL levels. Physically trained muscles have an increased ability for lipid metabolism. This is due to elevated blood flow in the muscle and increased activity of fat-mobilizing and fat-metabolizing enzymes[7]. Hence, a trained person uses more free fatty acids for energy than an untrained person.

It has been shown that exercise training reduces the rise in plasma insulin concentrations in response to a glucose load[2]. This would indicate that insulin action is improved through endurance training. Hyperinsulinemia stimulates the sympathetic nervous system, which elevates blood pressure. The increased insulin sensitivity brought about by exercise, and the subsequent decrease in circulating insulin, may therefore have significant effects in reducing blood pressure[6]. Increased insulin sensitivity will also help prevent the onset of type II diabetes, the complications of which include heart disease. Endurance trained muscles contain as much as twice the levels of GLUT-4 transporters as untrained muscles[2]. This contributes to a larger up-take of glucose in response to insulin, and, therefore, helps keep blood glucose levels within the proper range[6]. A decreased plasma insulin concentration during the fasting state is also beneficial because hyperinsulinemia is an independent risk factor for arteriosclerosis[2]. Total

body fat, and particularly abdominal fat, increase the risk of CHD by leading to increased blood triglycerides, lower HDL cholesterol levels, higher LDL cholesterol levels, depressed insulin metabolism (leading to increased plasma insulin levels), insulin resistance, and raised blood pressure[8]. Exercise helps to lower body fat and helps people maintain lost weight.

Exercise training has an important effect on blood coagulation and fibrinolysis. Training decreases platelet aggregation and increases fibrinolysis[5]. Enhanced fibrinolysis is due to an increase in the release of plasminogen activator from the vessel walls. Exercise can also augment the spontaneous lysis of small thrombi in the calf, and thereby prevent the formation of larger, more dangerous thrombi[5].

Endurance training improves myocardial cellular capacity. This leads to greater cardiac contractility and ejection fraction (percentage of end-diastolic volume ejected from the heart per beat[6]. Decreased vascular resistance results in reduced afterload on the heart and makes it easier for the heart to contract[6]. This will lighten the workload the heart has to do. The left ventricular hypertrophy brings about a reduction in the work each sarcomere in the ventricle has to do[1]. It also facilitates the maintenance of the high ejection fraction and stroke volume at high work rates and the development of a large maximal cardiac output[1].

Trained muscles have an increase in both the number and size of mitochondria, and also a potential twofold increase in the level of enzymes involved in aerobic metabolism[7]. This helps trained muscle extract higher amounts of oxygen from the circulating blood during exercise so as to increase the arteriovenous oxygen difference. This augmented arteriovenous difference is, however, also due to more effective distribution of cardiac output to working muscle and an enhanced ability of trained muscle to use oxygen[7].

Physical exercise helps stimulate the release of arterial natriuretic factor (ANF) by the heart, which increases sodium and fluid loss and thereby lowers blood pressure[6]. ANF also inhibits the sympathetic nervous system and helps decrease the amount of vasoconstriction of blood vessels. The weight loss brought about by exercise is crucial for blood pressure reduction. Up to a certain limit, every kilogram of weight loss results in approximately a 1.6 mmHg fall in systolic pressure and a 1.3 mmHg fall in diastolic pressure[6]. Meta analysis of 36 studies on this subject has shown that blood pressure can be reduced as much as 9.9 mmHg systolically and 7.6 mmHg diastolically[1], although moderate intensity exercise (below 70% of maximum heart rate) has been shown to reduce systolic pressure as much a 20 mmHg and diastolic pressure as much as 16 mmHg[6].

Many long term longitudinal studies have shown the enormous cardiovascular benefits of regular physical activity. Exercise reduces almost all known alterable risk factors for CHD from high blood pressure to high plasma choloesterol to hyperinsulinemia. It is recommended that people engage in 20-30 minutes of moderate-intensity exercise at least three days a week in order to improve cardiovascular health[9]. Moderate intensity is between 65% and 85% of heart rate reserve (HRR = maximum heart rate – resting heart rate)[9]. It would be prudent to follow health recommendations in order to reduce the chances of developing this common, yet in many ways preventable, disease.

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Surgical Weight Loss Options for the Obese

Seng Thipphavong and Gladys Chan, Meds 2004

In 1997, the estimated cost of obesity in Canada was more than $1.8 billion. Morbid obesity is defined as a BMI exceeding 40 and bariatric (gastrointestinal) surgery options may be considered as a last resort. Vertical banded gastroplasty (VBG) involves the reduction of the amount of food intake by creating a vertical pouch along the lesser curvature of the stomach using surgical staples. VBG is advantageous due to low morbidity and a lack of any bypass of the lower intestinal tract. However, a long-term failure to maintain weight loss is associated with VBG. Adjustable gastric banding creates a small compartment in the proximal stomach and has been shown to decrease BMI from 44 kg/m2 to 33.2 kg/m2 with stable results after a follow-up of up to 86 months (median 36 months). Biliopancreatic bypass involves a subtotal gastrectomy followed by transection of the proximal ileum to the ileocecal valve. The distal limb is anastomosed to the gastric pouch. Biliopancreatic bypass has been shown to have a short-term weight loss of 74% after 2 years while long-term weight maintenance has been reported at 78% after 14 years. The Roux-en-Y Gastric bypass involves transection of the jejunum and bringing the proximal jejunum retrocolic through an opening in the transverse mesocolon. The proximal jejunum is then anastomosed to a constructed gastric pouch. Long- term results of the Roux-en-Y Gastric bypass procedure are quite successful with a mean weight loss of 49.2% of preoperative body weight. General complications of bariatric surgery include deep venous thrombosis, pulmonary emboli, atelectasis, peritonitis, and cholelithiasis.

INTRODUCTION

Over the past decade, the proportion of obese adults in Canada has increased dramatically. The Canadian Community Health Survey (CCHS) showed that from 1994/95 to 2000/01, the number of obese Canadians between the ages of 20 to 64 increased by 24%. Men and women aged 45 to 54 showed the greatest increase and account for one-fourth of obese adults in Canada.[1] In the United States, similar trends were seen in the CDC Behavioural Risk Factor Surveillance System (BRFSS) report which showed a 61% increase in the prevalence of obesity among U.S. adults from 1991 to 2000.[2] Individuals who are obese are at higher risk for coronary artery disease, heart failure, diabetes, obstructive sleep apnea, arthritis and psychological problems. In addition, morbidly obese individuals have a 12 time reduction in life expectancy. In regard to health care costs, in 1997 the estimated cost of obesity in Canada was more than $1.8 billion, which accounted for 2.4% of total health care costs for all diseases.[3]

Obesity is measured by calculating an individual's body mass index (BMI), which is equal to mass (kg) divided by height squared (m2). An individual having a BMI greater than 30 would be classified as obese. Morbid obesity is defined as a BMI exceeding 40 and this generally reflects a body weight exceeding 100 lbs over ideal body weight. For morbidly obese individuals, bariatric (gastrointestinal) surgery may be considered as a last resort. Conservative therapy such as behaviour therapy and exercise for morbidly obese individuals show that only 5% to 10% maintain weight loss for more than a few years. iv On the other hand, bariatric procedures have shown a greater than 50% success rate in maintaining long-term weight loss.[4]

Indications for bariatric surgery recommended by the National Institutes of Health Consensus Development Conference Statement on Gastrointestinal Surgery for Morbid Obesity include a BMI greater than 40, or a BMI greater than 35 in association with a life-threatening condition such as severe diabetes mellitus or cardiopulmonary problems (such as severe apnea, pickwickian syndrome, and obesity-related cardiomyopathy).[5]

Bariatric surgery involves a restrictive component and/or a malabsorptive component. Restrictive methods involve removing or bypassing a portion of the stomach to reduce the volume of the stomach. This method restricts the amount of food that can be

eaten prior to becoming full. Restrictive operations include vertical banded gastroplasty and adjustable gastric banding (the Lap-Band). Malabsorptive methods involve redirection of bile and pancreatic secretions away from food, thus causing incomplete digestion and absorption of food. Malabsorptive operations include the Roux-en-Y Gastric bypass and biliopancreatic bypass.

RESTRICTIVE OPERATIONS

Vertical Banded Gastroplasty

Description of the operation

Vertical banded gastroplasty (VBG) was first described by Dr. Edward Mason in 1982 and involves the reduction of the amount of food intake by creating a vertical pouch along the lesser curvature of the stomach using surgical staples. The operation is performed through a midline supraumbilical incision. A window is created through both walls of the stomach above the crow's foot and next to the outlet along the lesser curvature. Staples are applied at a point 3 cm from the lesser curvature and 7 cm below the angle of His. The outlet is reinforced by two rows of staples and a polyproplylene mesh collar. The mesh collar is not sutured to the stomach itself. This procedure creates a pouch that holds less that 50 mL.[6]

Outcomes

VBG is advantageous due to a low morbidity and a lack of any bypass of the intestinal tract. Mason reported successful weight loss (defined as a loss of 50% or more of excess body weight) in only 30.2% of his VBG patients in a 10-year follow-up study. Another study of 70 VBG patients from 1985 to 1989 revealed weight loss was greatest during the first 6 months, continued until 1 year post-operatively and generally ceased after that period. The same study showed that only 38% of patients had lost and maintained 50% or more of their excess weight. Median weight loss at 1 year post-operation was 36.7 kg or 48% of excess body weight.[7] Long-term failure to maintain weight loss with VBG is generally associated with enlargement of the gastric pouch, increased rate of emptying of the pouch over time, staple line dehiscence, and diet change to high-calorie liquids or soft foods[8].

Complications

Potential complications of VBG include outlet stenosis, staple line dehiscence, wound infection, and band erosion. Patients who undergo VBG may not be able to tolerate red meat or untoasted bread and the Mayo Clinic study showed that 30% to 50% of patients continued to vomit once or more per week 3 years post-operation. Although VBG results are not satisfactory for long-term maintenance of weight loss, VBG continues to be performed due to its safety and lack of metabolic side effects.

Adjustable Gastric Banding

Description of the operation

Adjustable gastric banding devices were introduced in the 1990s and are made of Dacron or silicone. Adjustable bands create a small compartment in the proximal stomach. Adjustable banding can be performed laparoscopically. Five trocars are inserted at the supra-umbilical, sub-xiphoid, right upper quadrant, left upper quadrant, and left subcostal positions. The subcardial area is exposed and dissection of the lesser and greater curvatures is performed to create a retrogastric tunnel. The band is then put into place and closed. Calibration of the stoma needs to occur and retention sutures are then inserted. The band can be inflated via a subcutaneous reservoir pump containing saline to restrict food intake of the stomach. Advantages of laparoscopic surgery include less pain, faster postoperative recovery, and fewer wound infections.

Outcomes

In a study of 184 patients who underwent Lap-Band insertion laparoscopically, the mean excess weight loss was 16% in 4 weeks, 23% in 3 months, 31% in 6 months, 58% in 1 year, and 87% in 2 years. Over 90% of patients were satisfied with their outcome.[9] In another study, a 7 year retrospective review of the Lap-Band revealed that the mean BMI had decreased from 44 kg/m2 to 33.2 kg/m2 and was stable after a follow-up of up to 86 months (median 36 months).[10]

Complications

A 9% complication rate post-operatively has been reported. Complications included band erosion (1.1%) and slippage of the band (2.2%)9. Another common complication is total and irreversible food intolerance due to proximal pouch dilatation which occurred in 4.6% of patients[10].

MALABSORPTIVE PROCEDURES

Roux-en-Y Gastric bypass

Description of the operation

The first gastric bypass was described by Mason and Ito in 1967, where they performed a Billroth II retrocolic gastrojejunostomy which anastomosed the fundus of the stomach to the jejunum. The procedure was improved by Griffen through the construction of a Roux-en-Y gastrojejunostomy to prevent bile reflux gastritis.

Operating through a midline incision, the first opening is created at the lesser curvature of the stomach with a second opening at the angle of His. A gastric pouch is constructed through the two openings with a stapler, isolating the pouch from the remaining stomach. The jejunum is then transected and the proximal portion is brought retrocolic through an opening in the transverse mesocolon and anastomosed to the gastric pouch, creating the Roux-en-Y limb. This procedure can be altered by using different lengths of the limbs to adjust the malabsorption rate.

Outcomes

Patients who had this procedure experienced an average of sixty pounds weight loss with minimal liver dysfunction and good replacement of electrolyte and vitamin deficiencies. In a follow-up study of 608 patients who had the surgery, the long-term results of the procedures are quite successful with a mean weight loss of 49.2% of preoperative body weight[11]. The study also found that of 298 patients who were previously glucose intolerant, 91% had normal fasting glucose, glycosylated hemoglobins and insulin levels post-operatively[12]. Other satisfactory outcomes include lowering plasma levels of glucose, triglycerides and high-density lipoproteins.

Complications

Early complications include splenic injuries, anastomotic leaks, wound infections and pulmonary embolisms. Later complications include stenosis and obstruction of the gastric outlet

and small bowel, incisional hernia and gallbladder disease. Nutritional supplement is required to prevent iron, folate, calcium, and vitamins A, B_{12}, D, E deficiencies.

Biliopancreatic Bypass

Description of the procedure

The initial procedure was described by Scopinaro in 1981 and combines a subtotal gastrectomy, with a Roux-en-Y gastroileal anastomosis and jejunoileal anastomosis to the ileocecal valve. Although this procedure had excellent weight loss results, complications of protein malnutrition and malabsorption of vitamins occurred. Marceau and coworkers further improved the procedure by changing the subtotal gastrectomy to a sleeve gastrectomy and the gastroileal anastomosis to a Roux-en-Y duodenoileal anastomosis, thus reducing the incidence of malabsorption. Both procedures are routinely done in Canada and Europe.

A midline incision is made and a subtotal gastrectomy is performed, leaving around 200 to 500 mL of gastric pouch. The ileum is transected proximal to the ileocecal valve and the distal limb is brought retrocolically and anastomosed to the gastric pouch. The biliopancreatic limb is anastomosed end-to-side to the ileocecal valve. The biliopancreatic bypass with a duodenal switch is performed by changing the above procedure to create a gastric sleeve and transecting the duodenum distal to the pylorus. The ileum is transected proximal to the ileocecal valve and the distal limb is anastomosed to the proximal duodenum. The biliopancreatic limb is then anastomosed to the distal ileum.

Outcomes

For 1356 patients in Italy who had the biliopancreatic bypass, the short-term weight loss was 74% in 2 years while long-term weight maintenance was reported at 78% in 14 years[13]. Advantages also included improvement in hypoventilation, obstructive sleep apnea syndromes, hypertension and adult-onset diabetes. The modified procedure with the duodenal switch was performed on 465 patients, with a mean percentage excess weight loss at 51 months of 73%[14]. This procedure had a lower revision rate and improvement in calcium and iron homeostasis with no significant weight difference when compared to the biliopancreatic bypass.

Complications

Early complications include infection, pulmonary embolisms, and anastomotic leak. Late complications include marginal ulceration and protein malnutrition and bone demineralization.

SOME COMPLICATIONS OF BARIATRIC SURGERY

Deep Venous Thrombosis and Pulmonary Embolus

In general, morbidly obese patients have a more sedentary lifestyle and tend to suffer from degenerative joint disease. They may also suffer from polycythemia as a result of having respiratory insufficiency of obesity. These, together with undergoing a long abdominal surgical procedure in a supine position, predispose them to venous stasis disease leading to the formation of deep venous thrombosis. Some patients suffer from obesity hypoventilation syndrome that compromises their pulmonary reserve, making them vulnerable to death due to mild pulmonary embolism. In general practice, patients have sequential compres-

sion stockings placed on call to surgery and are provided with subcutaneous heparin before and after the surgery. For those at high risk, a vena caval filter placement before the procedure should be considered. However, the risks and complications of the procedure, such as pneumothorax and perforation of the right atrium, should be discussed with the patient.

Atelectasis

Retraction in open surgery and pneumoperitoneum in laparoscopic cases is a common cause of atelectasis postoperatively. Fever and tachycardia are two common symptoms that resolve with pulmonary toilet and nocturnal nasal continuous positive airway pressure.

Peritonitis

Leakage from anastomosis sites or staple-lines is a common but difficult diagnosis that is usually unrecognized until sepsis has occurred. Increasing abdominal pain, back pain or hiccups, combined with persistent tachycardia and fever with pulmonary dysfunction are some clinical signs that should alert clinicians to possible leakage. Failure to treat may lead to severe systemic sepsis, multiple organ failure and death. A contrast study with Gastrograffin can help identify the area of leakage for both proximal gastric bypass and divided gastric bypass. A relatively well patient with subclinical leaks should be closely observed, while patients with suspected leaks should undergo a laparotomy to repair the defect and drain the upper abdomen. Necrotizing wound infections are common after peritonitis and the wound should be left open until patient recovers.

Cholelithiasis

Rapid weight loss after bariatric surgery causes bile stasis and sludge formation in the gallbladder, leading to gallstones. Prophylatic use of ursodiol or cholecystectomy has been found to be effective in lowering the incidence of cholelithiasis.

PATIENT BENEFITS

The benefits of bariatric surgery are not only limited to metabolic and health improvement, it also has a large impact on the quality of life to the patient. The weight loss contributes greatly to the improvement in self-esteem and self-image, allowing patients to feel more confident about their abilities. They are also more accepted socially and face less discrimination within the workforce.

CONCLUSION

The care for obese patients has evolved into an enormous health-care concern with large economic costs needed for the treatment of obesity-related problems. Bariatric surgery remains the most effective long-term treatment for the morbidly obese, providing excellent results in weight loss and maintenance and possible reversal of other problems such as glucose intolerance. The most popular procedures are the Roux-en-Y gastric bypass and the vertical-banded gastroplasty with a high success rate of mean weight loss and maintenance. The most current procedures in development include laparoscopic Roux-en-Y gastric bypass and vertical-banded gastroplasty. Advantages of the laparoscopic procedures performed by experienced surgeons include less pain, faster postoperative recovery, fewer hernias and fewer wound

infections. Long-term benefits of laparoscopic procedures are currently being studied.

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Dr. Johann Aufreiter – An Appreciation

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Dr. Hans Aufreiter, professor in the Department of Psychiatry since 1972, passed away peacefully on February 24th, 2001 after a long battle with illness. He will be greatly missed by countless individuals whose lives have been touched in the sixty active years of his professional practice as a therapist, teacher, colleague and friend. Hans completed his medical training in Vienna in 1939 and subsequently studied internal medicine. After World War II he undertook psychoanalytic training in Vienna. In the early 1950's Hans and his wife, Dr. Gottfriede (Friedl) Aufreiter, were invited by Dr. Ewen Cameron to join the faculty at McGill University. They became training analysts with the British Psychoanalytic Society to prepare for the task of initiating psychoanalytic teaching and training in Canada, together with Dr. Clifford Scott with whom the Aufreiters became founding members of the Canadian Psychoanalytic Society.

Through his teaching and supervision, and particularly through the medium of personal psychoanalysis, Hans Aufreiter directly or indirectly influenced generations of psychoanalysts, psychiatrists and other psychotherapists in Canada. In this manner he had a considerable impact on the development of psychiatry in Canada in the second half of the twentieth century. In 1972 the Aufreiters moved to London, Ontario at the invitation of Dr. Gil Heseltine, the new chair of the Department of Psychiatry of the University of Western Ontario. At Western Hans was full professor and was the leading teacher of psychotherapy. With the support of Friedl and Dr. Bill Tillmann he was able to attract other psychoanalysts to London and to influence psychiatrists there to undergo psychoanalytic training in Toronto, where he was a training analyst, with the result that by the early 1980's Western's psychiatry program had a very strong psychodynamic foundation, and London enjoyed a community of psychoanalysts and psychotherapists far out of proportion to its size for a city in Canada.

Hans was the consummate clinical teacher and could hold an audience of professionals spellbound. He was a leading exponent in Canada of attachment theory and object relations theory. He downplayed the concept of the Oedipus complex, strongly believing that aggression was not inborn but a consequence of chronic frustration in interpersonal relationships. Hans could be provocative in his promulgation of his theoretical approach; for example, his 1975 Ruth Easser Memorial Lecture at Mount Sinai Hospital in Toronto was entitled "St. Oedipus and the Holy Penis". Hans was thoroughly grounded in psychoanalytic theory but always drew his conclusions close to the clinical data he was working with. He insisted that psychoanalytic formulation should be firmly based on what the patient has said about him or herself, rather than on speculation. He put much emphasis on the significance of the day residue in interpreting dreams, which underlines the emotional significance to the patient of what the patient had experienced that day. Hans was single-minded in his commitment to teaching psychoanalysis and psychotherapy, and was never too

busy to teach or advise a student, often reinforcing his teachings with personal and professional anecdotes. His dedication to teaching, his clinical acumen, and his infectious enthusiasm have been an inspiration to many mental health professionals. Hans was a very generous teacher, giving freely of his time and energy, but had little patience with ambivalent pupils and he could be quite sharp tongued when provoked. Although London, Ontario was a small and somewhat remote outpost of psychoanalysis, Hans constantly pushed for exposure to the very best teachers in the field, including Bowlby, Kernberg, Goldberg, Masterson, Volkan, Mitchell, and Gedo. One way in which Hans's tremendous teaching contribution has been recognized in London has been the Aufreiter Lecture to which eminent psychoanalysts are invited to present papers on an annual basis.

Hans's teachings were spiced with his peppery wit. He had the rare skill of distilling the essence of good practice and technique and of capturing complex issues in unforgettable and humorous vignettes. The need to be attentive, energetic, active and engaging with patients was summed up by his caution that if we fail in these tasks, we end up with "two stuffed shirts in the room, one in the chair and one on the couch". His analysands and trainees have largely populated and led psychoanalytic societies across Canada. It would not be going too far to say that Hans, with Friedl, transformed the face of Canadian psychiatry in general with respect to the foundation of the Canadian Psychoanalytic Society and Institute in Montreal, and of psychiatry in London in particular. They were the nidus around which the Southwestern Ontario Psychoanalytic Society formed. A measure of Hans' influence is that by the late 1970's, more than half of the psychiatry residents in London were undergoing personal analysis. Hans' psychoanalytic influence is not limited to Canada; his students have settled as far afield as Australia.

With Hans's death, Canadian psychiatry has lost a pioneering educator, an exceptionally astute clinician, and a highly valued mentor. His oft repeated first principle in life and treatment was to "be a mensch"; he provided us with the gold standard in this regard. Hans's menschlichkeit was evident to the many individuals he taught and treated with genuine interest, concern, and compassion.

Hypothyroidism: Should it be treated with T4 or a combination of T3 and T4? The controversy will soon be over…

Natalie Kotowycz, Meds 2005

For several decades, hypothyroidism has primarily been treated with thyroxine (T4) alone, despite the fact that a normal thyroid gland secretes both T4 and triiodothyronine (T3). Although T4 treatment restores thyroid hormone levels into the normal range, patients often complain that T4 supplementation does not alleviate all symptoms of hypothyroidism. Patients frequently continue to feel cold, fatigued and have problems with weight control. Recent data indicates that when treating patients with hypothyroidism, partial substitution of T3 for T4 may improve neuropsychological function and mood. The following is a brief synopsis of a study currently being completed at Toronto's Sunnybrook and Women's College Health Sciences Center. This study is comparing T4 with two different combinations of T4 and T3 treatment in euthyroid subjects with T4 treated hypothyroidism.

Thyroid gland abnormalities have been found to affect five percent of the Canadian population.[1] Hypothyroidism is one of the common manifestations of thyroid disease and it is characterized by an underproduction of thyroid hormones. A healthy thyroid gland produces two hormones – tetraiodothyronine, also known as T4 or thyroxine, and triiodothyronine, T3. The former comprises 80% of the gland's hormonal output, while T3, the active form of thyroid hormone, makes up 20%.[2]

The causes of hypothyroidism are numerous, with the most common being an autoimmune disease called Hashimoto's. In Hashimoto's thyroiditis, thyroid cells are primarily destroyed by cell mediated immunity, although thyroid antiperoxidase antibodies (TPOAbs) have also been implicated in its pathogenesis. These antibodies inhibit enzyme activity in thyroid cells and stimulate natural killer cell cytotoxicity.[3] Antithyroid antibodies are therefore primary diagnostic markers of this disease. The insufficient number of cells leaves the patient in a hypothyroid state.[4] Other causes of hypothyroidism include thyroid dysgenesis, radioiodine exposure, pituitary abnormalities as well as postpartum hypothyroidism.[5] Since thyroid hormones play a pivotal role in many bodily functions including growth, metabolism, and mood regulation, a deficit results in a wide array of symptoms. Typical presenting features of hypothyroidism include feeling cold, extreme fatigue despite adequate sleep, weight gain, and depression. Other symptoms include brittle nails, thin and dry hair, high cholesterol, heavier menstrual cycles, as well as muscle aches and cramps.[4]

Customarily, treatment for hypothyroidism has consisted of supplementation with T4 alone. Examples of T4 containing medications include Eltroxin and Synthroid. Although T4 treatment does restore thyroid hormone levels back into the normal range, not all symptoms resolve with this particular therapy. Patients often continue to complain about extreme fatigue, weight gain and depression.

It has generally been assumed that the T4 is adequately transformed into active T3 by the monodeiodination of T4 in extrathyroidal tissue; as a result, it was deemed unnecessary to supplement hypothyroid patients with both T4 and T3. Nonetheless, a 1999 study published in the New England Journal of Medicine found that in hypothyroid patients, partial substitution of T3 for T4 might improve mood and neuropsychological function.[6] This sparked the interest of two physicians in Toronto who decided to further pursue this topic. At Toronto's Sunnybrook and Women's College Health Sciences Center, Dr. Silverberg, an endocrinologist, and Dr. Levitt, a psychiatrist, decided to conduct a study that specifically compared T4 treatment with T3 treatment and two different combinations of T4 and T3 in hypothyroid patients.

This study began in the summer of 1999 and it directly compared T4 treatment with combined T3-T4 in 59 subjects with T4 treated hypothyroidism. In order to participate in the study, participants were required to have at least one persistent symptom of hypothyroidism. Patients had to be on a stable dose of T4 and their blood work had to reveal that they were in a euthyroid state as evidenced by a TSH in the normal range. Once participants

entered the study, they were divided into various treatment groups. The first received their current dose of T4, while the second group was given T3 alone in a concentration that physiologically matched their original dose of T4. The final two groups were put on combination treatments consisting of both T3 and T4. One group received T4 and T3 in a ratio of 1 to 15 assuming that the biopotency of T3 was equal to four times that of T4; the other combined group received T4 and T3 in a ratio of 1 to 15 assuming a biopotency of T3 equal to two and a half times that of T4. Both groups were given pills in a double blind twice daily dosing over a three to six month period. Blood tests were conducted every four weeks and once TSH levels were in the normal range for two months, various cognitive, psychosocial, physical and laboratory investigations were conducted.

The physical exam consisted of monitoring pulse rate and blood pressure, while the laboratory investigations looked at cholesterol, free T3, free T4, TSH, ferritin and Sex Hormone Binding Globulin concentrations. Electrocardiograms and echocardiograms were also conducted in order to look at cardiac function; more specifically, the rate of Left Ventricular contraction was measured on the subjects.

Participants completed a set of cognitive tests and also evaluated various Quality of Life measures. The former included the California verbal learning test, the 7/24 spatial recall test, various symbol-digit substitution tasks, as well as the logical memory test from the Wechsler memory scale (revised). The data from this study has been analyzed, but unfortunately the results cannot be presented at this point in time. They will be presented to the Canadian Society of Endocrinology and Metabolism this fall and then submitted for publication.

It has been estimated that more than 60% of euthyroid patients with T4 treated hypothyroidism continue to complain of symptoms of hypothyroidism despite normalization of all blood parameters.[7] If 5% of the Canadian population suffers from this condition1 and 60% remain symptomatic, there are therefore over 900,000 Canadians that could potentially benefit from improved treatment. Clearly, this study is of great significance as it will reveal whether there is a more suitable way of treating people that are suffering from the long-term effects of hypothyroidism.

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Is dementia in long-standing schizophrenia an entity distinct from Alzheimer's Disease?

Nina Ghosh, Meds 2005

Severe cognitive impairment is common in elderly patients with schizophrenia. Since Alzheimer's disease is the most common cause of dementia in the elderly, it is a plausible co-morbid disease contributing to the dementia observed in elderly patients with schizophrenia. Neuropathological surveys indicate that most cases of cognitive decline in schizophrenics cannot be explained by the development of neurofibrillary tangles within neurons nor the presence of amyloid senile plaques. Studies comparing the rate of cognitive decline in patients with schizophrenia and Alzheimer's also point to the dementia in Schizophrenia as a separate entity from that seen in Alzheimer's disease. Based on the evidence, the report contends that in most cases, dementia associated with schizophrenia involves pathophysiological mechanisms different from those involved in Alzheimer's disease. However, overlap in sites of pathological decline may result in some overlapping clinical findings.

CASE EXAMPLE

Miss X is a 65 year-old female who has been living a mental health facility since the age of 29 after being diagnosed with schizophrenia. Though she had struggled with persecutory auditory hallucinations most of her life, the most striking feature of her illness was a general lack of affect, extreme difficulty relating to others, and considerable lack of motivation. She was relatively stable on olanzapine until one year ago, when the nursing staff began to notice that Miss X was become increasingly "absent-minded" with regards to her belongings. On a few recent occasions she has had difficulty remembering her brother's name, Steven, who visits her on a weekly basis. She can no longer tell time and is usually unable to tell others where she is. Changes in her dose of olanzapine and a course on clonazapine did not seem to improve her cognitive decline.

INTRODUCTION

Severe cognitive impairment is common in elderly patients with schizophrenia.[1] Since Alzheimer's disease is the most common cause of dementia in the elderly, it is a plausible co-morbid disease contributing to the dementia observed in elderly patients with schizophrenia. Commonalities between dementia in the two illnesses include varying degrees of delusional manifestation, apathy, lateral/third-ventricular enlargement, reduced frontal lobe activity, and hippocampal atrophy.[3] Moreover, patients with either disease have shown comparable cognitive impairment on standardized neuropsychological tests.[2] The pattern of cognitive decline in the elderly with long standing schizophrenia may also vary with the predominance of negative versus positive symptoms.[2] Whether the clinical similarities and dissimilarities between cognitive decline in Alzheimer's disease and those in schizophrenia represent similar pathological processes have important implications for clinical practice. For instance, similar pathophysiological processes may mean a common pharmacological approach, such as acetylcholinesterase inhibitors, can be used to treat both dementia in Schizophrenia and dementia in Alzheimer's disease. This report reviews the current literature to address the question whether dementia associated with long-standing schizophrenia is really a form of Alzheimer's disease. Based on the evidence, the report will attempt to contend that in most cases, dementia associated with schizophrenia involves pathophysiological mechanisms different from those involved in Alzheimer's disease. However, overlap in sites of pathological decline may result in some similar clinical findings

EVIDENCE SUPPORTING/REFUTING THE DEMENTIA IN LONG-STANDING SCHIZOPHRENIA TO BE ALZHEIMER'S DEMENTIA:

Neuropathological studies are perhaps the gold standard in distinguishing dementia in chronic schizophrenics from Alzheimer's dementia. Deposition of the amyloid ß-peptide into

plaques in the brain parenchyma and cerebral blood vessel walls, accumulation of neurofibrillary tangles in neurons, neuronal loss, and synaptic pathology are all distinguishing features of Alzheimer's disease.[10] Patients with schizophrenia are commonly heavy smokers (prevalence between 74% and 92%) and nicotine can decrease amyloid ß-peptide toxicity and fibril formation.[11] It has been proposed that nicotine or nicotinic receptor agonists might improve cognitive functioning not only by supplementing cholinergic neurotransmission but also by protecting against amyloid ß-peptide neurotoxicity, probably through increased release of amyloid precursor proteins after activation of nicotinic receptors. As is addressed later, the above findings may have important implications for pharmacological therapy of dementia in elderly schizophrenics.

Despite superficial similarities in the clinical and neuropsychological profiles of patients with schizophrenia and comorbid dementias, extensive neuropathological probing has failed to find any evidence of neurodegeneration or neural injury beyond what is typically observed in brains of individuals without neuropsychiatric illness. Religa et al. examined the possible involvement of amyloid beta peptide in cognitive impairment in schizophrenia using immunosorbent assays in postmortem brain samples from Alzheimer's disease patients, from normal elderly comparison subjects and from schizophrenia patients showing cognitive decline. Although the levels of beta amyloid beta peptide in Alzheimer's patients were increased, the amyloid beta-peptide levels in schizophrenic patients were not significantly much different from control groups. These results suggest that causes of cognitive impairment in pure schizophrenia are different from those in Alzheimer's disease.[2] A similar neuropathological study which also included cognitive assessment, compared the degree of senile plaques between cognitively impaired schizophrenia patients, Alzheimer's patients, and age-matched controls. The number of senile plaques or neurofibrillary tangles was not different in the group with schizophrenia compared with the age-matched controls.[5] This study was paralleled by Dwork et al who showed that of the subjects with schizophrenia, 68% had definite cognitive impairment, but only 8% satisfied neuropathological criteria for Alzheimer's disease.[8] Thus, it is apparent from neuropathological surveys that most cases of cognitive decline in schizophrenics cannot be explained by the development of neurofibrillary tangles within neurons nor the presence of amyloid senile plaques. Thus, if there are clinical similarities and between these two types of dementia, they must be explained by other mechanisms – either those at the molecular level or cytoarchitectural level or due to different pathological processes affecting similar areas of the brain.

Studies comparing CSF markers in patients with schizophrenia and Alzheimer's also point to a difference in the underlying pathological process. For example, although increased cerebrospinal fluid (CSF) tau protein level provide a sensitive marker of Alzheimer's disease, there appears to be no significant differences in CSF total tau levels between patients with schizophrenia and normal controls.[4] Although these findings do not exclude a progressive neurodegenerative pathology in Schizophrenia, they provide evidence against an Alzheimer's Disease related pathology associated with increased CSF tau levels.

Studies comparing the rate of cognitive decline in patients with schizophrenia and Alzheimer's also point to the dementia in Schizophrenia as a separate entity from that seen in Alzheimer's disease. Palmer et al examined 1- and 2- year cognitive changes among patients having earlier-onset schizophrenia (EOSD), late-onset schizophrenia (LOSD) and Alzheimer's disease . Their results, based on MMSE and Mattis Dementia Rating Scale scores, showed that LOSD patients, EOSD patients and normal controls had similar rates of decline of cognition whereas Alzheimer's patients had greater decline.[3] In essence, their study points to dementia in both late and early onset schizophrenia as reflecting more static encephalopathies with slower rates of cognitive decline as compared to Alzheimer's disease.

A differential pattern of cognitive decline in Alzheimer's disease patients versus schizophrenia with comorbid dementia was also demonstrated by Heaton et al. (1994) Their study compared the performance of schizophrenia patients with AD patients on an expanded Halstead-Reitan Battery. Schizophrenia patient's pattern of deficits differed from AD patients in that AD patients showed less efficient learning and more rapid forgetting. This divergent pattern of cognitive decline between the two diseases suggests that most cases of cognitive decline in later life of chronic schizophrenics is a process separate from that occurring in AD. A distinct pattern of cognitive deficits was also discovered by Davidson et al.[8] Using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test battery, Davidson et al. compared differences in the specific patterns of cognitive performance of patients with AD with a group of elderly patients with schizophrenia. Geriatric subjects with schizophrenia scored lower than AD patients on tests of naming and constructional praxis, but performed better than AD patients a measure of delayed recall.

Interestingly, there are some clinical similarities between the pattern of cognitive deficits of Alzheimer's dementia and dementia in schizophrenia. Brodaty et al compared cognitive decline over five years in patients with schizophrenia diagnosed at age 59 years old or over and a healthy control group. They found that a much greater proportion (26%) of patients with late-onset schizophrenia was found to have Alzheimer's dementia compared to 0% of the control group. Although the subject number in this study was small, the results suggest that late-onset schizophrenia may be a prodrome of Alzheimer-type dementia.[1] Since late onset Schizophrenia may be a separate entity from early onset schizophrenia, the above study does not further evidence that cognitive decline in long-standing schizophrenia involves the same pathophysiological process as Alzheimer's disease. A study by Bosikas et al did compare the cognitive decline in Alzheimer's patients and long standing schizophrenic using the "Clock Drawing" test.[5] The study demonstrated that older patients institutionalized with schizophrenia and Alzheimer's Disease patients showed similar deficits on the clock drawing test compared to control patients. The results of this study show that in both schizophrenia and Alzheimer's disease cognitive decline arises in visual-analytic function, attention, receptive language, and executive functions such as planning, organization, and simultaneous processing. The same study found that patients with AD and schizophrenia could not be differentiated on the basis of specific types of errors. Unfortunately, such a comparison as Clock-drawing is at best a

crude measure of similarity and may yield similar results over a range of dementia types.

Recent cytoarchitectural, neuronal morphometric, and immunohistochemical studies have indicated overlap in sites of pathology, if not process of pathology, between schizophrenia and AD. Thus, similarities and differences in memory functions between the two patient groups may reflect the similarities and differences in the underlying sites and processes of neuropathology. Most studies show impaired memory performance relative to controls. This suggests overlap in the site of pathology including the hippocampus. However, the more significant impairment of AD patients on verbal recall and retention of information may be due to the more extensive pathology – amyloid plaques and neurofibrillary tangles - observed in the hippocampus in this group.[3]

Taking the above evidence as a whole, it would seem that cognitive decline and dementia in long-standing schizophrenia is an entity separate from that of Alzheimer's dementia. It is possible, however, that some patients with long standing schizophrenia do develop a superimposed Alzheimer's dementia. It is probably in the hands of the vigilant clinician to monitor signs and symptoms of cognitive decline in the elderly long-standing patient with schizophrenia and decipher from tests of cognition and patient history whether the pattern of cognitive decline reflects one of Alzheimer's disease or one of the natural history of schizophrenia. Such monitoring may influence the physician's decision as to the pharmacological approaches to take in treating dementia co morbid with schizophrenia.

APPLYING THE EVIDENCE TO CASE EXAMPLE:

The rate and degree of decline in Miss X's cognitive decline suggests that she may be one of the few patients with schizophrenia and comorbid dementia who is actually suffering from both schizophrenia-related dementia and Alzheimer's type dementia. Thus, after optimizing Miss X's antipsychotic medication, her physician may consider putting Miss X on an acetylcholinesterase inhibitor. Importantly, Miss X's physician should obtain baseline measures of cognition (ex MMSE) to monitor Miss X's course on the acetylcholinesterase inhibitor.

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LIPITOR
atorvastatin calcium
tablets

EFFICACY TO REACH TARGETS

"LIPITOR"
(atorvastatin calcium)
10 mg, 20 mg, 40 mg and 80 mg tablets
THERAPEUTIC CLASSIFICATION: Lipid Metabolism Regulator

ACTIONS AND CLINICAL PHARMACOLOGY

LIPITOR (atorvastatin calcium) is a synthetic lipid-lowering agent. It is a selective, competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

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 and catabolism of Low Density Lipoprotein (LDL).

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 Lipoproteins (IDL), as well as the number of apolipoprotein B (apo B) containing particles, but increases High Density Lipoprotein-Cholesterol (HDL-C). Elevated serum cholesterol due to elevated LDL-C is a major risk factor for the development of cardiovascular disease. Low serum concentration of HDL-C is also an independent risk factor. Elevated plasma TG is also a risk factor for cardiovascular disease, particularly if due to increased IDL, or associated with decreased HDL-C or increased LDL-C.

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions.

Mean distribution of atorvastatin is approximately 381 litres. Atorvastatin is ≥98% bound to plasma proteins. Atorvastatin is extensively metabolized by cytochrome P-450 3A4 to ortho- 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 following 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 20 to 30 hours due to the contribution of longer-lived active metabolites.

INDICATIONS AND CLINICAL USE

LIPITOR (atorvastatin calcium) is indicated as an adjunct to lifestyle changes, including diet, [at least equivalent to the Adult Treatment Panel III (ATP III) TLC 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 III);
- Hypertriglyceridemia (Type IV);
- 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 such treatments are not available.

LIPITOR also raises HDL-cholesterol and therefore lowers the LDL-C/HDL-C and total-C/HDL-C ratios in patients with primary hypercholesterolemia and combined (mixed) hyperlipidemia (Fredrickson Type IIa and IIb dyslipidemia). In pooled data from 24 controlled clinical trials, LIPITOR raised HDL-C levels 5%-7% in primary hypercholesterolemic (type IIa) patients and 10%-15% in mixed (type IIb) dyslipidemic patients. These changes in HDL-C with HMG-CoA reductase inhibitors should be considered as modest when compared to those observed in LDL-C and do not play a primary role in the lowering of LDL-C/HDL-C and total-C/HDL-C ratios.

In clinical trials, LIPITOR (10 to 80 mg/day) significantly improved lipid profiles in patients with a wide variety of hyperlipidemic and dyslipidemic conditions. In 2 dose-response studies in mildly to moderately hyperlipidemic patients (Fredrickson Types IIa and IIb), LIPITOR reduced the levels of total cholesterol (29-45%), LDL-C (39-60%), apo B (32-50%), TG (19-37%), and increased high density lipoprotein cholesterol (HDL-C) levels (5-9%). Comparable responses 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 hypertriglyceridemia (Type IV), LIPITOR (10 to 80 mg daily) reduced TG (25-56%) and LDL-C levels (23-40%). LIPITOR has not been studied in conditions where the major abnormality is elevation of chylomicrons (TG levels > 11 mmol/L), i.e. types I and V.

In an open-label study in patients with dysbetalipoproteinemia (Type III), LIPITOR (10 to 80 mg daily) reduced total-C (40-57%), TG (40-56%) and IDL-C + VLDL-C levels (34-58%).

In an open label study in patients with homozygous familial hypercholesterolemia (FH) LIPITOR (10 to 80 mg daily) reduced mean LDL-C levels (22%). In a pilot study, LIPITOR 80 mg/day showed a mean LDL-C lowering of 30% 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 PHARMACOLOGY, Clinical Studies).

For more details on efficacy results by pre-defined classification and pooled data by Fredrickson types, see PHARMACOLOGY, Clinical Studies.

Prior to initiating therapy with LIPITOR, secondary causes should be excluded for elevations in plasma lipid levels (e.g. poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, and alcoholism), and a lipid profile performed to measure total cholesterol, LDL-C, HDL-C, and TG. For patients with TG <4.52 mmol/L (<400 mg/dL), LDL-C can be estimated using the following equation:

$$LDL\text{-}C\ (mmol/L) = total\text{-}C - [(0.37 \times (TG) + HDL\text{-}C)]$$

$$LDL\text{-}C\ (mg/dL) = total\text{-}C - [(0.2 \times (TG) + HDL\text{-}C)]$$

For patients with TG levels >4.52 mmol/L (>400 mg/dL), this equation is less accurate and LDL-C concentrations should be measured directly or by ultracentrifugation.

Patients with high or very high triglyceride levels, i.e. >2.2 mmol/L (200 mg/dL) or >5.6 mmol/L (500 mg/dL), respectively, may require triglyceride-lowering therapy (fenofibrate, bezafibrate or nicotinic acid) alone or in combination with LIPITOR.

In general, combination therapy with fibrates must be undertaken cautiously and only after risk-benefit analysis (see WARNINGS, Muscle Effects, PRECAUTIONS, Pharmacokinetic Interaction Studies and Potential Drug Interactions).

Elevated serum triglycerides are most often observed in patients with the metabolic syndrome (abdominal obesity, atherogenic dyslipidemia [elevated triglycerides, small dense LDL particles and low HDL-cholesterol], insulin resistance with or without glucose intolerance, raised blood pressure and prothrombotic and proinflammatory states).

(For the treatment of specific dyslipidemias refer to the Report of the Canadian Working Group on Hypercholesterolemia and Other Dyslipidemias or to the US NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III], under SELECTED BIBLIOGRAPHY in product monograph).

When drugs are prescribed attention to therapeutic lifestyle changes (reduced intake of saturated fats and cholesterol, weight reduction, increased physical activity, ingestion of soluble fibres) should always be maintained and reinforced.

The Atorvastatin Versus Revascularization Treatments (AVERT) study examined the effect of intensive lipid-lowering in patients with stable coronary artery disease and LDL-C at least 3.0 mmol/L in patients referred for percutaneous transluminal coronary angioplasty (PTCA). Patients were randomized for 18 months to LIPITOR 80 mg daily or to PTCA with usual medical care which could include lipid metabolism regulators. The results of the AVERT study should be considered as exploratory since several limitations may affect its design and conduct. In the medical-treated group with LIPITOR there was a trend for a reduced incidence of ischemic events and a delayed time to first ischemic event. The results also suggest that intensive treatment to target LDL-C levels with LIPITOR is **additive and complementary** to angioplasty and would benefit patients referred for this procedure (see SELECTED BIBLIOGRAPHY in product monograph).

CONTRAINDICATIONS

Hypersensitivity 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).

WARNINGS

Pharmacokinetic Interactions

The use of HMG-CoA reductase inhibitors has been associated with severe myopathy, including rhabdomyolysis, which may be more frequent when they are co-administered with drugs that inhibit the cytochrome P-450 enzyme system. Atorvastatin is metabolized by cytochrome P-450 isoform 3A4 and as such may interact with agents that inhibit this enzyme. (See WARNINGS, Muscle Effects and PRECAUTIONS, Drug Interactions and Cytochrome P-450-mediated Interactions).

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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 interrupted or discontinued, serum transaminase levels returned to pretreatment levels. The increases were generally not associated with jaundice or other clinical signs or symptoms. Most patients continued treatment with a reduced dose of LIPITOR without clinical 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 in 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 have 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.

Muscle Effects

Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatinine phosphokinase (CPK) values to greater than ten times the upper limit of normal, should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. LIPITOR therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy and rhabdomyolysis during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, clarithromycin, niacin (nicotinic acid), azole antifungals or nefazodone. As there is no experience to date with the use of LIPITOR given concurrently with these drugs, with the exception of pharmacokinetic studies conducted in healthy subjects with erythromycin and clarithromycin, the benefits and risks of such combined therapy should be carefully considered (see PRECAUTIONS, Pharmacokinetic Interaction Studies and Potential Drug Interactions).

Rhabdomyolysis has been reported in very rare cases with LIPITOR (see PRECAUTIONS, Drug Interactions).

Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has also been reported with HMG-CoA reductase inhibitors. LIPITOR therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (such as severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

PRECAUTIONS

General

The effects of atorvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol on cardiovascular morbidity or mortality or total mortality have not been established.

Before instituting therapy with LIPITOR (atorvastatin calcium), an attempt should be made to control elevated serum lipoprotein levels with appropriate diet, exercise, and weight reduction in overweight patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). Patients should be advised to inform subsequent physicians of the prior use of LIPITOR or any other lipid-lowering agents.

Effect on the Lens

Current long-term data from clinical trials do not indicate an adverse effect of atorvastatin on the human lens.

Effect on Ubiquinone (CoQ10) Levels

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure (see SELECTED BIBLIOGRAPHY in product monograph).

Effect on Lipoprotein (a)

In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in Lp(a) lipoprotein concentrations. Present knowledge suggests the importance of high Lp(a) levels as an emerging risk factor for coronary heart disease. It is thus desirable to maintain and reinforce lifestyle changes in high risk patients placed on atorvastatin therapy (see SELECTED BIBLIOGRAPHY in product monograph).

Hypersensitivity

An apparent hypersensitivity syndrome has been reported with other HMG-CoA reductase inhibitors which has included 1 or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. Although to date hypersensitivity syndrome has not been described as such, LIPITOR should be discontinued if hypersensitivity is suspected.

Use in Pregnancy

LIPITOR is contraindicated during pregnancy (see CONTRAINDICATIONS).

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause harm to the fetus when administered to pregnant women.

There are no data on the use of LIPITOR during pregnancy. LIPITOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking LIPITOR, the drug should be discontinued and the patient apprised of the potential risk to the fetus.

Nursing Mothers

In rats, milk concentrations of atorvastatin are similar to those in plasma. It is not known whether this drug is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking LIPITOR should not breast-feed (see CONTRAINDICATIONS).

Pediatric Use

Treatment experience in a pediatric population is limited to doses of LIPITOR up to 80 mg/day for 1 year in 8 patients with homozygous familial hypercholesterolemia. No clinical or biochemical abnormalities were reported in these patients.

Geriatric Use

Treatment experience in adults 70 years or older (N=221) with doses of LIPITOR up to 80 mg/day has demonstrated that the safety and effectiveness of atorvastatin in this population was similar to that of patients <70 years of age. Pharmacokinetic evaluation of atorvastatin in subjects over the age of 65 years indicates an increased AUC. As a precautionary measure, the lowest dose should be administered initially (see PHARMACOLOGY, Human Pharmacokinetics; SELECTED BIBLIOGRAPHY in product monograph).

Renal Insufficiency

Plasma concentrations and LDL-C lowering efficacy of LIPITOR was shown to be similar in patients with moderate renal insufficiency compared with patients with normal renal function. However, since several cases of rhabdomyolysis have been reported in patients with a history of renal insufficiency of unknown severity, as a precautionary measure and pending further experience in renal disease, the lowest dose (10 mg/day) of LIPITOR should be used in these patients. Similar precautions apply in patients with severe renal insufficiency [creatinine clearance <30 mL/min (<0.5 mL/sec)]; the lowest dosage should be used and implemented cautiously (see WARNINGS, Muscle Effects; PRECAUTIONS, Drug Interactions).
Refer also to DOSAGE AND ADMINISTRATION.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Clinical studies with atorvastatin and other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma cortisol concentration or impair adrenal reserve and do not reduce basal plasma testosterone concentration. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

Patients treated with atorvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution

should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone or cimetidine) that may decrease the levels of endogenous steroid hormones.

Pharmacokinetic Interaction Studies and Potential Drug Interactions

Pharmacokinetic interaction studies conducted with drugs in healthy subjects may not detect the possibility of a potential drug interaction in some patients due to differences in underlying diseases and use of concomitant medications (see also Geriatric Use; Renal Insufficiency; Patients with Severe Hypercholesterolemia).

Concomitant Therapy with Other Lipid Metabolism Regulators: Combined drug therapy should be approached with caution as information from controlled studies is limited.

Bile Acid Sequestrants:

Patients with mild to moderate hypercholesterolemia: LDL-C reduction was greater when LIPITOR 10 mg and colestipol 20 g were coadministered (-45%) than when either drug was administered alone (-35% for LIPITOR and -22% for colestipol).

Patients with severe hypercholesterolemia: LDL-C reduction was similar (-53%) when LIPITOR 40 mg and colestipol 20 g were coadministered when compared to that with LIPITOR 80 mg alone. Plasma concentration of atorvastatin was lower (approximately 26%) when LIPITOR 40 mg plus colestipol 20 g were coadministered compared with LIPITOR 40 mg alone.

However, the combination drug therapy was less effective in lowering the triglycerides than LIPITOR monotherapy in both types of hypercholesterolemic patients (see PHARMACOLOGY, Clinical Studies).

When LIPITOR is used concurrently with colestipol 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.

Fibric Acid Derivatives (Gemfibrozil, Fenofibrate, Bezafibrate) and Niacin (Nicotinic Acid): Although there is limited experience with the use of LIPITOR given concurrently with fibric acid derivatives and niacin, the benefits and risks of such combined therapy should be carefully considered. The risk of myopathy during treatment with other drugs in this class, including atorvastatin, is increased with concurrent administration (see WARNINGS, Muscle Effects and SELECTED BIBLIOGRAPHY in product monograph).

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

Digoxin: In healthy subjects, digoxin pharmacokinetics at steady-state were not significantly altered by coadministration of digoxin 0.25 mg and LIPITOR 10 mg daily. However, digoxin steady-state concentrations increased approximately 20% following coadministration of digoxin 0.25 mg and LIPITOR 80 mg daily (see Human Pharmacokinetics). Patients taking digoxin should be monitored appropriately.

Antihypertensive agents (amlodipine): In clinical studies, LIPITOR was used concomitantly with antihypertensive agents without evidence to date of clinically significant adverse interactions. In healthy subjects, atorvastatin pharmacokinetics were not altered by the coadministration of LIPITOR 80 mg and amlodipine 10 mg at steady state (see Human Pharmacokinetics).

(quinapril): In a randomized, open-label study in healthy subjects, steady-state quinapril dosing (80 mg QD) did not significantly affect the pharmacokinetic profile of atorvastatin tablets (10 mg QD) (see Human Pharmacokinetics).

Oral Contraceptives and Hormone Replacement Therapy: Coadministration of LIPITOR with an oral contraceptive, containing 1mg norethindrone and 35 µg ethinyl estradiol, increased plasma concentrations (AUC levels) of norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive. In clinical studies, LIPITOR was used concomitantly with estrogen replacement therapy without evidence to date of clinically significant adverse interactions.

Antacids: Administration of aluminum and magnesium based antacids, such as Maalox® TC Suspension, with LIPITOR decreased plasma concentrations of LIPITOR by approximately 35%. LDL-C reduction was not altered but the triglyceride-lowering effect of LIPITOR may be affected.

Cimetidine: Administration of cimetidine 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%.

Cytochrome P-450-mediated Interactions: Atorvastatin is metabolized by the cytochrome P-450 isoenzyme, CYP 3A4. Erythromycin, a CYP 3A4 inhibitor, increased atorvastatin plasma levels by 40%. Coadministration of CYP 3A4 inhibitors, such as grapefruit juice, some macrolide antibiotics (i.e. erythromycin, clarithromycin), immunosuppressants (cyclosporine), azole antifungal agents (i.e. itraconazole, ketoconazole), protease inhibitors, or the antidepressant, nefazodone, may have the potential to increase plasma concentrations of HMG-CoA reductase inhibitors, including LIPITOR (see SELECTED BIBLIOGRAPHY in product monograph). Caution should thus be exercised with concomitant use of these agents (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Endocrine Function; DOSAGE AND ADMINISTRATION; SELECTED BIBLIOGRAPHY in product monograph).

In healthy subjects, coadministration 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 QTc interval remained unchanged. However, since an interaction between these two drugs cannot be excluded in patients with predisposing factors for arrhythmia, (e.g. preexisting prolonged QT interval, severe coronary artery disease, hypokalemia), caution should be exercised when these agents are coadministered (see WARNINGS, Pharmacokinetic Interactions; DOSAGE AND ADMINISTRATION).

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

Macrolide Antibiotics (azithromycin, clarithromycin, erythromycin): In healthy adults, coadministration of LIPITOR (10 mg QD) and azithromycin (500 mg QD) did not significantly alter the plasma concentrations of atorvastatin. However, coadministration of atorvastatin (10 mg QD) with erythromycin (500 mg QID) or clarithromycin (500 mg BID), which are both CYP 3A4 inhibitors, increased plasma concentrations of atorvastatin approximately 40% and 80%, respectively (see WARNINGS, Muscle Effects; Human Pharmacokinetics).

Protease Inhibitors (nelfinavir mesylate): In healthy adults, coadministration of nelfinavir mesylate (1250 mg BID), a known CYP 3A4 inhibitor, and atorvastatin (10 mg QD) resulted in increased plasma concentrations of atorvastatin. AUC and C_{max} of atorvastatin were increased by 74% and 122% respectively.

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

Drug/Laboratory Test Interactions

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 fractions of these enzymes 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 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to LIPITOR. Of these 2502 patients, 1721 were treated for at least 6 months and 1253 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 1. Associated Adverse Events Reported in ≥1% of Patients in Placebo-Controlled Clinical Trials

	Placebo % (n=270)	LIPITOR % (n=1122)
GASTROINTESTINAL		
Constipation	1	1
Diarrhea	1	1
Dyspepsia	2	1
Flatulence	2	1
Nausea	0	1
NERVOUS SYSTEM		
Headache	2	1
MISCELLANEOUS		
Pain	<1	1
Myalgia	1	1
Asthenia	<1	1

The following additional adverse events were reported in clinical trials; not all events listed below have been associated with a causal relationship to LIPITOR therapy: Muscle cramps, myositis, myopathy, paresthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, rash, impotence, hyperglycemia, and hypoglycemia.

Post-marketing experience: Very rare reports: severe myopathy with or without rhabdomyolysis (see WARNINGS, Muscle Effects; PRECAUTIONS, Renal Insufficiency and Drug Interactions). Isolated reports: thrombocytopenia, arthralgia and allergic reactions including urticaria, angioneurotic edema, anaphylaxis and bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis). These may have no causal relationship to atorvastatin.

Ophthalmologic observations: see PRECAUTIONS.

Laboratory Tests: Increases in serum transaminase levels have been noted in clinical trials (see WARNINGS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no specific treatment for atorvastatin overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

DOSAGE AND ADMINISTRATION

Patients should be placed on a standard cholesterol-lowering diet [at least equivalent to the Adult Treatment Panel III (ATP III) TLC diet] before receiving LIPITOR, and should continue on this diet during treatment with LIPITOR. If appropriate, a program of weight control and physical exercise should be implemented.

Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia, Including Familial Combined Hyperlipidemia. The recommended dose of LIPITOR is 10 mg once a day. The majority of patients achieve and maintain target cholesterol levels with LIPITOR 10 mg/day. A significant therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 2-4 weeks. The response is maintained during chronic therapy. Doses can be given at any time of the day, with or without food, and should preferably be given in the evening. Doses should be individualized according to baseline LDL-C and/or TG levels, the desired LDL-C and/or TG target (see the Detection and Management of Hypercholesterolemia, Working Group on Hypercholesterolemia and other Dyslipidemias [Canada] and/or the US National Cholesterol Education Program [NCEP Adult Treatment Panel III]), the goal of therapy and the patient's response. Adjustments of dosage, if necessary, should be made at intervals of 4 weeks or more. The recommended dose range for most patients is 10 to 40 mg/day. The maximum dose is 80 mg/day, which may be required in a minority of patients (see section below).

Lipid levels should be monitored periodically and, if necessary, the dose of LIPITOR adjusted based on target lipid levels recommended by guidelines.

The following reductions in total cholesterol and LDL-C levels have been observed in 2 dose-response studies, and may serve as a guide to treatment of patients with mild to moderate hypercholesterolemia:

TABLE 2. Dose-Response in Patients With Mild to Moderate Hypercholesterolemia
(Mean Percent Change from Baseline)[a]

Lipid Parameter	LIPITOR Dose (mg/day)			
	10 (N=22)	20 (N=20)	40 (N=21)	80 (N=23)
Total-C: 7.1 mmol/L[b] (273 mg/dL)[b]	-29	-33	-37	-45
LDL-C: 4.9 mmol/L[b] (190 mg/dL)[b]	-39	-43	-50	-60

a. Results are pooled from 2 dose-response studies.
b. Mean baseline values.

Severe Dyslipidemias

In patients with severe dyslipidemias, including homozygous and heterozygous familial hypercholesterolemia and dysbetalipoproteinemia (Type III), higher dosages (up to 80 mg/day) may be required (see WARNINGS, Pharmacokinetic Interactions, Muscle Effects; PRECAUTIONS, Drug Interactions).

Concomitant Therapy
See PRECAUTIONS, Drug Interactions.

Dosage in Patients With Renal Insufficiency
See PRECAUTIONS.

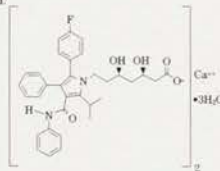### PHARMACEUTICAL INFORMATION

Drug Substance
Proper Name: Atorvastatin calcium

Chemical Name: [R-(R*,R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate

Empirical Formula: $(C_{33}H_{34}FN_2O_5)_2Ca•3H_2O$
Molecular Weight: 1209.42
Structural Formula:

Description: Atorvastatin calcium is a white to off-white crystalline powder that is practically insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer and acetonitrile, slightly soluble in ethanol, and freely soluble in methanol.

Tablet Composition:

Each tablet contains either 10 mg, 20 mg, 40 mg or 80 mg atorvastatin as the active ingredient. Each tablet also contains the following non-medicinal ingredients: calcium carbonate, candelilla wax, croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, talc, titanium dioxide, polysorbate 80 and simethicone emulsion.

Stability and Storage Recommendations:
Store at controlled room temperature 15 to 30°C.

AVAILABILITY OF DOSAGE FORMS
LIPITOR (atorvastatin calcium) is available in dosage strengths of 10 mg, 20 mg, 40 mg and 80 mg atorvastatin per tablet.

10 mg: White, elliptical, film-coated tablet, coded "10" on one side and "PD 155" on the other. Available in bottles of 90 tablets.

20 mg: White, elliptical, film-coated tablet, coded "20" on one side and "PD 156" on the other. Available in bottles of 90 tablets.

40 mg: White, elliptical, film-coated tablet, coded "40" on one side and "PD 157" on the other. Available in bottles of 90 tablets.

80 mg: White, elliptical, film-coated tablet, coded "80" on one side and "PD 158" on the other. Blisters of 30 tablets (3 strips x 10).

References:

1. LIPITOR (atorvastatin calcium) Product Monograph, Pfizer Canada Inc., February 2002. **2.** IMS Global Services; March 1997 – September 2002. **3.** Pitt B, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. N Engl J Med 1999;341:70-76. **4.** Data on File, Pfizer Canada Inc. **5.** Simon Day. Dictionary for Clinical Trials, 1999, John Wiley & Sons Ltd. 137-38.

For a copy of the Product Monograph or full Prescribing Information, please contact:

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