1997

UWOMJ Volume 66, No 2, Summer 1997

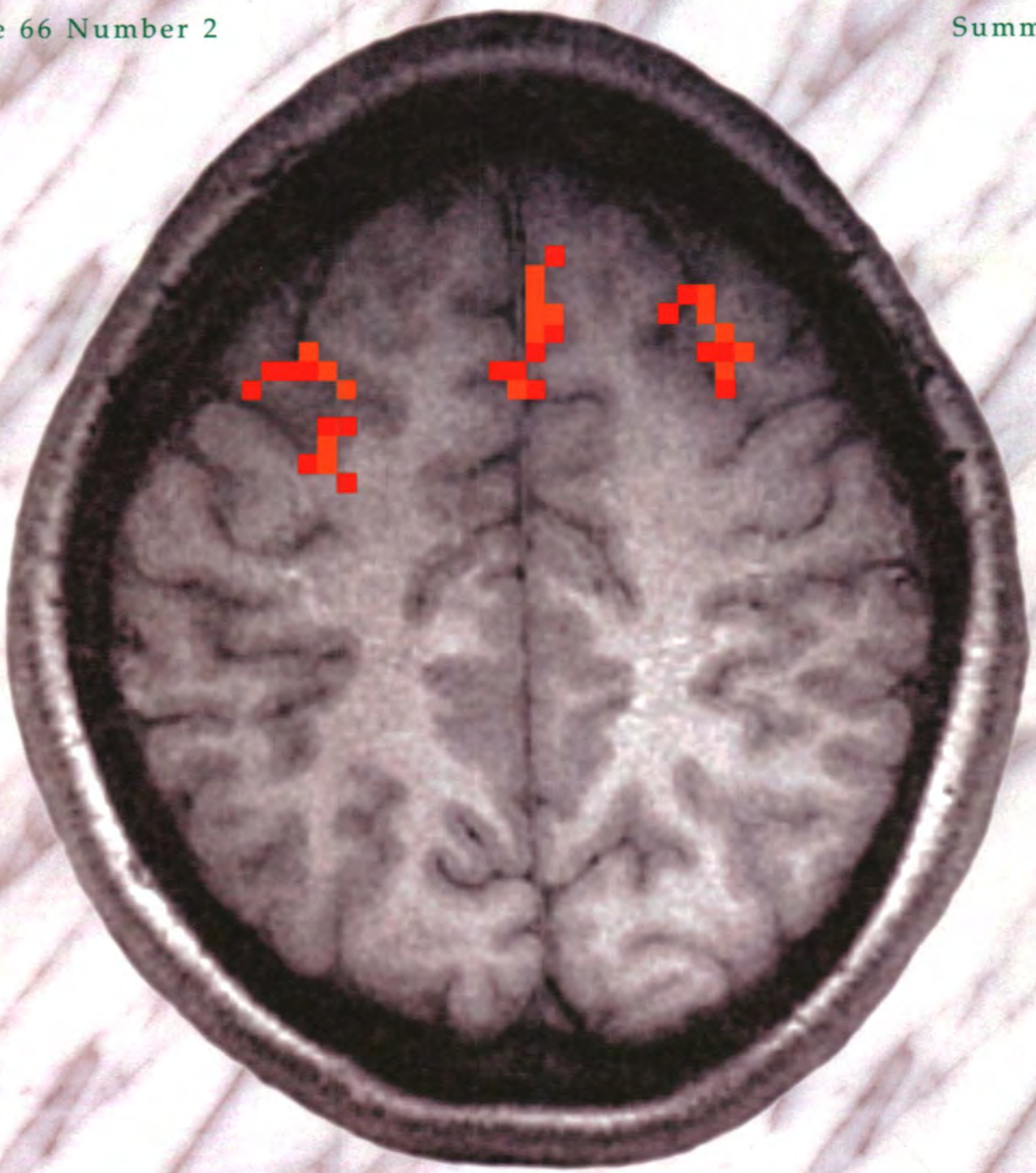
Western University

The UNIVERSITY *of* WESTERN ONTARIO

MEDICAL JOURNAL

- An interdisciplinary medical science publication; established 1930 -

Volume 66 Number 2 Summer 1997



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COVER IMAGE:

An axial-oblique image of functioning human brain during saccadic eye movements showing increased activity in the frontal eye fields and supplementary eye fields. This experiment was conducted at the 4 Tesla Magnetic Resonance Imaging facility at the Robarts Research Institute.

Sean Peter Dukelow and Joseph Francis X. DeSouza

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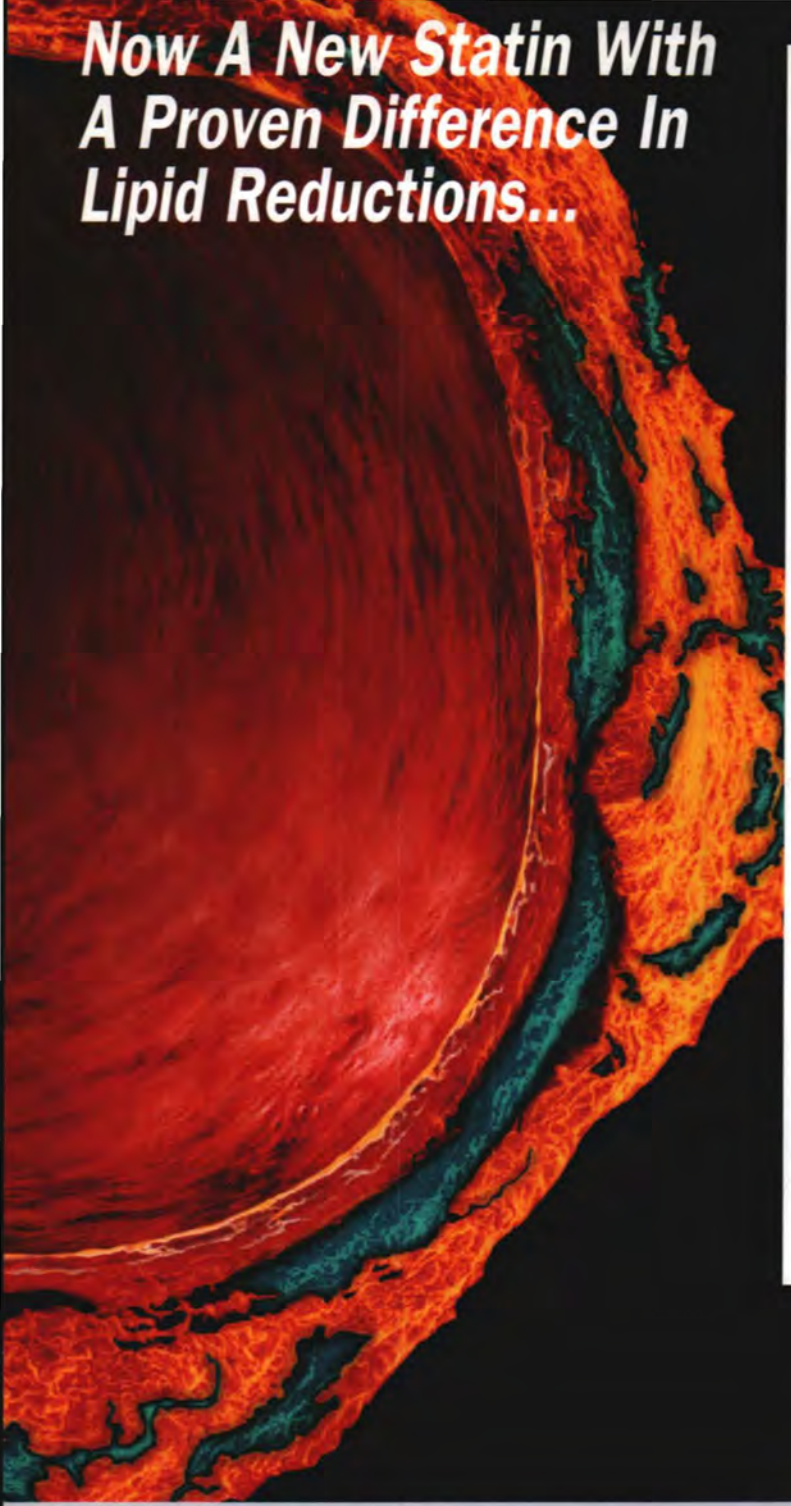

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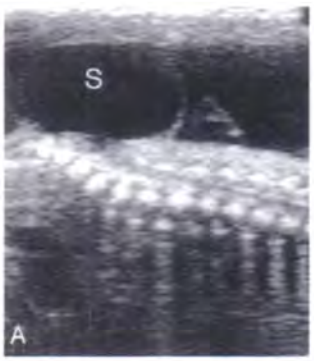

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GUIDELINES TO AUTHORS

The purpose of the UWO Medical Journal is to provide a single forum for original articles based on clinical or research medicine of topical or historical interest. Since readership of the Journal is interdisciplinary, articles published will attempt to reflect a wide range of medical interests. In this regard, submissions should be directed towards the general medical reader. Articles which do not pertain to the feature topic will be given lower priority as will those with excessive technical jargon. Please restrict submissions to under 2,000 words.

Informal peer review is required, i.e., non-specialist authors are encouraged to collaborate with, or at minimum, have their work reviewed for content by a specialist in the field. This individual, if not a co-author, is to be acknowledged at the end of the paper. In addition, it is recommended that all submissions be proof-read for significant stylistic or grammatical errors. The editors will not assume responsibility for corrections of this nature and articles requiring such revisions will be returned to the author.

Submissions are to include a cover letter, two double spaced paper copies, and the full text on 3.5" computer diskette in Microsoft Word or WordPerfect format. The cover letter should be signed by all authors and indicate that the manuscript has not been published previously.

Figures should be professionally drawn; photocopying of illustrations from texts, without the permission of the publisher, is copyright infringement. Figures and tables should each be submitted on a separate page and any illustration with a grey-scale should be in the form of a photograph. Two copies of figures or tables should be included with labels on the back indicating number as well as the first author. Legends, which are to be included at the end of the text, should start on a separate page with arabic numerals corresponding to the figures and tables.

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References are indicated numerically in the text[1] and listed as endnotes in order of appearance.[2] Do not use the 'endnote' feature of your word processing program; list references as part of the text on a separate page immediately following the body of the document. Punctuation comes before reference numbers and sentences are separated by one space only. Examples of Journal reference format follow below:

1. *Douglas NJ, Thomas S, Jan MA. Clinical value of polysomnography. Lancet 1992; 339(2):347-50.*

2. *Dement WC, Carskadon MA, Richardson G. Excessive daytime sleepiness in the sleep apnea syndrome. In: Guilleminault C, Dement WC, eds. Sleep Apnea Syndromes. New York: Alan R Liss, 1978:23-46.*

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Submissions which do not follow these guidelines will not be accepted for publication.

Ω

Technology has always been a driving force in history. In the Bronze Age, according to one theory, barbarian tribes of the steppe were able to overrun much of Europe and Asia because they had chariots while their victims were still running around on foot. As a result, half the world today speaks one or another of the Indo-European languages, descended from the speech of the charioteers. Around 1500 AD, European navies began to dominate the world's oceans, in part because their shipyards turned out wide-bottomed boats that could fire a cannon without tipping over. In World War II, Alan Turing and others at Bletchley Park, Britain's secret cryptanalysis centre, helped change the course of the war when they used a rudimentary version of a computer to crack Nazi Germany's Enigma cipher.

These examples are military, but the role of technology is equally clear in the history of medicine. Today's physicians are better healers than their leech-wielding predecessors thanks mainly to applied science. Major advances in medicine, like those in warfare, are often achieved by scientists and technicians working far from the front line, far from the clinics and the hospital wards.

Medical imaging, for example, is largely an achievement of physicists. It was a physicist, Wilhelm Röntgen, who discovered Xrays in the first place, and it is his successors from physics faculties who have more recently provided us with PET and MRI. In this issue, Sean Dukelow and Joseph DeSouza describe the latest variant, functional MRI, which is a fast-growing field and a new focus of research here at Western. Another imaging tool, discussed by Jamie Mangin in these pages, is ultrasound, which is used by bats and dolphins, followed again by physicists and finally obstetricians.

Mathematicians, too, have driven medical progress. Around 1917, Johann Radon was working out how to reconstruct surfaces based on certain mathematical "shadows" of them. He can scarcely have guessed the extreme clinical importance of what he was doing. As a mathematician, he was presumably motivated by the sheer intellectual beauty of such concepts as integrals, manifolds, and tenure. But his formulae, dusted off and adapted by Godfrey Hounsfield and others in the 1970s, are the basis for the algorithms behind computerized tomography.

Computer scientists have given us, or are trying hard to give us, Virtual Reality, which may be part of the OR of the future, as Erik Viirre points out in this issue. And the list continues: chemists, statisticians, evolution theorists, basic medical scientists, all have driven clinical advances. Of course clinicians themselves have played a crucial part as well, but in the struggle against disease, clinical medicine is just the thin front line of a huge, scientific war effort.

We at the UWO Medical Journal are also keeping pace with technology. We no longer employ roomfuls of tonsured clerks to copy the journal onto scrolls of parchment. We now desktop publish on a Pentium Computer.

What will the future bring? Forecasters, particularly when they are technophiles, often overestimate the rate of progress to come. As a child, I read several old books that tried to predict the state of the world in the year 2000. By now, we were supposed to be wearing silver body suits and flying around in hovercars. We'd have names like "Citizen XZ1A9" and would call to each other in buzzing, metallic voices.

Sadly, we've not yet come so far, but technology's progress is impressive all the same. The Pentium 133 I'm typing on is obsolescing so fast I can see the moss growing up the sides. So one safe prediction is that computers will play an ever-greater role in medicine. Soon it may be commonplace for physicians to seek advice from medical expert systems, which are computer programs that take in data about a patient's history and physical exam, and suggest diagnoses and further tests. Already there are pleasing stories of prominent human consultants who have scoffed at some Robo-Doc's surprising diagnosis and later had to eat their words.

We can expect more of this. Recently IBM's chess-playing computer, Deep Blue, defeated the world's best human player, Garry Kasparov, in a six-game match. If IBM put their resources behind the project, they could likely build a digital diagnostician, Deep Clerk, that could similarly surpass any human specialist.

This sort of thing troubles some observers. They fret and make excuses whenever a computer program beats us at something we had regarded as our own game. But in medicine, surely the sane attitude is that we need all the help we can get.

Besides, there are other medical skills on which to hang our human pride. Running through a differential diagnosis is just the sort of thing that computers excel at: it is largely a matter of memorizing a huge database and applying some fairly simple logic, essentially a branching chain of "if-thens". But other aspects of medicine, for example the sensory-motor skills like physical examination and surgery, are much harder to reduce to a program, and will likely remain a human province for decades or centuries to come. But the rate of progress is unequal in different areas of technology. Cars, for instance, are not improving as fast as computers are. If they were, then my ten-year-old K-car would weigh as much as a tank and would have a top speed of 5 km/h, whereas in reality it can do 20 on long downhills.

Medicine may be the field where technology's progress has been most disappointing. One reason is that the task is so difficult. "They can put people on the moon but they can't cure the common cold" largely because lunar voyages are child's play compared with selectively deactivating viruses. On the scale of complexity, the human body is off the high end of the range that usually interests technophiles. A malfunctioning car will magnetically attract a crowd of amateur mechanics

around its open hood, whereas simpler or more complex cases, like a bent spoon or a person with diabetes, will not excite the same analytic interest.

The sick person, however, can sometimes excite a stronger emotional response, and this is the second reason that medicine's progress is disappointing: our hopes are so high and so intense. In medicine, the gap is unusually large between what we would like to achieve and what we can actually manage. For example, with more advanced cranes and building materials, we could presumably build skyscrapers ten times higher than what we have now, and do it ten times as fast. But no one is fervently wishing for a breakthrough here the way many of us are hoping for breakthroughs in therapy for cancer or strokes.

One reliable forecast is that our personal taste for new technology will decline with age. Right now, I love new gadgets, but when I'm 70 my grandchildren will urge me to use the teleporter, and I'll resist, saying I prefer to get around the old-fashioned way, in the hovercar. Ω

Cindy Hawkins,
Editor-in-Chief

Interview With Dr John Howard, New Assistant Dean of Undergraduate Medicine

by Jordan B Solmon

Dr. John Howard is a gastroenterologist at the London Health Sciences Centre whose practice is largely comprised of pediatric patients. He is a husband, and the father of three children, and enjoys a spectrum of activities ranging from his involvement in their hockey games to cottaging, theatre and travel, tennis and golf.

Dr. Howard is the newly appointed Assistant Dean for Undergraduate Medicine. This office is most appropriate for the clinician and teacher, who has, until recently, been integrally involved in the organization and execution of Clinical Methods, one of the most critical courses that is taught to undergraduate medical students; moreover, he continues to travail as Director of Undergraduate Curriculum and Evaluation. This latter post has been an ongoing and arduous task as Dr. Howard has collaborated with a multitude of dedicated contributors to create, and ultimately to implement, a new paradigm for medical education at the University of Western Ontario.

ABOUT THE AUTHOR

Jordan Solmon is a third-year medical student at UWO with a BSc from the University of Toronto. He is interested in paediatric surgery and has participated in the curriculum renewal process.

Medicine is unique, and for some, enrapturing, in that it is an ever-evolving multidisciplinary profession based on clinical and laboratory practices, and includes as essential components the ability to be both humane and an excellent communicator. Underlying the myriad constituents of the art and science of medicine is the system which educates and empowers physicians-to-be. The new and innovative curriculum that will be in place for the class of 2001 may be described as systems based, but not in the traditional sense. It is student driven, and community responsive, and most importantly it is patient centred. Dr. Howard explains that being patient-centred is recognizing the unique experience a patient has when he has a disease," We will focus not just on identifying and 'fixing' the disease, but we will equally focus on understanding the unique experience a patient has as he experiences a disease. To achieve this focus we need to have a full understanding of the 'context' of that patient - the cultural, spiritual, and community needs to name a few "Indeed, this is the frontier of medicine."

For as long as many students are able to recall, you have been involved in some capacity in our medical education why the recent change in your focus?

"I have been rather heavily involved in hospital administration over the last couple of years, and I have been interested in leadership". I have taken some courses in leadership and I was contemplating getting out of education because I saw some opportunities in the hospital management sector. But then there was the merger, and when you merge two things together, the opportunities are halved. Shortly thereafter, the Dean approached me about taking on the task of renewing the curriculum, and it seemed like a great leadership thing for me, and so that's what I did."

And here you are today

"Well, I'm basically someone who wants to change the world a little bit, and if you can effect the lives of a thousand medical students that's kind of neat!"

Often, we ask our patients why they are presenting now, why not yesterday, or wait until tomorrow. I would ask the same of you regarding changing the curriculum: why now?

"There are a couple of things to say about that. The decision to change the curriculum was made four years ago when there was a process put in place called the Green Paper. It was authored by a task force that was chaired by Michael Clarke. The Green Paper itself was based on recommendations, and was an excellent document, but it came out at a time when faculty were quite reactive. Interestingly, I think everyone agreed with seventy or eighty percent of the Green Paper, but it was a different seventy or eighty percent for each individual. And so, we are actually in the fourth year of 'curriculum changing', but the present structure has only been around for about twelve months. The Green Paper had a number of conclusions, and those conclusions were to set up a curriculum coordinating team, and that there would be subject development groups, and that it would be a case based curriculum. When I came onto the scene, I think there was some concern because it was at a time when people were reacting rather than creating, so an initial part of the process for me was building bridges. and creating a consensus curriculum finding out what we as a group need to be doing. So, the decision to change the curriculum came about four or five years ago, but when I came to the project, I needed to discover for myself why it needed changing, and it became clear after a while that there were two things. One was that the curriculum was locked inasmuch as it was exceedingly difficult to make any modifications, to add a course, or to subtract a course; there were new things coming up and we were unable to address them, partly because it was difficult to make time in the existing curriculum. The second thing was readily apparent, and that was that over the last ten or fifteen years, the courses had each become excellent, but these courses do not necessarily fit together well. The analogy which I have been using is that of a chair. The curriculum is like building a chair, and what we had done was taken each part of the chair and given them to the course committees, and they have, over the course of ten or more years, honed their pieces so that they are near perfect. So, we have a curriculum that has perfect pieces, but each piece is a different size, style, and design and when you put them all together, they just don't fit as well as they should. You lose the perspective of the overall curriculum at the expense of perfection of the courses, and so the drive right now is the integration of the content of the courses, and the other theme of the renewal is to create a curriculum that can continue to change. Hopefully, we will never have another curriculum renewal per se; rather, the curriculum will always be renewing itself. I would guess that 50 percent of the changes will occur in the first year, then I hope we will see 25 percent of the change for many years thereafter!!"

There have been rumors of the imminent closure of one of the medical schools in Ontario, how much did this influence the current effort?

"There is nothing to that component. But, I think you have to look at the environment around us, and I think we have to recognize that we are in a competitive environment, and we have to position ourselves. We need to consider the possibility, although there is nothing to it right now, that the Ontario Government could suggest the closure of a medical school, which would save money -we are seeing the closure of hospitals, the closure of school boards, why not consider the closure of secondary institutions or medical schools? The best thing we can do is to take Western and to make it the leading medical school in Canada and as such, it would be very hard to close. Essentially, the best defense is a good offense."

Many students who have been drawn to Western up to now have recognized that it was a traditional school with a largely didactic curriculum. What do you say to new and prospective students who saw that as a distinguishing feature of Western?

"I would reiterate that this is a renewal and not an overhaul. Our strength has been our courses, and part of our future is to maintain the quality of the courses. So, in some respects, our curriculum will be traditional, but in the context of something which is more holistically radical. We have listened to the students as a mandatory part of this process, and they will continue to have a strong voice in the process of change."

What repercussions will the new tenets of the curriculum have on the admissions and selections process?

"We want to have a curriculum that respects all of the EFPO values. Thus far, there has been a tendency to emphasize the medical expert. Independently, but coincident to the renewal process there have been some changes to admissions criteria. These include an emphasis being placed on communication skills, and the introduction of the community into the selection process."

In the effort to include the community in this process, community representatives have been asked what they expect in a physician. Predictably, they respond with wishes for an expert who is accessible and available, but a doctor on every block who is open for business twenty-four hours a day is an impossibility. Also, skeptics have remarked that we do not expect social workers to be medical scientists, and that we should be teaching basics and not everyone else's business. How do you answer these remarks?

"We have to remember who the boss is in all this; the taxpayer. The EFPO organization came to their conclusions based on interviews they conducted with all aspects of society. We are not ignoring the medical expert in this; it is the number one EFPO expectation. But I think its very clear that you have to have someone who can express their expertise, who can use their expertise to advocate sound health policy. You definitely need physicians who can understand the costs of medical care today, and if you are going to rely on other people to provide things like social work, you have to be a team player. To me there is a balance, and we will probably still spend seventy percent of our time developing the medical expert, but traditionally we have spent ninety-five percent of our time doing that.

One of the toughest things about this endeavor has been that it is happening "just in time". We will not have a whole package ready to go next year. We will roll out the new first year plan, and then incorporate another new year each year thereafter. If we had the whole curriculum ready for September, by the time the first class got to their fourth year, the curriculum would already be four years old. I don't know what it will look like when its done. Over 250 people have been empowered to enact the changes, and so one idea cannot then be thrust upon those people. What I do foresee is a new and flexible paradigm for medical education that will make Western the leading medical school in Canada, and one that will be recognized world wide. Ω

Gene Therapy: Blessing or Curse?

by Cameron Pallett

Recent advances in gene therapy present the very real possibility that inherited metabolic diseases will become easily treatable in the near future. Target-cell-specific virus vectors will soon be able to deliver and incorporate virtually any known gene or combination of genes into specific chromosomal target locations. Patients who suffer horribly merely because they inherited a defective gene now have hope. Doctors may be able to end these patients' suffering once and for all through the simple injection of a virus vector carrying a properly functioning copy of their defective gene. Once within the host cell, the viral mechanisms will cause the gene to become inserted into the DNA of the cell. The inserted gene will then operate to produce an effective gene product.

The possibilities for good are almost limitless. Insertion of the genes responsible for identifying and destroying pre-cancerous and cancerous cells into a host's cytotoxic T cells or Natural Killer cells may provide a future vaccine for cancer. There is no question of the enormous benefit to mankind that this procedure would provide. Most of us have lost someone we know to what has been described as the plague of the 20th century. The notion that we may have the opportunity to rid the world of cancer the way we once rid the world of smallpox is truly intoxicating. Unfortunately, the possibilities for misuse are also easy to imagine.

The day may come when we will be able to walk into a doctor's office and purchase any gene combination we desire. Sylvester Stallone's biceps, Elizabeth Taylor's violet eye colour, Stephen Hawking's intellect: all may become commercial commodities. What about the parents who want to give their child all the advantages in life? Parents already tend to imprint their children with their own hopes and aspirations. Imagine what effect it would have if they could alter their child's genetic structure to fit their ideals as well.

We may end up with a society where the disparity between the rich and the poor is much more significant than mere money. Those who can afford to purchase the genes they want will be larger, stronger, more intelligent and live longer than those who cannot afford them. The nightmare spectre of the Master Race potentially may become reality. What can and should we do about it?

We can and must have a legislative framework in place before gene therapy technology becomes commonplace. History teaches us that when the law lags behind the technology, economic considerations tend to outweigh moral and ethical ones when a legal framework is finally created. We simply cannot afford to wait and see what the effects of widespread gene therapy will be before we enact legislation. The stakes are too high, the potential for abuse too great.

For example, several genes have been identified and sequenced that are associated with longevity. What would an injection that could increase your life span by 25-30% be worth? A million units at $25,000 each could easily be sold within six months. That comes to 25 billion dollars and represents only the tip of the iceberg. Recently scientists isolated a gene associated with obesity. Turning off or inactivating a gene is currently easier than inserting a gene with complete and accurate regulation of manufacture of the gene product. How about an injection that inactivated the obesity gene for say, a month at a time, marketed at $500 per injection? Considering the ongoing obsession with weight control, the only foreseeable sales problem would be maintaining stock. These are just two possibilities among many.

The Human Genome Project is a world-wide collaboration of scientists whose purpose is to identify, map and sequence the entire library of human genes. They share the concern that this library may someday be used inappropriately. A portion of their budget has been set aside to examine the ethical, legal and moral concerns of gene therapy. There are no easy answers. Where do we draw the line between what is legitimate therapy and what is abuse? Shouldn't people have the freedom to choose to alter their genetic makeup and improve their lives if that is their wish? What about the theological implications of playing God? These complex issues and a myriad of others will require years of discussion with input from a wide variety of experts and interested parties. We cannot afford to wait and see how the technology develops and then decide how we want to control it. There is simply too much money involved and the potential societal ramifications are too grave.

Doctors, lawyers, scientists, clergy and all concerned parties owe it to themselves and to their communities to turn their minds to the issues and begin discussions about how we wish to control this technology without delay. Considering the complexity of the issues and the competing interests involved, it would be naive to think that any consensus could be achieved without years of discussions. We simply must have a legislative framework in place before the technology arrives or we risk losing all the advances in social consciousness and equality that we have achieved. The potential impact is too great for us just to shrug our shoulders and adopt a wait-and-see attitude. A world where some can point to themselves with pride and say that they are definitively genetically superior terrifies me and it should terrify you.

Ω

ABOUT THE AUTHOR

After studying microbiology at the University of Toronto, Cameron Pallett researched immunotoxins at the University of Texas Health Science Centre at Dallas, while teaching lab courses at Southwestern Medical School. He is currently in second-year law at UWO.

The Evolution of a Value-Laden Disease State

by Daniel Rabinovitch and David Szwajcer

Science is meaningless because it gives us no answer to our question, the only question important for us, "What shall we do and how shall we live?". L Tolstoy

Science alone cannot differentiate health from disease. Disease demands for its definition a system of values. This is immediately problematic; we live in a secular society in which values are commonly seen relativistically, as a matter of personal choice. It thus seems likely that there can be no objective conception of disease. Medicine is on thin ice indeed.

What is science? Science is a descriptive endeavour; by observing the world it attempts to answer questions such as the following: "What state is the world in now?", and "Given that the world is in state X now, will it enter state Y at some later time?", and "Given that the world is in state X, what performed action, A, will guarantee that state Y is entered?"

Yet this vast question set is also limited. It does not include questions like "Is state X good or bad?", or "Given that the world is in state X now, what state Y should we strive to enter?", or "Should I perform action A at the moment?" These latter questions do not ask what the world is like, but what it should be like. By claiming that the world should be in state Y, or that state Y is especially good, or that state X is especially bad, we are setting up a value system in which state Y is more valued than state X.

The process of medicine is inherently value-laden; it establishes certain physiological/psychological states as pathological, thus devaluing them and implicitly claiming that treatment should be undertaken. Two case studies, of Alzheimer's disease and of obesity, may help to provide evidence of the role played by values in constituting a disease.

BIOMEDICALIZING SENILITY

In 1907, Alos Alzheimer wrote the first case report of a patient suffering from what would later become known as Alzheimer's disease. On autopsy the patient's brain revealed neurofibrillar tangles in approximately 1/4 of the ganglion cells, coupled with glial cell proliferation. Vascular infiltration was absent.[1] Today Alzheimer's disease is considered one of the most prevalent dementing illnesses of the elderly in North America. Clinical manifestations of the disease involve a progressive deterioration in mental functioning, where the victim suffers variously from confusion, forgetfulness, depression, disorientation, and agitation.

Over the course of the 20th century, perceptions of the aging process in the occident have changed dramatically. At the beginning of this century, senility was considered an inevitable part of aging. Over the past 25 years, Alzheimer's disease has evolved from a relatively obscure diagnosis into a significant health policy issue and public concern.[2] The Alzheimer's disease experience is inherently interpersonal, in that it involves the patient and the caregiver. For the patient, Alzheimer's disease represents a gradual loss of mind, whereas the caregiver has the uncomfortable duty of deciphering the needs of the patient. Treating the Alzheimer's patient devolves into a balancing act between the actual requirements of the patient, the caregiver's perception of those requirements and the needs of the care giver and the community at large.

The proportion of elderly citizens in North America is slowly but surely growing. In 1900, 4% of the American population was over the age of 65, by 1994 the proportion had grown to 12.7%.[3] The emergence of Alzheimer's disease into the public arena has overturned the paradigm of senility as a natural part of aging. It is estimated that approximately 20% of people above 80 years of age will be affected with a dementing illness.[4] Governments are consequently motivated to find a "cure" for a potential epidemic in the coming century. The late 1970s saw the emergence of several large support groups such as the Alzheimer's Disease and Related Association (ADRA) which, as part of its mandate, formed a powerful lobby to compel the US government to invest in Alzheimer's research.[5] Funding for Alzheimer's disease research through both the NIH and NIMH has increased dramatically during the 1980s.

Over the past half-century there has been a trend to biomedicalize illness and the aging process. The downside of this has been a lack of consideration given to the psychosocial dynamics involved in the patient/caregiver relationship. The biomedical model of senile dementia, of which Alzheimer's disease makes up a large part, consists of the following points: the dementia is pathological and has a somatic etiology, the disease process manifests itself in universal typified stages of progressive deterioration, and finally, while there is no cure for the disease, it can be managed.[2] Viewing senile dementia in terms of a biomedical model

ABOUT THE AUTHORS

Daniel Rabinovitch and David Szwajcer are both first-year medical students at UWO. Daniel Rabinovitch completed an MEng in computer science at Cornell University and David Szwajcer completed a BSc in medical biophysics at UWO prior to beginning medical studies.

brings order to the care of patients. By labeling the condition and identifying its stages, the caregiver's stress is lowered by having expectations of particular outcomes.

Once a diagnosis of Alzheimer's disease is made, family caregivers tend to adopt a "therapeutic nihilism," in which the inevitability of intellectual decline and self deterioration are assumed.[5] Observation of caregivers in several settings has found that once the label "Alzheimer's" is applied to a patient, behaviours that in unaffected people would be viewed as normal are interpreted as deviant. Difficult, ornery behaviour (such as a desire for a modicum of independence) is generally frowned upon by both family and facility caregivers. Physical and chemical restraints are commonly used to control the elderly and are justified in light of perceived deviant behaviour. Such restraint can make patients more dependent, whereas increasing the patient's personal responsibility has been correlated with improved well-being among patients.[6] Thus restraint mechanisms may not always be in the patient's best interest.

The presumption that Alzheimer's disease follows a set progression makes it easier for families to consider institutionalization. As families become both financially and emotionally drained by the burden of long-term care of a family member diagnosed with Alzheimer's disease, they may find some comfort in justifying institutionalization because of a perceived disease progression, whether or not the patient's state has actually worsened.[2]

At a time when there is still no cure for Alzheimer's disease, a conflict may arise between the dual goals of public funding in order to search for a cure and developing infrastructure to care for the patient in the interim. Alzheimer's disease has two victims: the patient and the principle family caregiver. Both are put in difficult positions because of the illness. It is clear that the social values of caregivers influence treatment of the patient. The choice of treatment decisions in turn has a direct influence on the conceptual framework by which the caregiver understands the disease. It is important for caregivers to recognize that there is a person behind the illness.

FLUCTUATING FASHIONS

Erotica, Joycean style:

Farrington gazed admiringly at the plump arm which she moved very often and with much grace; and when, after a little time, she answered his gaze he admired still more her large dark brown eyes.[7]

And if, in our time, beauty and grace can no longer be found in the plumpest and fattest, it may be worth calling forth still more witnesses from fashion's tumultuous history. The Gothic nude, for instance, typically had a bulging stomach that appeared almost 5 months pregnant. Likewise, the nudes of Leonardo da Vinci, Raphael, and Titian established as aesthetic ideals women with large stomachs, wide pelvises, and broad arms. By the early 1600s a bodily ideal had developed that approximated the waves of adiposity found in the work of Rubens.[8]

Ideals of beauty vary not only historically but also geographically. Even today, many cultures view fatness as a sign of prosperity, success, and abundance. Thus the !Kung San food foragers deride thinness as a sign of starvation, and both the Nigerian Tiv and Mexican Spanish words for fatness (kehe and gordura, respectively) carry definite positive connotations. In fact, the latter group has had to invent a new word to express the modern dissatisfaction with high body weights (gordura mal). Several other cultures demand a degree of fattening prior to marriage. Amongst the Nigerian Efik people, pubescent girls spend up to two years in "fattening huts", at the end of which they are accepted as marriageable. Plumper Kenyan brides can demand higher bridal payments; and amongst the American southwest's Havasupai, fat women stand on top of thin girls to ritualistically aid them in the plumpening process.[9]

If, as we will argue below, our medical conception of obesity depends on cultural values and fashions, this historical and anthropological survey will pose a disturbing question. The fact that medical practice relies on values that are so prone to fluctuations suggests that our current conception of obesity lacks a solid foundation.

STIGMA AS DISEASE

We live in a society where 6-year-olds are prepared to pre-judge obese children as "lazy, dirty, stupid, ugly, cheats, and liars"; where the obese are less likely to be accepted into prestigious universities than equally qualified peers of average weight; and where 16% of employers refuse under any circumstances to hire an obese woman. Indeed, Industry Week has found that each pound of fat costs corporate executives $1000 in salary per year.[10] It is clear that the overweight may face tremendous psychological and social pressures on account of their bodies. Indeed, in listing the burden of obesity on patients, physicians do not stop with the increased risk it poses for medical conditions such as coronary heart disease and diabetes. Rather, the psychosocial problems posed by obesity are explicitly listed as both a burden to the patient and a justification for considering his or her condition a disease worthy of treatment. This approach was already apparent in an early report of the Metropolitan Life Insurance Company (MLIC): the overweight, wrote the MLIC Statistical Bulletin, should reduce weight because otherwise they will be ostracized as youngsters, denied equal employment, and obstructed in their quest for marriage.[8] This analysis is commonly heard. The Nelson Essentials of Pediatrics lists peer discrimination and negative stereotypes of the obese among the principal complications of obesity.[11] Likewise, Dwyer notes that "In a weight-conscious society such as ours, obesity is a handicap. These [psychosocial] disadvantages may be more potent than medical risks in motivating many patients to seek

obesity treatment."[12] A similar view was articulated by an NIH panel convened to build a consensus on the health implications of obesity. In considering the adverse effects of obesity they first note that "Obesity creates an enormous psychological burden. In terms of suffering, this burden may be the greatest adverse effect of obesity."[13] Indeed, a typical recommendation to the physician dealing with overweight patients is as follows: recommend weight reduction if the patient is in the highest 5% of weight for height, or if the patient is in the highest 15% and exhibits psychosocial difficulties with his or her weight.

Each of the above writers elevates the risks associated with the obese by noting the psychological and social ills that may result from obesity. Yet these psychosocial problems stem directly from society's pre-existing ideals and the patient's deviance from them. By using these psychosocial ills in their classification of obesity as a disease these physicians place themselves in a double bind. To their credit, they are conscientiously paying attention to the psychosocial dimensions of illness; by empathizing with the patient's experience they are truly being patient-centred. On the other hand, they run the risk of labeling people as diseased solely for their deviance from standards of fashion and beauty. This is especially worrisome since as outlined above these aesthetic ideals have varied tremendously from culture to culture and from time to time; our conceptualization of obesity as an objective disease state lies in stark contrast with our fluid aesthetics of personal beauty.

SO WHAT? RECONCEPTUALIZING DISEASE

disease (di'zi:z) 1. a. Absence of ease; uneasiness, discomfort; inconvenience, annoyance; disquiet, disturbance; trouble. (Obsolete.)[14]

An obsolete definition, claims the Oxford English Dictionary; and yet our analysis reveals that the definition remains relevant in contemporary times. It may be thought that obesity and Alzheimer's disease, by virtue of the controversies surrounding them, may be more susceptible to value judgements than diseases such as tuberculosis or pneumonia. This is not the case. What differentiates the first pair of illnesses from the latter is the degree of consensus with which society has adopted the relevant values. The values underlying obesity, for instance, have only recently taken root in our fashion sensibilities. The lack of consensus over body image, fluctuating rapidly over time and space, opens up a chasm from which our craving for slimness may be critiqued. Thus Naomi Wolf castigates our fashion sensibilities for leading to the imprisonment of contemporary women.[15] The interpersonal nature of Alzheimer's disease establishes tension between the values of the caregiver and those of the patient. The caregiver is presumed to act in the best interests of the patient, while it is not always desirable or even possible for the caregiver to do so. The values underpinning both obesity and Alzheimer's disease lack widespread consensus. They therefore appear much more prominently in the social discourse concerning them. In contrast, a very widespread agreement exists about the values that constitute tuberculosis as a disease: pain and death should be avoided. Indeed, it is precisely to the extent that such a consensus can be attained that we can talk of an 'objectively defined disease'. It seems, then, that the obsolete definition quoted above is accurate when it describes disease not in its current biomedical definition, but in reference to the wider notion of the illness process.

A LONELY DIALECTIC, OR WHAT DOES ALL OF THIS MEAN FOR THE PRACTICING PHYSICIAN?

The physician-value relationship is not a one-way street. Just as values affect what the physician considers to be a disease, so also the physician's

conception of disease reinforces certain values within the wider societal arena. By over-prescribing weight-loss medication, or by chemically restraining an Alzheimer's patient because of perceived deviant behaviour, we run the risk of solidifying our preconceived notions of beauty and aging respectively. The responsibility for participating in such a subtle dialectic is immense, and it is made all the more difficult by the disappearance of the grand moral consensus that once guided whole communities. It is only haltingly and with trembling uncertainty that the medical community gropes towards ethical certitude.

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The History of Cleanliness and Infection Prevention in Surgery and the Treatment of Wounds

by Evan Propst

The history of bacteria goes back two billion years, and infection has existed since long before the first trace of man. There is evidence, however, that mammals have always instinctively treated wounds in a manner that has battled infection and ultimately prevented premature death. Chimpanzees, for example, dab and lick their wounds clean to promote rapid and complete healing.[1] The fact that apes make no attempt to hold their wounds together coincides with the present truism that sutures favour infection, and that dirty wounds are better left unsewn.[2] Even primitive man trepanned successfully 10,000 years ago, and primitive tribes in the mountains of Algeria attained close to a 100% rate of survival in this practice in the early 1900s.[3] Although people's beliefs have differed greatly about the reasons why their practices have been effective, the history of cleanliness and infection prevention in surgery and the treatment of wounds has been continuous. Man has always striven to battle infection. This article will discuss several representative examples from this historical continuum.

Documentation of the history of cleanliness and infection prevention can be traced back to ancient Egypt. The Edwin Smith Surgical Papyrus dating from 1650 BC reveals a technique for closing "a gaping wound in the eyebrow" that requires binding "fresh meat upon it, and treating it with grease and honey every day until [the patient] recovers."[4] Grease prevents lint bandages from sticking to wounds, as do present-day first-aid creams. Further, meat applied to wounds as a clotting agent was used in neurosurgery well into the 20th century when safer methods became available.[5] Honey appears in 500 of the 900 recorded Egyptian remedies for wounds, and was a key factor in embalming the dead to preserve them against bacterial action; honey is extremely hypertonic, and thus kills bacteria by drawing water from their cells. It also contains the antibiotic enzyme inhibine which is secreted by the pharyngeal glands of the bee.[6] Honey was probably chosen because it is soothing, does not spoil, and, like grease, prevents bandages from adhering to wounds. The Egyptians probably used gum to fasten linen bandages over wounds as they did around mummies, for tapes spare the presence of foreign stitches which often lead to infection. Natron and resins were used both to embalm and to treat wounds, for natural soda forms a mild sodium-detergent when mixed with fat.[7] Even though a religious motivation to prepare for the afterlife was the force behind embalming for the ancient Egyptians, one cannot help but admire their successful fight against bacteria evident today in the preserved remains.

Ancient Greek wound treatment in 400 BC is evident in the Hippocratic writings where a "drug for fresh wounds" is prescribed, containing "copper acetate, lead oxide, alum, myrrh, frankincense, and grease of wool, all diluted in wine."[8] Although Greek medicine was based on the belief that everything in nature must remain in balance, practitioners still managed to prevent infection in wounds. Copper is currently used to treat the staphylococcal skin infection impetigo.[9] As well, brass is a source of zinc that, when heated with water and stirred with a "calamus" reed, produces calamine.[10] Alum today is an ingredient in the Hepatitis B virus vaccine.[11] Myrrh is currently used to combat gingivitis, being an effective anti-microbial agent that also stimulates the production of white blood corpuscles.[12] As well, "cold, white or red, astringent wines are used for wounds, because of their heat."[13] Greek wines from Samos and other islands are effective for wound sterilization because they contain polyphenol, a complex form of Lister's phenol that is 33 times more powerful.[14] For a society that spoke of sepsis without knowing about bacteria, the Greeks' emphasis on cleanliness and wine is remarkable, and their treatments rightfully survived for many centuries.

Roman medicine contained traditional folk remedies for the treatment of wounds for many years before these were taken up in medical literature. By 79 AD, Pliny the Elder had completed his Historia Naturalis, which compiled 20,000 of these remedies from over 100 authors. Among them are "admitted medical aids, [including] wool and eggs."[15] Wool was applied with honey, and the whites of eggs were used to close inflamed wounds. Amazingly, Dr Alexander Fleming would publish an article in the Lancet in 1924 "On the antibacterial power of egg-white."[16] Reinforced by charms, incantations and superstition, poultices were believed to be more efficacious if "laid upon [the wounded] by a naked maiden."[17] Pliny's choice of antiseptic wound dressings, however, could not possibly have been an accident. Of the 34 plasters and ointments he records, all but 5 contain heavy doses of alum, lead and copper salts, mercury, antimony, sulphides, oils and vinegars, substances possessing powerful antiseptic properties. Pliny even states that "copper ores and mines supply medicaments, [by which] all kinds of ulcers are healed with the greatest

ABOUT THE AUTHOR

Evan Propst has recently completed a BA in psychology at UWO and is hoping to pursue a career in medicine.

Fig. 1 *Achilles treats the wounded Telephos with scrapings from his bronze lance. Pliny may have seen this bas-relief of the first century.*

rapidity."[18] Pliny most likely recognized that common plants possess active healing properties, for he ironically remarks that for "remedies, nobody looks into his own kitchen garden."[19] One might even argue that Romans of Pliny's time knew why they used these remedies, for in 26 BC, Varro had already clearly stated that "in the neighbourhood of swamps...there are bred certain minute creatures which cannot be seen by the eyes, which float in the air and enter the body through the mouth and nose, and there cause serious diseases."[20]

Even though Hugo of Lucca had never heard of bacteria in 1200 AD, he strove for aseptic measures in surgery, stating that wounds "should be abraded, cleansed, wiped with lint soaked in warm wine, the lips of the wound [should be] reunited, and [it should be] bound with a light bandage."[21] Hugo's son Theodoric upheld this tradition, and, reverting to the Hippocratic doctrine of Ulcers, declared that it "is necessary that [wounds] be made dry."[22] This was an important revelation, for it countered the contemporary belief in "laudable pus", that encouraged the formation of pus as a necessary stage in healing, and prevented the aseptic treatment of wounds.

In 1747 George Berkeley wrote a letter to Thomas Prior on the usefulness of tar-water in the Plague. He writes that bleeding and wine "are both to be suspected; whereas Tar-water cools without weakening, and gives spirits without heating, a sure indication of its sovereign virtue in all inflammatory cases."[23] This comes as no surprise to us, since today the majority of phenols used to manufacture disinfectants are obtained from tar produced in the distillation of coal.[24]

In 1826, John Bell recounted the common antiseptic practices of the French army in his Principles of Surgery: "One [cure] in particular was called the secret dressing, in which [the drummer would lay] the lips of the wound together to suck out all the blood."[25] Although the effectiveness of this procedure was believed to lie in signing the wound with a cross, the use of saliva became a popular practice throughout France. Even La Motte, the most eminent surgeon of the time, is quoted as saying that it "is more successful than any method that we surgeons use"[26], and that "speedy adhesion [allows] no danger from bad consequences of the wound."[27]

In 1847, Ignaz Semmelweis of Vienna noticed that after performing autopsies, physicians and students retained particles of decaying matter on their hands. Believing these particles to be the cause of "childbed fever", a fatal condition of new mothers, he declared that it was "necessary to clean the hands with chlorine water"[28] before examining these patients in order to decrease the mortality rate from sepsis. By October that year, he had discovered that childbed fever was also carried from living people, and through the air. In 1860, Jules Lemaire recommended the use of disinfectants during surgery, and in 1890 the American surgeon William Halsted introduced rubber gloves in the operating room, to prevent the septic infection of wounds.

While studying under James Syme in 1852, the British surgeon Joseph Lister became interested in preventing infection or "sepsis" in wounds; this led him to try carbolic acid, a dark, tar-like substance, to promote clean healing and close wounds. Although Lister was not the first to use carbolic acid, he was the first to understand why he used it. His first clinical success occurred in March of 1865, when he healed a boy who had been run over by a cart wheel. He later developed the method of dissolving the carbolic in four parts of boiled linseed oil to clean his surgical utensils, and mixed carbolic oil with carbonate of lime to make an "antiseptic putty" for wounds. By 1867, Lister had prevented infection and subsequent death in so many of his patients, that he declared in the Lancet that "the element of incurability has been eliminated."[29] Lister's methods allowed doctors to open bodies for surgical purposes for the first time, and he himself went so far as to perform an operation to straighten a foot by opening the ankle joint. He even soaked catgut in carbolic, and thus created the first non-infective sutures. Lister had successfully "cleaned up" infection in Edinburgh and Glasgow, and in July of 1870, Dr Saxtorph of Copenhagen wrote that he had "never tried any innovation which answered so admirably as this treatment of wounds."[30] In 1872, von Volkmann prevented a hospital closure by combatting ruthless gangrene with Lister's method of "washing with diluted carbolic acid in the proportion 1:8."[31] Lister's ways were popularized by von Bardeleben in Berlin, von Busch at Bonn, Duplay in France, and most of all at the Congress of German Surgeons in Berlin, where the chairman said he "could not find words enough to tell of the good of it."[32] Von Nussbaum wrote in April of 1875, that "Lister's treatment is already being greeted by the whole civilized world as an enormous advance."[33] A diluted carbolic

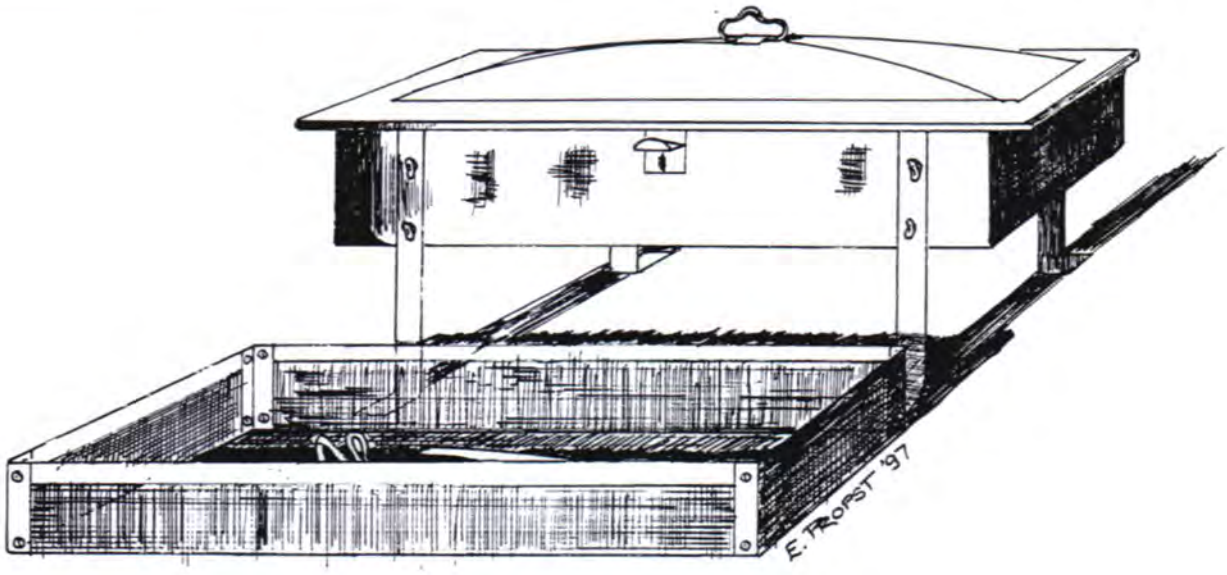

Fig. 2 Curt Schimmelbusch's soda sterilizer for instruments: battling sepsis full steam. (1895)

"spray was [later] devised [for use in operations] in response to the idea that sepsis was largely due to airborne organisms."[34]

In Curt Schimmelbusch's 1895 Guide to the Antiseptic Treatment of Wounds, he indicated that during surgery:

> The surface is actively brushed for at least 1 minute with soap and water, as hot as can be borne.
> It is carefully rubbed and dried with sterile towels.
> The skin is rubbed for about a minute with 80% alcohol.[35]

As well, he described surgeons' materials "asepticized in a steam sterilizer [and] put in closed tin boxes," and "surgeons [wearing] long, white sterilized linen gowns."[36] The surgeon was also to disinfect his hands with the utmost precaution. This thorough method of sterilization to prevent wound infection would set the standard for many years.

The 20th century brought a new outlook on the treatment of sepsis in surgery. In 1904, Paul Ehrlich discovered that dyes selectively absorbed by cells could be effective as antibacterial drugs. With Kiyoshi Shiga, he prepared the 606th arsenical substance in 1907, and ventured to London in 1909 to share his discovery with others. In London, Ehrlich entrusted a man by the name of Alexander Fleming with the task of trying this Salvarsan 606, as it came to be known, on a patient. In 1917, Fleming assisted S. Douglas in preparing his "Studies in Wound Infections" for publication in the Lancet, which stated that "bacterial symbiosis may play a very important role in wound infections."[37] In 1922, Fleming reported the discovery of an anti-bacterial substance, lysozyme, derived from the mould Penicillium notatum. Unknown to Fleming, Lister had abandoned an experiment noted in his "Commonplace Book" of 1871, where he noted that the presence of a soft mass (which he thought was penicillium glaucum) "was making the bacteria completely immobile and languid."[38] In January of 1929, the use of penicillin to prevent bacterial infections in man was first suggested in the British Journal of Experimental Pathology. The first therapeutic test with purified penicillin, made possible by a decade of research by Howard Florey and Ernst Chain, took place on the evening of August 6, 1942, and their patient recovered from meningitis on August 27. An article in the Times hailed their success, and urged that "methods of producing penicillin on a large scale should be developed as quickly as possible."[39] By 1943, the most active form, benzyl penicillin, had been crystallized, and the United States Armed Forces already had a sufficient supply of Fleming's drug. In 1944, Florey predicted that "some chemist will manipulate the penicillin molecule to improve its performance,"[40] and in 1957 synthetic penicillin was produced for the first time at the Massachusetts Institute of Technology by John Sheehan and his collaborators. By 1961, acid-resistant strains were already being produced for oral ingestion.

Current guidelines for cleanliness and infection prevention state that a surgeon must: Scrape/brush nails and apply antiseptic soap or detergent e.g., chlorhexidine or povidone iodine, to hands and forearms using a defined technique for a minimum of two minutes. Dry hands on sterile towel. Alternatively, clean hands with soap and water and apply two or more applications of an alcohol hand rub.[41]

It is interesting to note that the current method of sterilizing skin is almost identical to that proposed by Schimmelbush in 1895. As well, alcohol is used today as a disinfectant, as it was by the ancients nearly 5000 years ago. Current surgical books on the management of war injuries prescribe "gentle and copious irrigation with saline,"[42] which was foreshadowed in John Bell's 1826 description of the French army's use of saliva. Furthermore, this technique is described in the book of

Genesis of the Old Testament, where saliva is applied in circumcision to prevent inflammation.[43] One might even argue that such a practice is innate, for we have seen that other primates instinctively lick their wounds clean to promote rapid and complete healing.[44]

Whether based on magic, religion, sorcery, observation or experimentation, human practices have always existed to battle infection. It can therefore rightfully be said that the history of cleanliness and infection prevention in surgery and the treatment of wounds has been continuous.

But even today diseases remain for which cures do not exist, and we do not know what mankind will face in the future. In 1959, a continuing quest for new antibiotics led to a review of 2222 plants, of which 1362 were reported as having some antibiotic effect.[45] Pliny's observation that Arabia and India were considered the storehouses of remedies, while nobody looked into his own garden has retained its validity. With this in mind, and five thousand years of effective medical knowledge at our fingertips, it is clear that we must not forget the ancients as we boldly enter the third millennium.

ACKNOWLEDGEMENT Many thanks to Dr Paul Potter for his support, encouragement and advice.

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Ω

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ACTION AND CLINICAL PHARMACOLOGY

NORVASC (amlodipine besylate) is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist). Amlodipine is a member of the dihydropyridine class of calcium antagonists.

INDICATIONS AND CLINICAL USE

Hypertension

NORVASC (amlodipine besylate) is indicated in the treatment of mild to moderate essential hypertension. NORVASC should normally be used in those patients in whom treatment with diuretics or beta-blockers was found ineffective or has been associated with unacceptable adverse effects. NORVASC can be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects. Combination of NORVASC with a diuretic, a beta-blocking agent, or an angiotensin converting enzyme inhibitor has been found to be compatible and showed additive antihypertensive effect.

Chronic Stable Angina

NORVASC is indicated for the management of chronic stable angina (effort-associated angina) in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents. NORVASC may be tried in combination with beta-blockers in chronic stable angina in patients with normal ventricular function. When such concomitant therapy is introduced, care must be taken to monitor blood pressure closely since hypotension can occur from the combined effects of the drugs.

CONTRAINDICATIONS

NORVASC (amlodipine besylate) is contraindicated in patients with hypersensitivity to the drug or other dihydropyridines and in patients with severe hypotension (less than 90 mmHg systolic).

WARNINGS

Use in Patients with Congestive Heart Failure

Safety and efficacy of NORVASC (amlodipine besylate) in patients with heart failure has not been established. Caution should therefore, be exercised when using NORVASC in patients with compromised ventricular function, particularly in combination with a beta-blocker. In a controlled clinical trial using a small number of patients (58 Norvasc and 60 Placebo) with well compensated congestive heart failure (NYHA Class II-III), addition of NORVASC to digoxin and diuretic therapy with or without angiotensin converting enzyme inhibitors did not lead to worsening of heart failure in the majority of patients treated.

Increased Angina and/or Myocardial Infarction

Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

Outflow Obstruction (Aortic Stenosis)

NORVASC should be used with caution in a presence of fixed left ventricular outflow obstruction (aortic stenosis).

Use in Patients with Impaired Hepatic Function

There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild to moderate hepatic impairment given single dose of 5 mg, amlodipine half-life has been prolonged. NORVASC should, therefore, be administered with caution in these patients and careful monitoring should be performed. A lower starting dose may be required (see **DOSAGE AND ADMINISTRATION**).

Beta-blocker Withdrawal

NORVASC gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker.

PRECAUTIONS

Hypotension

NORVASC (amlodipine besylate) may occasionally precipitate symptomatic hypotension. Careful monitoring of blood pressure is recommended, especially in patients with a history of cerebrovascular insufficiency, and those taking medications known to lower blood pressure.

Peripheral Edema

Mild to moderate peripheral edema was the most common adverse event in the clinical trials (see **ADVERSE REACTIONS**). The incidence of peripheral edema was dose-dependent and ranged in frequency from 3.0 to 10.8% in 5 to 10 mg dose range. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Use in Pregnancy

Although amlodipine was not teratogenic in the rat and rabbit some dihydropyridine compounds have been found to be teratogenic in animals. In rats, amlodipine has been shown to prolong both the gestation period and the duration of labor. There is no clinical experience with NORVASC in pregnant women. NORVASC should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Nursing Mothers

It is not known whether amlodipine is excreted in human milk. Since amlodipine safety in newborns has not been established, NORVASC should not be given to nursing mothers.

Use in Children

The use of NORVASC is not recommended in children since safety and efficacy have not been established in that population.

Use in Elderly

In elderly patients (≥65 years) clearance of amlodipine is decreased with a resulting increase in AUC. In clinical trials the incidence of adverse reactions in elderly patients was approximately 6% higher than that of younger population (<65 years). Adverse reactions include edema, muscle cramps and dizziness. NORVASC should be used cautiously in elderly patients. Dosage adjustment is advisable (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions

Beta-blockers: When beta-adrenergic receptor blocking drugs are administered concomitantly with NORVASC, patients should be carefully monitored since blood pressure lowering effect of beta-blockers may be augmented by amlodipine's reduction in peripheral vascular resistance.

Digoxin, Cimetidine, Warfarin: Pharmacokinetic interaction studies in healthy volunteers have indicated:

- amlodipine did not change serum digoxin levels or digoxin renal clearance.
- cimetidine did not alter the pharmacokinetics of amlodipine.
- amlodipine did not change warfarin induced prothrombin response time.

ADVERSE REACTIONS

NORVASC (amlodipine besylate) has been administered to 1,714 patients (805 hypertensive and 909 angina patients) in controlled clinical trials (vs placebo alone and with active comparative agents). Most adverse reactions reported during therapy were of mild to moderate severity.

Hypertension

In the 805 hypertensive patients treated with NORVASC in controlled clinical trials, adverse effects were reported in 29.9% of patients and required discontinuation of therapy due to side effects in 1.9% of patients. The most common adverse reactions in controlled clinical trials were: edema (8.9%), and headache (8.3%).

The following adverse reactions were reported with an incidence of ≥0.5% in the controlled clinical trials program (n=805):

Cardiovascular: edema (8.9%), palpitations (2.0%), tachycardia (0.7%), postural dizziness (0.5%). **Skin and Appendages:** pruritus (0.7%). **Musculoskeletal:** muscle cramps (0.5%). **Central and Peripheral Nervous System:** headache (8.3%), dizziness (3.0%), paresthesia (0.5%). **Autonomic Nervous System:** flushing (3.1%), increased sweating (0.9%), dry mouth (0.7%). **Psychiatric:** somnolence (1.4%). **Gastrointestinal:** nausea (2.4%), abdominal pain (1.1%), dyspepsia (0.6%), constipation (0.5%). **General:** fatigue (4.1%), pain (0.5%).

Angina

In the controlled clinical trials in 909 angina patients treated with NORVASC, adverse effects were reported in 30.5% of patients and required discontinuation of therapy due to side effects in 0.6% of patients. The most common adverse reactions reported in controlled clinical trials were: edema (9.9%) and headache (7.8%).

The following adverse reactions occurred at an incidence of ≥0.5% in the controlled clinical trials program (n=909):

Cardiovascular: edema (9.9%), palpitations (2.0%), postural dizziness (0.6%). **Skin and Appendages:** rash (1.0%), pruritus (0.8%). **Musculoskeletal:** muscle cramps (1.0%). **Central and Peripheral Nervous System:** headache (7.8%), dizziness (4.5%), paresthesia (1.0%), hypoesthesia (0.9%). **Autonomic Nervous System:** flushing (1.9%). **Psychiatric:** somnolence (1.2%), insomnia (0.9%), nervousness (0.7%). **Gastrointestinal:** nausea (4.2%), abdominal pain (2.2%), dyspepsia (1.4%), diarrhea (1.1%), flatulence (1.0%), constipation (0.9%). **Respiratory System:** dyspnea (1.1%). **Special Senses:** abnormal vision (1.3%), tinnitus (0.6%). **General:** fatigue (4.8%), pain (1.0%), asthenia (1.0%).

NORVASC has been evaluated for safety in about 11,000 patients with hypertension and angina.

The following events occurred in <1% but >0.1% of patients in comparative clinical trials (double-blind comparative vs placebo or active agents; n = 2,615) or under conditions of open trials or marketing experience where a causal relationship is uncertain.

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrilation), bradycardia, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension. **Central and Peripheral Nervous System:** hypoesthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dysphagia, vomiting, gingival hyperplasia. **General:** asthenia†, back pain, hot flushes, malaise, rigors, weight gain. **Musculoskeletal System:** arthralgia, arthrosis, myalgia. **Psychiatric:** sexual dysfunction (male† and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** epistaxis. **Skin and Appendages:** pruritus†, rash erythematous, rash maculopapular. **Special Senses:** conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, sweating increased. **Metabolic and Nutritional:** thirst. **Hemopoietic:** purpura.

†These events occurred in less than 1% in placebo controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

The following events occurred in ≤0.1% of patients: cardiac failure, skin discoloration, urticaria, skin dryness, alopecia, twitching, ataxia, hypertonia, migraine, apathy, amnesia, gastritis, increased appetite, coughing, rhinitis, parosmia, taste perversion, and xerophthalmia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Overdosage can cause excessive peripheral vasodilation with marked and probably prolonged hypotension and possibly a reflex tachycardia. In humans, experience with overdosage of NORVASC (amlodipine besylate) is limited. When amlodipine was ingested at doses of 105-250 mg some patients remained normotensive with or without gastric lavage while another patient experienced hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg of amlodipine with benzodiazepine developed shock which was refractory to treatment and died. In a 19 month old child who ingested 30 mg of amlodipine (about 2 mg/kg) there was no evidence of hypotension but tachycardia (180 bpm) was observed. Ipecac was administered 3.5 hrs after ingestion and on subsequent observation (overnight) no sequelae were noted.

Treatment

Clinically significant hypotension due to overdosage requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Clearance of amlodipine is prolonged in elderly patients and in patients with impaired liver function. Since amlodipine absorption is slow, gastric lavage may be worthwhile in some cases.

DOSAGE AND ADMINISTRATION

Dosage should be individualized depending on patient's tolerance and responsiveness. For both hypertension and angina, the recommended initial dose of NORVASC (amlodipine besylate) is 5 mg once daily. If necessary, dose can be increased after 1-2 weeks to a maximum dose of 10 mg once daily.

Use in the Elderly or in Patients with Impaired Renal Function

The recommended initial dose in patients over 65 years of age or patients with impaired renal function is 5 mg once daily. If required, increasing in the dose should be done gradually and with caution (see **PRECAUTIONS**).

Use in Patients with Impaired Hepatic Function

Dosage requirements have not been established in patients with impaired hepatic function. When NORVASC is used in these patients, the dosage should be carefully and gradually adjusted depending on patient's tolerance and response. A lower starting dose of 2.5 mg once daily should be considered (see **WARNINGS**).

DOSAGE FORMS

Availability

NORVASC is available as white octagonal tablets containing amlodipine besylate equivalent to 2.5, 5 and 10 mg amlodipine per tablet. The respective tablet strengths are debossed on one tablet face as "NRV 2.5", "NRV 5" and "NRV 10" with "Pfizer" on the opposite face. The 5 mg tablet is scored. Supplied in white plastic (high density polyethylene) bottles of 100 tablets for each strength. Also the 5 mg and 10 mg are supplied in bottles of 250 tablets.

STORAGE

Store at 15-30°C. Protect from light.

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Product Monograph Available Upon Request.

The Origins of Medicine in Early Greek Mythology

by David I Beile

> If the poet's tongue might breathe the prayer that is on the lips of all, I would pray that Cheiron, son of Philyra, who is dead and gone, were now alive again, ¯he who once ruled far and wide as the offspring of Cronus, who was the son of Heaven. Would that that rugged monster with spirit kindly unto men, were reigning still in Pelion's glens, even such as when, in olden days, he reared Asclepius, that gentle craftsman who drove pain from the limbs that he healed, ¯that hero who gave aid in all manner of maladies (Pindar. Py. 3.1-7, Sandys).

For nearly three thousand years Asclepius has been the patron of physicians in the West, first as a mortal, then as a god, and now as an iconographical fragment. Like the Cheshire cat's lingering grin, all that remains today of Asclepius's once-meaningful cult-image is his snake-entwined staff. His body has been absented from our visual representations and his story has passed from our repertory of tales. Yet, however faintly his name is known to us, we are in need of Asclepius to link us to the mythological past from which he sprang and to introduce us to places and individuals whose remembrance is far fainter. These figures of Greek mythology, the associates of Asclepius, reveal by their interconnection and commonality the origins of a medical tradition which is ancestor to our own.

It is likely that Asclepius dates from at least as far back as the Greek Dark Ages (1200 BC-800 BC), since the brevity of his citations in Homer's Iliad (c. 750 BC) suggest that the poet's audience was already familiar with his mythology. The same poem also documents his character as a physician, for he is said to have received certain medicines from Cheiron (Iliad 4.219), the most righteous of the centaurs (and a later subject of this article). To turn to the earliest recollections of Asclepius' parentage, a fragment of Hesiod (contemporaneous with Homer) mentions an unnamed maid, who dwelt in the Plain of Dotium by the River Amyrus and washed her feet in the Boebian Lake (MW fr. 59). Another fragment preserves the tidings brought by the raven to Apollo at Delphi that Ischys Eilatides had wed Coronis the daughter of Phlegyas (MW fr. 60). The Homeric Hymn to Apollo describes Ischys and the god as rival suitors (3.209-10), while the Hymn to Asclepius proclaims the celebrity's Apollonian paternity as well as his birth by Coronis in the Dotian plain (16.1-4). However, not until Pindar (c. 500 BC) is a full account of the myth provided. There, Coronis had previously consorted with Apollo and carried within her the pure seed of the god, but, without her father's knowledge, she consented to be wedded to Ischys son of Eilatus. Apollo in Delphi, cognizant of this deception by his characteristic omniscience and the word of his raven messenger, wrathfully sent his sister, Artemis, to Lacheria where

Fig. 1 Map of Thessaly, in ancient Greece, showing sites associated with the myths of Cheiron and his followers. Presumed to be Coronis, the mother of Asclepius by Apollo. We will reencounter the geographical features which allude to her identity in subsequent versions of the myth.

Coronis dwelt near the banks of the Boebian Lake. There the resistless might of the goddesses destroyed both the offending girl and many of her neighbours. Yet, when her body was placed upon the funeral pyre, and the pyre kindled, Apollo could not bear to lose his innocent child in the fulfillment of its mother's doom. He reached through the flames, snatched Asclepius unborn from the corpse and bore him away to Cheiron to learn from the centaur to heal all mortals of disease. He grew to become a great physician, but in the end was tempted by a payment in gold to raise a man from the dead. This deed outraged Zeus, who killed both Asclepius and the one he resurrected with the divine justice of his lightning-bolt (Py. 3.8-58).

The belief, which Pindar expresses, that Cheiron and not Apollo instructed Asclepius in the art of medicine was general among the ancient Greeks. It seems strange, however, that the god who could both bring and remove plagues, who healed Glaukus in the Iliad (16.527-29), and whose sister and mother healed Aeneas (5.447-48), was not, himself, the inceptor of his son's prodigious medical ability. Yet, the question of why Apollo was excluded from the honour of educating his own son can be easily answered by turning to an analysis of the period when the myths of Asclepius were being formed. For although Apollo gradually acquired a reputation as a god of healing, this characteristic had not been fully assimilated to his divine identity even by the time of the Archaic period (800 BC-500 BC). This is clearly shown by the fact that Paeon, a physician-god who existed before the Dark Ages (Burkert, 43f.), appears twice in the Iliad and once in the Odyssey independently of Apollo (Gantz, 96). It must be assumed, therefore, that in the Dark Ages the separation of Apollo from the medical attributes which he possessed in later periods was even more pronounced.

We are left, however, with a second and more perplexing question which concerns the apparent opposition between Cheiron, whom Pindar characterizes as a pher agroteros (rugged monster) (Py. 3.4), and the inherent humanity of the craft of healing that he advances. By the Greek agroteros is meant the wildness of the open countryside (agros) in distinction to the sophistication of the polis, while pher (descriptive of the animal component of the centaur's hybrid body) is cognate with the Latin fera and the ancestor of the English "feral". The combination of these two words leaves no doubt of the wildness of the centaur (Robbins, 96ff.). How then can a creature which haunts the wilderness around Mt. Pelion and dwells in a cave on the slopes of that Thessalian mountain be imagined to cultivate and teach the civilized medical craft? A reconciliation of this seeming contradiction can be achieved, however, by inspecting the common geographical situation of the mythological characters who, like Asclepius, profited from the centaur's tutelage.

Before we proceed, it is necessary to place the landmarks introduced by the Asclepius myth in their proper geographical context, that is, within the larger region of Thessaly. From Mt. Pelion, which is at the base of Cape Sepias and overlooks both the Gulf of Pagasae and the Aegean Sea, Lake Boebias, the Dotian Plain and the River Amyrus each lie north-eastward as successive points in a gradual arc. In distinction, Achilles, who was another ward of Cheiron (Nem. 3.43-63.), is described at the time of the Trojan War as ruling various cities somewhat further down the coast of Thessaly and around the Malian Gulf (Il. 2.681-85). Yet his father, Peleus, had found amnesty in the city of Iolcus, had been aided by Cheiron, and had solemnized a marriage which led to Achilles' own birth all within sight of Mt. Pelion. In addition to Achilles' doubly Thessalian provenance, the Iliad reveals that he possessed a knowledge of medicines which had been shown to him by Cheiron (11.829-31). As well, one finds from book 16 of the same poem that Achilles' ash spear, too, came from the centaur, who originally cut it from the forests atop Mt. Pelion as a gift for his father (16.143-44). Like the Thessalian medicines obtained from Cheiron, this Pelian spear also seems to have demonstrated curative properties in the hands of the hero. With it, Achilles healed a wound which he had formerly dealt to Telephus, the king of Mysia, thus fulfilling the famous prophecy of the Delphic Oracle that ho trosas kai iasetai (he who wounded will also heal) (Iths. 8.49-50; Ap.E. 3.17-20).

Jason, son of Aeson, is the third and last of the young heroes whom Pindar mentions as the students of Cheiron (Py. 4.102-19; Nem. 3.54). His birth in the city of Iolcus (south-eastward below Mt. Pelion, at the top of the Pagasaean Gulf) confirms him as a native of the same corner of Thessaly with which we are becoming familiar. Yet Jason is a special case, and there is a reason why Pindar neglects to describe his receipt of any medicines or medical instruction from the centaur. Since Iason in ancient Greek means healer, there was certainly no reason for the poet to specify the type of education that a hero of that name necessarily underwent. Be that as it may, the examples of Jason employing his healing craft are comparably rare. One, however, is provided by some recently published fragments of a Corinthian column crater dated to around 575 BC (Vojatzi 1982, 71-86). The fragments sort themselves out into two groups, on the first of which Jason is pictured reaching forward from behind the blind seer, Phineus, to place his hands over his sightless eyes. The first publisher of these fragments has suggested, on analogy with the literary accounts, that this action is meant to signify the healing of Phineus' blindness by a "laying on of hands" (Gantz, 355).

In returning full circle back to Asclepius, it is appropriate to add the Homeric account of his sons, Machaon and Podaleirius, to the mythological characterization of the country around Mt. Pelion and of its native physicians. According to the "Catalogue of Ships" in the Iliad, both the sons of Asclepius were lords over a region in the interior of southern Thessaly the centre of which was Tricca (2.729-32). They thus ruled westward from the coastal area in which their father experienced his god-induced birth and north-westward from where Jason's city stood, once home to Peleus (Nem. 3.33-34; 4.54-56). Their distance from the area around Mt. Pelion is commensurate with their lack of direct contact with Cheiron. It must be noticed that Machaon, in treating the arrow-wound of Menelaus, "laid healing medicines upon it that Cheiron in friendship had long ago given his father (Il. 4.218-19 (italics mine))." Yet this passage also shows that, despite their removal from the eastern coast of Thessaly, the brothers were part of a tradition of medical skills and medicines from Cheiron to Asclepius and from Asclepius to them. As an exemplar of this tradition, it is Podaleirius who

provides the means of answering the second of the questions posed earlier: why, after all, was Cheiron the instructor of Asclepius?

Following an explication of a passage in the Iliad, Eustathius, a Byzantine commentator on the Homeric poems, supplies the missing detail by revealing the etymological significance of Podaleirius' name:

moreover, Podaleirius is the "flower-footed" (lit. "lily-footed") not only, as is stated elsewhere because of his good fortune, but also because he diligently studied flowers. For as a physician he was for the most part an herb-gatherer (rhizotomos), as was fitting (Eustathius, XIII.830).

This ancient conception of physicians as gatherers of herbs finally explains away the discrepancy between Cheiron as agroteros and his role as the originator and disseminator of medical art. For only one who lived in close proximity to the wild could take advantage of what the earth, unaided, puts forth. In the same way, Homer in the Odyssey calls all Egyptians doctors not because they were the sons of Paeon, but because they dwelt "where the fertile earth produces the greatest number of medicines (4.229)." Even more than the Nile valley, the area around Mt. Pelion was famed in antiquity for its pharmacological wealth (Kern, 2.304). It was told that Medea, another rhizotomos (Radt, 410), in her flight through the nearby Thessalian plain scattered her collection of drugs and caused the entire region to sprout with herbs of equal virtue (Aristides, Oratio 38.15). The Latin elegists (50 BC-50 AD) as well, reflecting upon the compedia of Archaic Greek texts produced by their Hellenistic predecessors, remember Thessaly as a proverbial source of drugs, poisons, and those skilled in their use (Tib. 2.4.56; Prop. 1.5.4.). Cheiron, therefore, the "Magnesian centaur (Py. 3.45)" who "reigned in Pelion's glens (Py. 3.4)", was ideally situated to benefit from this local abundance of medicines. It is in such a proprietary capacity that Catullus describes him, his characteristic drugs transmuted to blossoms for the marriage of Peleus and Thetis: first from the summit of Pelion came Cheiron, bearing sylvan gifts; for all the flowers that the plains bear, all that the Thessalian region brings forth on its mighty mountains, all the flowers that near the river's streams the fruitful gale of warm Favonius discloses, these he brought himself... (Cat. 64.278-83).

The Cheironidae, or the descendants of Cheiron, perpetuated this sense of his rural claims as can be seen from the boast that they possessed pharmacologicals which originally belonged to their father. Moreover, the Magnesians (a local people from eastern Thessaly), worshipped the centaur as a healer and the inventor of the gentle science of medicine (Edelstein, 5). Since early medicine as attested in Homer was primarily surgical and pharmacological, and since the latter branch, as observed by Eustathius, seems to have been the dominant one, it is easy to see why Cheiron as the rhizotomos par excellence was also a physician par excellence. It is also easy to see why all the mythological heroes who had some experience in the practice of healing were not only born in Thessaly, but were raised and educated in the herb-bearing wilderness belonging to Cheiron. With the advent of Dark-Age pharmacology, this small area and its legendary produce became the fountainhead of a physicianship which was to be remembered throughout ancient Greece.

Our story, however, cannot end without first attending to Podaleirius, the author of our solution. In the aftermath of the Trojan War, he eventually settled in the Carian Chersonese (on the S.W. corner of Asia Minor) and fathered a line of children who, like those of his brother, were called the Asclepiadae (Ap. E. 6.18). In the intervening centuries between the period which Greek mythology remembers and that which is documented from historical knowledge, it may be imagined that a number of the Carian Asclepiadae migrated elsewhere, some along the coast of Asia Minor, some to the Ionian Islands, and some back to the Greek mainland. For historically, the neighbouring island of Cos boasted a family of Asclepiadae, pre-eminent among its nobility, who traced their ancestry back to Podaleirius and their geographical origin to Thessaly (Kerenyi, 52). Into this family that Hippocrates was born whose subsequent renown attracted an entire corpus of medical writings to his name. It is a testament to the medical importance of Cheiron and the land over which he presided, that this man, the greatest of the ancient physicians, named his eldest son Thessalus, "the one from Thessaly" (Kerenyi, 56).

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2..Cf. also MW fr. 50 = Pausanias 2.26.7. For an overview of the ancient contention between Thessalia, Epidauria, and Messenia regarding Asclepius's nativity, see Edelstein, 24-32; for an interpretation of the Hesiodic fragments see West, 69-72. For the purposes of this article, it is enough to realize that the Thessalian version of the Asclepius myth possesses an antiquity and self-consistency greater than the others.

Thessaly was an area in ancient Greece corresponding to the north-central portion of the Balkan peninsula today.

Cf. note 2. Ω

FEATURE SECTION

Frontiers in Medicine

Mapping the Human Brain with Functional Magnetic Resonance Imaging

by Sean P Dukelow and Joseph FX DeSouza

A Brief Introduction

Since Seiji Ogawa discovered functional magnetic resonance imaging (fMRI) in 1992, the world of functional brain mapping has never been the same. This new technology, which offers distinct advantages over Positron Emission Topography (PET) and Single Photon Emission Computed Tomography (SPECT), has sent researchers across the globe racing to functionally map the human brain. Recently, the Robarts Research Institute became the first centre outside the US to house an fMRI machine with a strength of 4 Teslas, which is about 80,000 times as strong as the earth's natural magnetic field (Figure 1). This is one of only seven 4-Tesla machines in the world. Although costly ($4-5 million), this machine allows us to view objects as small as ocular-dominance columns in human visual cortex (0.8mm X 1.6 mm)[1]. And unlike PET, where subjects typically must be injected with or inhale a radioactive tracer to measure regional cerebral blood flow, fMRI is non-invasive. Subjects can be scanned repeatedly without exposure to ionizing radiation.

The clinical applications of fMRI are many. It is already being used in presurgical mapping of primary motor and speech areas, and researchers at the Robarts Research Institute are currently using it to investigate epileptic foci, early degeneration in prefrontal and motor cortex in patients with Amyotrophic Lateral Sclerosis, early detection of glaucoma through examination of structural changes in primary visual cortex, cerebrovascular and cerebrorespiratory regulation, neural circuits which may be responsible for schizophrenia, brain plasticity in response to removal of an eye, and areas that are responsible for speech and swallowing. This paper will focus on research conducted in Dr Tutis Vilis's laboratory, part of the UWO Vision and Motor Imaging Group.

ABOUT THE AUTHORS

About the Authors: Sean Dukelow is a first-year MD/PhD student in the Neuroscience program at the University of Western Ontario. He will be joining the class of 2002 after completing his first two years of research. Prior to entering the MD/PhD program, he completed a BSc at the University of Guelph. Joseph DeSouza is a first-year PhD student in the Neuroscience program at the University of Western Ontario. Prior to starting his PhD, he completed an MSc in Neuroscience and a BA in Psychology at the University of Western Ontario.

VISUAL CORTICES

Anatomists divide the visual system into two processing streams, the dorsal and the ventral.[2] Originally, theorists proposed that the ventral stream handles visual form recognition while the dorsal stream deals with spatial vision[2], but more recently it has been proposed that the dorsal stream handles on-line control of visually guided movement while the ventral stream works off-line, building up a visual model of the world[3].

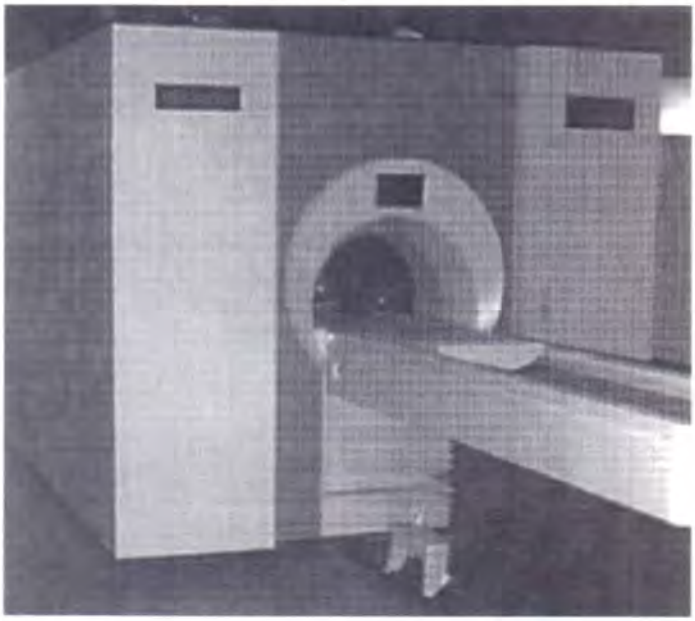

Fig. 1. The new 4-Tesla Varian functional Magnetic Resonance Imaging machine in the Cuddy Wing of the Robarts Research Institute.

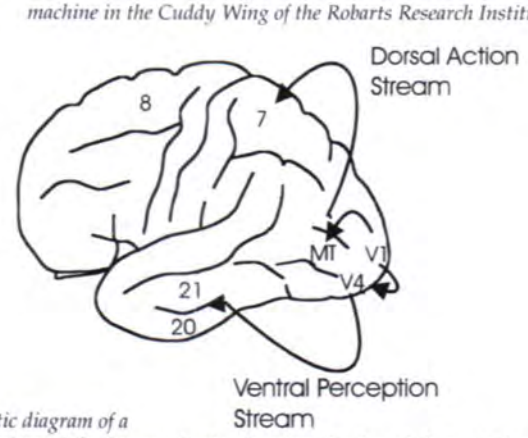

Fig. 2. Schematic diagram of a lateral view of the human brain showing the dorsal & ventral processing streams. The dorsal stream, running mainly through the posterior parietal cortex, is responsible for encoding visual motion & visually guided movements while the ventral stream is thought to be more involved in object recognition. (Numbers represent Brodmann's areas.)

As shown in Figure 2, both streams originate from primary visual cortex, also known as V1. The dorsal, action-oriented stream runs through regions in the posterior parietal cortex where neural activity correlates with visual motion and visually guided movements. Deficits to this stream can cause optic ataxia and/or disorders of spatial attention. The ventral stream runs mainly through regions of the inferotemporal cortex that deal with object recognition. Deficits in this stream may lead to visual form agnosia, prosopagnosia (problems recognizing faces) and/or achromatopsia (colour recognition deficits). The ventral stream is currently under investigation by a number of researchers[4] in the Vision and Motor Imaging Group, but in this article we shall focus on the dorsal stream.

Our studies to date have dealt with areas in the dorsal stream that respond to moving visual stimuli and/or saccadic and pursuit eye movements. We aim to determine the physiological response properties of these areas using fMRI. Our research into visual motion has concentrated largely on the human homologues of the macaque monkey's Middle Temporal (MT) and Medial Superior Temporal (MST) Areas. In monkeys, almost all cells in MT and MST show directional[5] and speed selectivity, meaning they respond best to objects moving with some favoured speed and direction[6]. fMRI work has shown that human MT is likewise activated by moving stimuli[7] and is located posterior to the junction of the ascending limb of the inferior temporal and lateral occipital sulci[8]. Currently we are investigating stimulus-speed sensitivity in this area. As well, we are attempting to determine the responses of MT and MST to pursuit eye movements.

In some of our experiments we have the subject make visually guided eye movements. It is known that electrical recordings from neurons in the monkey parietal regions in the Lateral Intraparietal Area and Area 7a show an increased firing rate during saccadic eye movements[9]. Once these cortical areas are determined in our group of subjects, we will employ various memory-guided saccade tasks in order to study areas in the parietal lobe processing the intention to make a movement and the attention to the task. One of the initial eye movement experiments we have conducted has investigated differences in activity for small and large saccadic eye movements in the posterior parietal cortex (PP) and frontal eye fields (FEF).

METHODS

In our imaging protocol, we use Blood Oxygenation Level Dependent (BOLD) contrast imaging. In this technique, areas of the brain which receive increased blood flow show up brighter. As increased blood flow is thought to indicate increased neural activity, we can visualize regions of the brain which display increased activity by performing a functional subtraction.

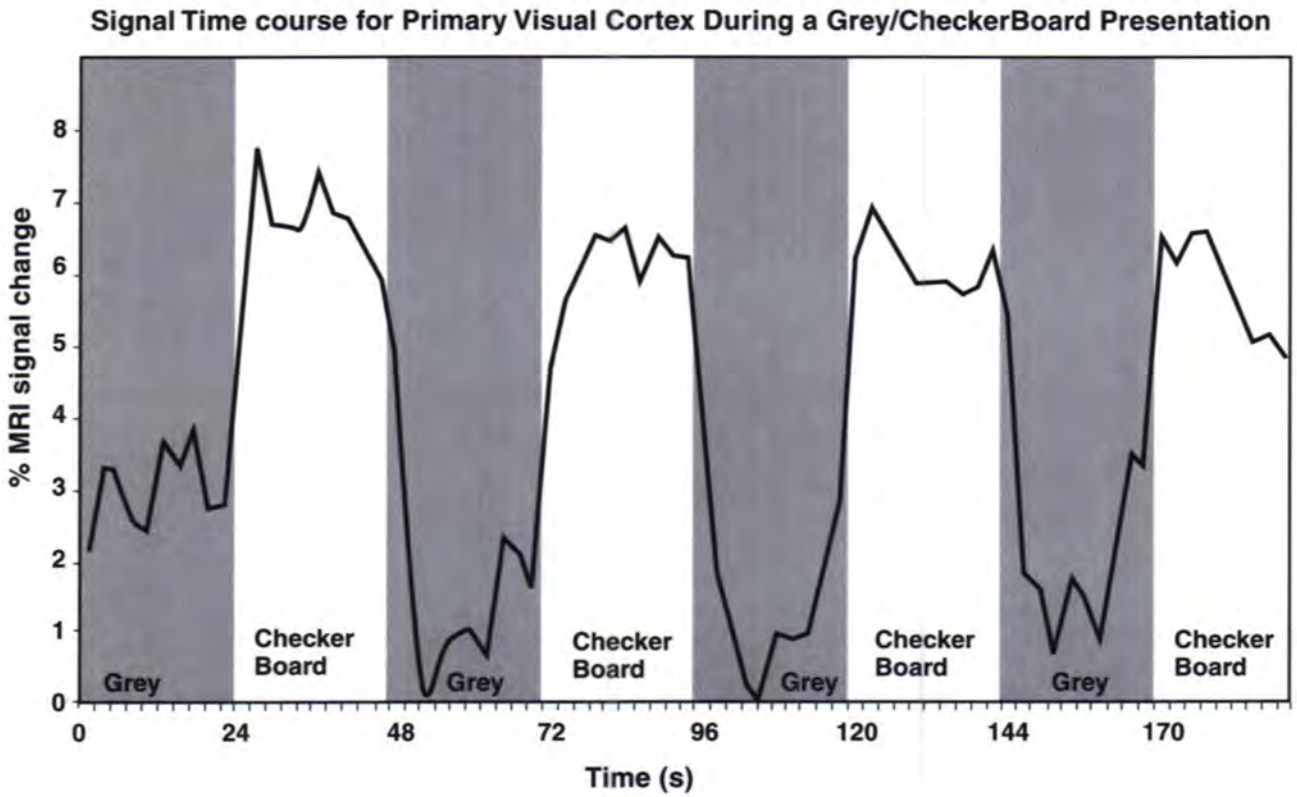

Fig. 3.

A signal time course taken from the primary visual cortex (V1) during a two-state experiment. Subjects viewed a stationary grey display followed by a checkerboard stimulus flashing at 8 Hz. During each state, 10 images were collected over a 24-s period. Both states were repeated 4 times. Area V1 shows a significant increase ($p<0.01$) in signal during presentation of the flashing checkerboard and this response is consistent across trials.

A functional subtraction, performed using the software package Stimulate[8], removes the basal level of neural activity on a voxel-by-voxel basis. A voxel is a small volume of the brain, and in our experiments we typically scan with a voxel size of about 2-3mm x 2-3 mm x 5-6 mm, although much higher spatial resolution is possible with this machine. One image (slice) in our experiments is composed of a matrix of 64 x 64 voxels. Larger matrices are also possible.

To use a functional subtraction we must design a stimulus condition that is closely related to the control condition in all but one respect. For example, images collected during the presentation of a stationary stimulus on our MRI video goggles are subtracted from images collected during the presentation of a leftward moving stimulus to reveal motion-sensitive areas within the brain. All other attributes of the visual stimulus such as luminance and contrast are held constant. This allows us to conclude that any changes in activation are likely to have resulted from the stimulus motion.

After generating a functional map using the Stimulate software, we plot the signal time course for specific regions of interest (ROIs), as shown in Figure 3. The signal time course plots the signal of activated voxels contained within the ROI. From the signal time course we can determine the response of the area during the control and one or more stimulus conditions. This response can then be compared across stimulus conditions and we can draw conclusions about the inherent properties of certain areas of the brain.

CURRENT INVESTIGATIONS

One of our current projects is to determine the sensitivity of human area MT to the speed of a visual stimulus. In this study, a "shutter" is moved rightward, once every second, across the central 8 degrees of the display at various speeds (0°/s, 8°/s, 16°/s). A functional subtraction is performed, removing activity during a stationary stimulus from activity occurring during movement of the "shutter" at 8°/s, to generate the map depicted in Figure 4. Analysis of the signal time course generated by this experiment has allowed us to conclude that human area MT responds significantly more strongly to a stimulus speed of 8°/s than to 16°/s ($p<0.05$). Further studies will involve a wider range of speeds (0°/s, 2°/s, 4°/s, 8°/s, 16°/s, 32°/s, 64°/s and possibly 128°/s). Research on stimulus speeds will help us determine the optimal stimulus speed for future movement paradigms.

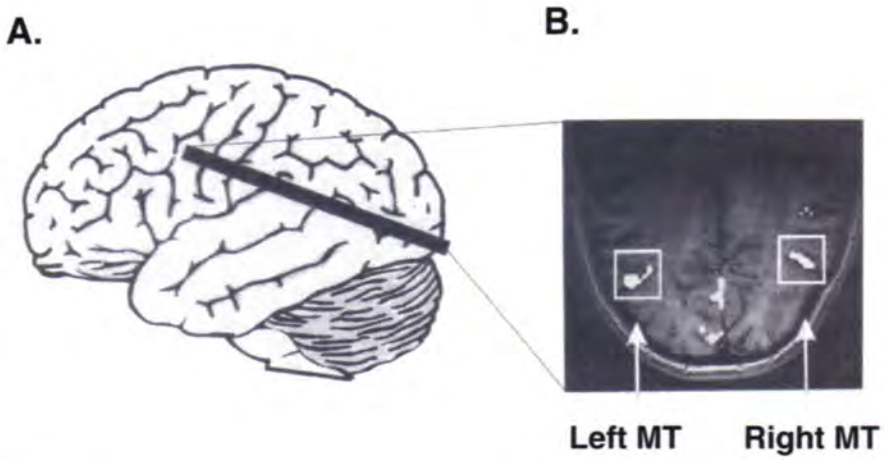

Fig. 4. Data from a subtraction: neural response to a "shutter" moving at 8°/s minus the response to a stationary stimulus. A) Left-side view of a schematic brain showing orientation of the image slice. B) Image through the human homologue of area MT showing bilateral activity during shutter movement (8°/s) compared to stationary.

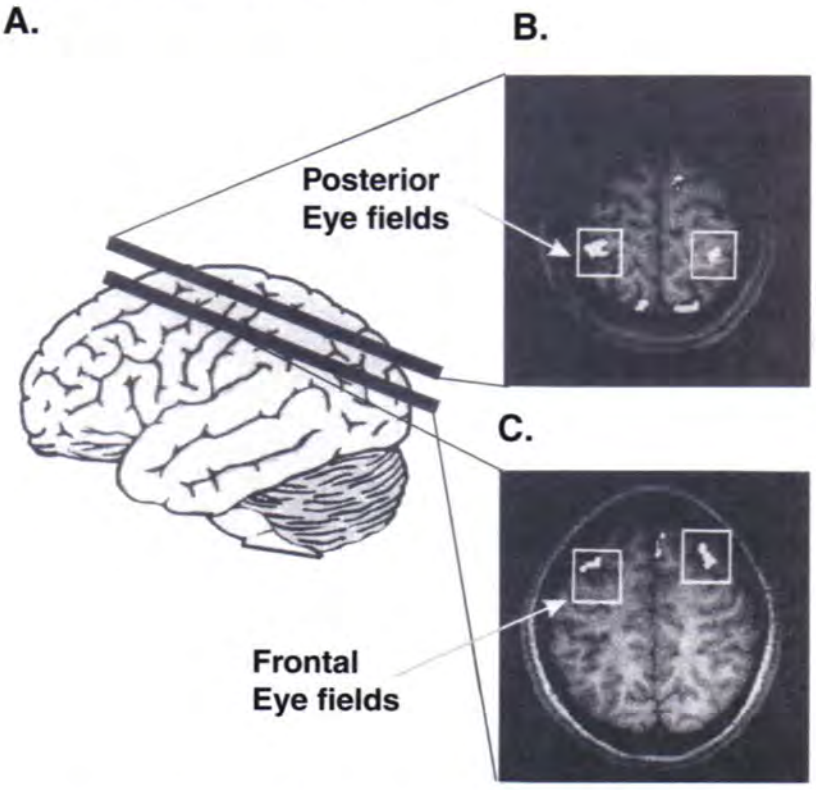

Fig. 5. Data from the subtraction of large (28°) saccadic eye movements with fixation for Subject LA. A) Left-side view of a schematic brain showing orientation of the image slices. B) Image through parietal cortex (PEF) showing activity during large (28°) saccadic eye movements compared to fixation. C) Image through frontal eye field (FEF) during the same experiment.

In another study, we compared activity during large (28°) and small (3°) saccades. Subjects viewed a small white dot against a black background. To analyse this experiment we "subtracted" each saccade task from a control task in which the subject fixated a central cross. This subtraction revealed activation in the visual cortex (Brodmann's Area [17,18]), frontal cortex (FEF, Frontal Eye Fields, Brodmann's Area [8]), and parietal cortex (PEF, Parietal Eye Fields, Brodmann's Area [7]; see Figure 5). Subtraction of the small saccade task from fixation revealed the same areas activated by the large saccade task, but these areas displayed a significantly decreased ($p<0.05$) signal during the small saccades. When recording electrophysiologically in the monkey, Douglas Munoz and Robert Wurtz[10] noted that large saccades cause more firing in the superior colliculus than do smaller eye movements. It would appear that our results support increased neural activity at higher cortical levels in both the parietal and frontal eye fields (PEF and FEF).

DISCUSSION

Our studies have shown stimulus-speed-related changes in activity in area MT as well as saccade-amplitude-related changes in PEF and FEF, which were quantified by changes in fMRI signal. Future studies will continue to map dorsal- stream areas to further determine the topography and regional functional specialization of the human visual system.

Our investigations into dorsal-stream neural activity using fMRI have allowed us to map regions of the brain with a spatial resolution that was previously unattainable. High spatial resolution and the ability to repeat scans in individuals make the fMRI a valuable tool for both researchers and clinicians. Over the past year we have functionally mapped out our own primary visual cortices, motion-sensitive areas, primary motor, and saccade-related areas. Our current studies have focused on only a few extrastriate visual areas within the human brain, but these investigations are amongst thousands in a worldwide push to functionally map the human brain.

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Ω

The Development of Laparoscopic Surgery: a Historical Overview

by Daniel Hackam

This year marks the tenth anniversary of the first laparoscopic cholecystectomy to be performed on a human being. It was carried out by Philippe Mouret in Lyon, France.[1] Since that time, the technologically exciting and innovative field of laparoscopic surgery has expanded to encompass a number of other intraperitoneal operations, as well as finding regular use in thoracic surgery, orthopaedics, and otolaryngology. Because laparoscopy is revolutionizing surgery in the late 20th century, now is an appropriate time to review its evolution and, in particular, its bearing on surgical practice.

Physicians' attempts to examine the interiors of body cavities most likely began with the Greeks around 400 BC.[2] Chronicles from that time reveal students of Hippocrates' school employing rectal and vaginal specula. These devices were refined through the centuries, with Arabic physicians adding mirrors around 1000 AD. In 1806, Bozzini used lantern-light and a tube to view the urethra and vagina.[2] Thomas Edison's invention of electric light in 1879 provided the precursor for the light sources used in 20th-century laparoscopy.

Modern-day laparoscopy has its roots in the work of three early 20th-century pioneers. In 1901, Kelling established a pneumoperitoneum in a live, anaesthetized dog, with air filtered through sterile cotton.[3] Using a Nitze cystoscope (designed in 1877), he inspected the stomach, oesophagus and other viscera of this first laparoscopic subject, reporting his results at the German Biological and Medical Society meeting of the same year. Although his methods and instruments were primitive, Kelling contributed substantially to the development of laparoscopy.

In the same year, Dimitri Ott, a gynaecologist from Petrograd, pioneered his own version of laparoscopy, which he termed "ventroscopy".[4] Making an incision in the anterior abdominal wall of a pregnant patient, he examined the inside of the cavity using light reflected from a head mirror. Ott's technique resembled laparotomy more than laparoscopy because no endoscope was actually used, but the incision was held open with a speculum.

If Kelling and Ott were pioneers in the development of laparoscopic tools and techniques, H.C. Jacobeus, in 1912, was the first to apply their innovations in a systematic, clinical fashion.[5] Jacobeus, moreover, did not restrict himself to examining the abdominal cavity, but also devised endoscopic methods for examining the thorax. The Swedish surgeon performed 115 examinations of the peritoneal and thoracic cavities in 75 patients, making laparoscopic diagnoses of syphilis, tuberculosis, cirrhosis, and malignancy. With the publication of his report,[5] the modern era of laparoscopy was born.

The following years brought many advances, with contributions from physics and surgery. The German hepatologist Kalk introduced a number of new innovations, including an oblique viewing scope with a 135-degree lens system, and the dual-trocar technique.[6] The latter advance, in which two incisions are made so that two instruments can be employed, laid the foundation for modern-day laparoscopic surgery. Veress of Hungary developed a spring-loaded needle for safely creating a pneumoperitoneum; the Veress needle, almost unchanged, is still used to this day.[7] Also of note is Semm's work, which involved the invention of a number of endoscopic instruments, most importantly an automatic insufflation device which carefully monitors abdominal pressure and gas flow.[8]

ABOUT THE AUTHOR

Daniel Hackam is a first-year medical student at UWO. He will be pursuing electives in paediatric general surgery and emergency medicine this summer in Vancouver.

The development of light sources and optics did not lag behind that of other instrumentation for laparoscopy. Originally, light was provided by a bulb positioned at the end of the laparoscope.[2] This proved to be unsatisfactory, however, as the device became very hot and often burned the hands of the operator. The first cold light source was developed by Fourestiere in 1943, who used a quartz rod to deliver light from an external source to the laparoscope[2]. Fibre-optic cables were added to the laparoscopic armamentarium in 1957, providing the cold light source of today.

Until the late 1980s, the role of laparoscopy was confined to diagnosis and selected gynaecologic procedures. In the 1930s, for instance, Kalk and Ruddock used laparoscopy to diagnose intraperitoneal disease, especially of the liver.[9] Ruddock, a general practitioner in the US, published a series of 500 cases (in which 39 laparoscopic biopsies were taken) in a major surgical journal, possibly in an attempt to interest surgeons in the technique.[10] But the perception of laparoscopy among general surgeons as a blind and incomplete procedure, in which the surgeon was limited in viewing or palpating the interior of the abdomen, remained.

This stereotype lingered until 1987, when the first laparoscopic cholecystectomy was performed in a human patient. The event that made this possible was the development of the silicon chip television camera.[2] This lightweight attachment to the endoscope allowed the laparoscopic image to be magnified on a viewing screen. Hence, a surgeon could be free to operate with the videolaparoscope held by an assistant.

The advent of laparoscopic cholecystectomy has revolutionized the management of gallbladder disease, and indeed the whole field of general surgery in the late 20th century. In a mere three-year period, the percentage of gallbladders removed by the conventional open approach fell from 100% to 10-20% in most hospitals.[11] Moreover, it is estimated that over 5000 surgeons were trained in the laparoscopic procedure in 1990 alone.[11] The benefits of gallbladder resection by laparoscopy are by now well-known: minimized post-operative pain, reduced hospital stays, and a faster return to full activity.[1]

Driven by patient demand and the curiosity of intrepid, innovative surgeons, a number of other intra-abdominal procedures have been adapted to the less invasive laparoscopic approach. Inguinal hernia repair, appendectomy, and the treatment of benign gastro-oesophageal disease have all been approached by laparoscopy.[2] Moreover, as noted above, therapeutic laparoscopy has found broad applicability in urology, gynaecology, ENT, orthopaedics and thoracic surgery.

The vigorous enthusiasm for laparoscopic surgery exhibited by many patients and surgeons has been noted. It is critical, however, that any new application be subjected to rigorous scientific evaluation and analysis. If a laparoscopic procedure is accepted because it is easier on the patient, despite the possibility that outcomes are substandard, then the operation will have been a "triumph of technique over common sense".[12]

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Ω

Management of Leg-Length Discrepancies: Past, Present and Future

by AM Glickman and CVA Bowen

INTRODUCTION

Deformity resulting from damage to the epiphyseal plate is one of the most difficult problems in Orthopaedic Surgery. Congenital anomalies, injury, tumour and infection can all lead to growth abnormalities (Figure 1) in the form of limb-length discrepancy and/or directional deformity. Historically, many techniques have been used to manage these problems, but none of the limb-lengthening methods currently available in clinical practice is ideal. The number of clinical cases may not be large compared with some diseases, but the burden is heavy because each patient is faced with a lifelong challenge.

Presently, leg-length discrepancy can be managed using a number of different techniques including : (1) epiphysiodesis; (2) epiphyseal stapling; (3) single-stage shortening of the longer limb; (4) single-stage lengthening of the shorter limb; (5) stimulation of epiphyseal-plate growth; (6) gradual lengthening by distraction; or (7) gradual biological lengthening (epiphyseal-plate transplantation). Each approach is discussed below with particular attention paid to the future possibility of epiphyseal plate transplantation.

EPIPHYSIODESIS

Epiphysiodesis is a procedure that arrests growth in the longer limb. The first reported case was published in 1933 by Phemister.[63] A method of prematurely arresting epiphyseal plate growth in one or more of the epiphyseal plates in the longer limb was outlined. The procedure involves the complete destruction of the epiphyseal plate in the longer limb.[14] It has to be timed very carefully to allow the increasing length in the shorter limb to catch up exactly to that of the longer limb at the time of skeletal maturity.

This procedure is completely reliable and can produce limbs of equal length. Many consider it the treatment of choice for the correction of limb-length discrepancies as it is straight forward and the child is disabled only minimally and for a short time.[69,79] Its drawback, however, is that it shortens the longer limb and therefore results in two legs that are shorter than normal.

ABOUT THE AUTHORS

Aaron Glickman is a first-year medical student at UWO. He completed his BA here and recently received an MSc from the University of Toronto. Dr CVA Bowen is an associate professor of Surgery at the University of Toronto and an orthopaedic reconstructive microsurgeon. He is interested in vascularized bone transfers. For many years his research focus has been the transfer of vascularized epiphyseal plates.

EPIPHYSEAL PLATE STAPLING

Epiphyseal stapling is a technique which, hypothetically, should result in a temporary retardation of growth of the longer limb. In 1948 Haas demonstrated that when epiphyseal plate growth was interrupted by a wire loop, growth could resume upon its removal.[28] The concept of epiphyseal stapling was subsequently introduced by Blount and Clark in 1949.[8] This procedure differs from epiphysiodesis in that it can theoretically be reversed by removing the staples when the limb-length discrepancy is corrected.[29] This technique was attractive because it alleviated the need to make accurate predictions of future growth.

The effect of stapling is primarily a mechanical restraint of growth but, perhaps secondarily, it has been shown to cause a decrease in epiphyseal plate glucose uptake, lactate formation, cellular proliferation and matrix synthesis.[34] Stapling does not, however, inhibit growth as efficiently as epiphysiodesis. In addition, problems have occurred because there is no guarantee that epiphyseal plate growth will resume after the staples are removed; the growth may continue as it should, or the plate may fuse prematurely.[13,25] This is also a leg-shortening procedure resulting in limbs of less than ideal length.

SINGLE-STAGE LIMB SHORTENING

Single-stage skeletal shortening procedures are often carried out after skeletal maturity has been reached.[70] The operation involves resecting a portion of the shaft of a long bone. It is different from epiphysiodesis in that it is not based on predictions of future growth.

Skeletal shortening, although reliable, can unfortunately produce muscle weakness if 3 cm or more of the tibia or 5-7 cm or more of the femur are removed.[52] Single-stage shortenings are, therefore, best done in cases where relatively small changes in length are required.

SINGLE-STAGE LIMB LENGTHENING

Techniques to lengthen the shorter limb are theoretically preferable to those that shorten the longer limb because they aim to correct the abnormal limb and produce an end result where the limbs are of normal length.

The first documented single-stage lengthening of the femur was attempted in 1905 by Codivilla with an oblique osteotomy and a sudden pull on a nail inserted into the calcaneus.[16] He reported increases in length of 3 to 8 cm in 26 cases. Tibial lengthening was introduced in 1927 by Abbott.[1] In the two decades that followed, lengthening of the tibia fell into relative disuse as a result of numerous complications including shock, paralysis, sepsis, amputation and death. Since that time, many different techniques have been used where the gap between the bone ends is maintained by autograft or allograft bone and/or varying types of internal fixation devices.[2,10,18,47]

EPIPHYSEAL PLATE STIMULATION

Another method by which limb-length discrepancies have been managed is epiphyseal plate stimulation in the shorter limb. A variety of techniques have been used to do this.

Both experimental[20,26,31,33,36,42,44,75,81,83] and clinical[15,43,80,40] examples of periosteal division or stripping have resulted in increased epiphyseal plate growth. There are a number of theories as to how this works. A favoured explanation is related to the release of tension exerted by the periosteum on the epiphyseal plate.[54]

Moss put forward this biomechanical theory.[53] It was proposed that the periosteum acts as an elastic sleeve which is subject to tensile forces when the epiphyseal plate grows. As a result, the chondrocytic columns are indirectly compressively loaded through their collagenous network and growth is slowed. The periosteum counters this stress by growing interstitially resulting in a decompression of the epiphyseal plate and growth stimulation. This is based on the Heuter-Volkmann Thesis which postulates that epiphyseal plate compression causes a decrease in growth and decompression the opposite.[35,73]

The biomechanical explanation is further supported by studies which have demonstrated that incomplete periosteal transection tends to lead to growth stimulation only on the side where the periosteum is released.[6,23,36] Surgical trials have shown that the most favourable results are achieved in younger patients with faster growing epiphyseal plates and when the division is made close to the epiphyseal plate that is to be stimulated.[43,44,75,80] It has not, however, been shown to be clinically useful as the overgrowth is small and inconsistent.[52]

Another technique that has been used to stimulate the epiphyseal plate is inserting foreign material in the subepiphyseal region.[9] Cases have been reported in which ivory or metallic screws have been inserted into the subepiphyseal region of the proximal end of the tibia and distal end of the femur resulting in growth stimulation varying from 0.2 to 2.2 cm. Unfortunately, no standard amount of length increase could be predicted, making this technique unreliable.[61] Other techniques have also been proposed but none has been very useful clinically.[5,7,32,45,62]

GRADUAL LENGTHENING BY DISTRACTION

Several different techniques that rely upon the distraction of bone or cartilage to lengthen the limb have been used. They are discussed below.

Distraction and Bone Grafting

Gradual distraction followed by the filling of the gap with bone graft has been done for many years.[17,24,60,74,76,77] For these techniques, the bone and periosteum are cut. Although it is possible to attain large increases in bone length, these procedures are associated with many hazards and complications often related to the number of operations required.[52]

Epiphyseal Plate Distraction

Chondrodiatasis, introduced by DeBastiani[21,22], is another distraction technique. It involves slow and gradual epiphyseal plate distraction resulting in bone lengthening by extending epiphyseal plate width without forming a fracture gap. The increase in epiphyseal blood supply and the tension exerted on the epiphyseal plate induce a increase in its activity.[22] Upon completion of the distraction, the epiphyseal plate continues to function. This results in an increase in total bone length.

Epiphysiolysis, introduced by Monticelli and Spinelli and others[21,49,50,51], is a different technique which employs traction forces that exceed the strain tolerance of the epiphyseal plate, resulting in a fracture at the junction of the epiphyseal plate and the metaphysis. The heights of the proliferative and hypertrophic zones expand.

Increased proliferation is detected adjacent to the fracture gap in the hypertrophic (only initially) and proliferative zone cell populations.[4] The longitudinal expansion of the epiphyseal plate is in part associated with increased epiphyseal and decreased metaphyseal blood supplies.[3] The bone length increase is the result of biologic processes comparable to those of the Ilizarov technique discussed below.[21]

When considering epiphyseal plate distraction it should be noted, however, that the complication rate is high, the procedures are painful, and the epiphyseal plate may be irreversibly damaged.[30,19]

Distraction Osteogenesis

Today, Ilizarov's experimental and clinical studies on controlled mechanical distraction osteogenesis have permitted the lengthening of limbs through conditions that allow new bone formation in distraction gaps.[37]

The biological principle behind Ilizarov's technique, called the Law of Tension-Stress, purports that well-vascularizsed, weight-bearing tissues that are subjected to slow consistent traction are metabolically activated, triggering proliferative and biosynthetic cellular processes.[38]

Distraction osteogenesis involves a metaphyseal or submetaphyseal corticotomy followed by the application of an external fixation device that allows loading. Ilizarov's technique differs from others because the periosteum is not cut and distraction is delayed until fracture callus forms so that it may be distracted. After a specified waiting period, the limb is gradually distracted. Osteogenic activity within the distraction space results in lengthening of the shorter limb[38] The process correlates fracture repair with distraction.[59] With highly stable fixation and specific rates of distraction (approximately 1 mm/day)[38,39], the gap is eventually filled with newly formed bone. The resulting trabeculae lie parallel, in both directions, to the longitudinal axis of elongation initiated at the centre of the defect.[38] In children, the procedure is designed so as to minimize tension at the epiphyseal plate.[65]

It has been recommended that distraction techniques be used only for limb-length discrepancies of 5 cm or greater. The joints proximal and distal to the elongated bone must be stable, the neuromuscular function and circulation must be normal and the patient must have the mental capacity to cooperate with the imperative postoperative schedule associated with distraction devices. These procedures, however valuable in certain cases, may not be ideal in situations involving joint instability, paralysis (lengthening could further weaken musculature or promote hypertension as a result of stretched nerve fibers), poor bone structure, mental instability or young children.[70] It should also be noted that the distraction period is painful, not well tolerated, and subject to numerous complications.[70]

GRADUAL BIOLOGICAL LENGTHENING VIA EPIPHYSEAL PLATE TRANSPLANTATION

The possibility of carrying out revascularized epiphyseal plate transplantations has interested microvascular surgeons for some time. In theory, microvascular epiphyseal plate transplantations could form the ideal solution to a wide variety of clinical problems, particularly those involving congenital absence of an epiphyseal plate or damage/destruction of an epiphyseal plate at an early age.

Unlike conventional limb-lengthening techniques, a revascularized epiphyseal plate transplant should maintain its ability to grow and increase bone length until it fuses at skeletal maturity. The technology necessary to carry out microvascular epiphyseal plate transplantations is available and investigators have shown that, providing that the microvascular anastomoses are patent, these grafts remain viable and continue to grow in length.[12] A small number of clinical autograft transplantation operations have now been done.[27,55,56,57,58,64,66,68,71,72,82,84]

Allograft epiphyseal plate transplants offer theoretical advantages over autografts as they reduce donor-site morbidity and allow the surgeon to choose from a large number of donor sites to find the ideal graft. Although experimental allograft transplants have been successfully carried out in the laboratory[12,11,48,67], current immunosuppression techniques are sufficiently toxic that clinical cases must still rely on autograft donor tissue.

CONCLUSION

It is clear that there are a variety of options available to today's reconstructive surgeon for managing paediatric leg-length discrepancies. All of the alternatives pale, however, when compared with the possibility of epiphyseal plate transplantation because this is the most gradual technique and therefore does not require a sudden unexpected pull on the surrounding soft tissues. In addition, it allows both limbs to grow at similar rates. This should theoretically allow a child to grow to his/her predetermined height (if the graft is well matched to the recipient) with little disability during the years of active epiphyseal plate growth.

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Ω

Minimally Invasive Coronary Artery Bypass Grafting

by Nimesh Desai

INTRODUCTION

Minimally invasive direct coronary artery bypass grafting (MIDCAB) is a surgical intervention aimed at revascularizing cardiac tissue without using cardiopulmonary bypass (CPB) or performing a median sternotomy. The idea of performing coronary artery bypass grafting (CABG) without using CPB is not new. In 1958, Longmire performed the first left internal mammary artery (LIMA) to left anterior descending coronary artery (LAD) bypass on a human as a complication of a thrombo-endarterectomy procedure on the beating heart.[1] Beating-heart surgeries continued until the late 1960s, when cardioplegia with CPB gained widespread use. Hypothermic cardiac arrest with CPB and microsurgical anastomotic techniques was utilized by Spencer in 1964 leading to excellent long-term patency of the LIMA-LAD graft.[2]

Traditionally, CABG has been performed using the median sternotomy technique in which the sternum is divided longitudinally, the ribs are laterally retracted and the pericardium is exposed. Cardioplegia is achieved by thermal or chemical means and CPB is initiated providing oxygenation and driving circulation. Anastomosis is performed on the arrested heart allowing for maximum control of the operating field and simplified technique. World-wide, over 800,000 bypass surgeries aimed at revascularizing cardiac tissue are performed each year utilizing both arterial and vein grafts.[3] In-hospital mortality of this procedure is less than 1% for elective cases and morbidity is very low.[2] One of the most significant causes of post-operative morbidity in patients who have undergone traditional bypass grafting are complications related to the cardiopulmonary bypass itself. The use of extra-corporeal circulation can cause a systemic inflammatory response, which can lead to organ injury and postoperative morbidity.[4] Implicated factors include surgical trauma, contact of blood with the extracorporeal circuit, and lung reperfusion injury on discontinuing bypass.[4] Owing to these complications and the invasiveness of the procedure, the rationale for developing new methods of revascularizing the heart is apparent.

Currently, two therapeutic options are available for patients with inadequate coronary circulation. Cardiac revascularization is accomplished by CABG or percutaneous transluminal coronary angioplasty (PTCA). Randomized trials comparing the two treatment options in cases of multivessel disease have shown that the procedures have similar mortality rates and occurrence of composite end points (death, Q wave myocardial infarction, or large ischemic defect on thallium scanning).[5] However, PTCA-treated cases are substantially more likely to require repeat revascularization. According to the EAST investigation, which involved 392 participants, after three years 13% of patients who received CABG as their method of treatment required repeat revascularization and over 50% of PTCA patients required repeat revascularization.[5] The surgery group also showed a greater degree of perfusion and fewer angina symptoms.[5]

Similar studies in Germany (GABI trials) involving 359 participants found that 44% of PTCA patients required further intervention within one year, while only 6% of CABG patients required a follow-up procedure.[6] However, median hospitalization time for the PTCA group was only five days in comparison with 19 days for the CABG group.[6] Additionally, new advances in PTCA, including the increasing use of stents, may substantially enhance the long-term patency of this form of revascularization.

Reviewing the common current therapies, there appears to be the opportunity to develop a procedure which is less invasive than traditional CABG and more definitive than PTCA. Minimally invasive bypass techniques through a left thoracotomy may eventually service this need, providing a definitive surgical solution with diminished post-operative morbidity and hospital cost.

SURGICAL PROCEDURE

As a developing surgical technique, there is considerable variation in how the MIDCAB procedure is performed. The original MIDCAB procedures were single LIMA to LAD anastomoses, although more recent advances in technology and technique have allowed multiple bypasses using both left and right internal mammary arteries as well as inferior epigastric and gastroepiploic arteries. Typically, standard cardiac anesthesia is applied and the patient is intubated with a double-lumen endotracheal tube, which can deflate the left lung, facilitating thoracoscopic dissection of the LIMA.[7,8] Transesophogeal echocardiography may be employed to follow ventricular wall motion.[8]

The LIMA is revealed through a left anterior thoracotomy with the patient in the 30-degree left lateral decubitus position, often with left arm raised over head.[8,9] It can also be harvested using a thoracoscope placed either through a trocar in the fourth intercostal space at the posterior axillary line or through the thoracotomy itself.[7] The pedicle of the LIMA is dissected and mobilized towards its origin and distally to approximately the sixth costal cartilage.[9] The patient is heparinized and the dissected pedicle is injected with papaverine, a smooth muscle relaxant, preventing arterial spasm.

ABOUT THE AUTHOR

Nimesh Desai is a first-year medical student at UWO.

Pericardial incision is made and control of the LAD on the beating heart is established using snare sutures proximally and distally to the site of anastomosis. Since performing the anastomosis may require up to 20 minutes of coronary-vessel occlusion, monitoring ventricular wall motion is critical to ensuring that hemodynamic stability is maintained.[10] In vessels which are less than 75% occluded, significant segmental wall motion disturbance has been noted when occlusion times are in excess of twenty minutes.[10] Ischemic preconditioning by repeatedly occluding and releasing the vessel or using drugs such as adenosine has been proposed as a method of diminishing hypocontractility while the anastomosis is being performed.[8]

If necessary, the heart is slowed, and the anastomosis is performed under direct vision using traditional suturing techniques with a blower device to keep the operative field clear.[9]

CLINICAL DATA

Although this technique has only recently gained interest in North America, in nations with limited access to CPB equipment it has been used on hundreds of patients and clinical information is available. In Brazil, Buffolo et al. have performed over 1200 bypass surgeries without CPB and completed several studies comparing their outcomes to those of traditional CABG with CPB. In one study, they found that patients with CPB had a statistically significant ($p<0.05$) increased risk of arrhythmias, pulmonary, and neurological complications than those who did not go on CPB.[11] Average hospital stays were 5.2 days for those operated without CPB and 9.6 days for those operated with CPB. Total hospital costs were about US $3300 less per case when CPB was not used, with most savings coming from the use of less disposable equipment in the operating room.[11]

In Italy, Calafiore found that in a study of 378 patients undergoing MIDCAB, 24-month survival was 97.9%, which compares favourably with the traditional CABG 24-month survival rate of 94% as determined in the EAST trails.[5,12] In the US, Landreneau et al. performed MIDCAB on 46 patients and reported patent anastomoses in all cases as verified using ultrasound Doppler flow assessment.[13] Their study reported a median hospital stay of 4.3 days.[13] Similar hospital stays were reported by Benetti et al. in studies in Argentina, Italy, and the Netherlands.[9,14] In Germany, Reichenspurner et al. performed 12 MIDCAB operations and reported a mean hospital stay of 8.0 days.[15] By comparison, the GABI study, also from Germany, reported a mean hospital stay of 19 days for traditional CABG.[6]

Unfortunately, much of the information available about MIDCAB is not based on trials in which patients are randomly assigned to traditional CABG and MIDCAB groups and the outcomes of the two groups are followed over a long period.[16] There are few North American data, and virtually none from Canada about this procedure to date. A joint committee of the Society of Thoracic Surgeons and the American Association of Thoracic Surgeons has recently started critically evaluating the use of this procedure.[16]

CONCLUSION

The initial studies regarding MIDCAB appear to be very encouraging. The promise of shorter hospital stays, decreased morbidity with no CPB-related complications, and lower hospital costs with definitive surgical results is very enticing. With continued refinement of surgical technique and technological innovation, MIDCAB is providing a viable, minimally invasive, definitive intervention to revascularize cardiac tissue. It will provide the patient with a new therapeutic option in addition to PTCA and traditional CABG, which have both improved the lives of millions of patients around the world. With the development of methods to perform two and three grafts using the MIDCAB approach and the promising results of new stent techniques with PTCA, significant longitudinal studies will be necessary to determine the exact niche of each therapeutic modality in an era of declining health care resources and an aging population.

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Ω

Obstetrical Ultrasound: Past, Present and Future

by Jamie Mangin

Since the introduction of ultrasound to the field of obstetrics in the early 1960s, its number of uses and its ability to image the fetus have dramatically increased.[1] Advances in ultrasound technology have permitted imaging of the fetus in both static and dynamic states, opening the door to earlier determination of fetal age, early detection of multiple pregnancies, diagnosis of fetal anomalies and evaluation of fetal well-being.

WHAT IS ULTRASOUND?

Diagnostic Ultrasonography uses sound waves in the ultrasound frequency range to create images. Ultrasound is any sound wave with a higher frequency than is audible to the human ear. The range of frequencies that can be heard by humans is approximately 20 to 20,000 Hz. Ultrasound images are created by transmitting a sound wave from an emitter through a medium: air, fluid or solid. These waves travel faster through denser objects. When a sound wave crosses an interface between objects of different densities, some of the wave is reflected back and some is transmitted through. The receiver positioned next to the emitter picks up the reflected wave. A processor then calculates the distance to this object from the emitter by measuring the time it took for the reflected wave to return. This method, known as the A-mode, is the basis for SONAR detection of submarines. It was used on the first diagnostic ultrasound machines.[2]

Types of Ultrasound Scanners

In the early to mid-1970s, B-mode grey-scale static imaging became the dominant scanning mode in diagnostic ultrasound. B-mode measures the distance the object interface is from the emitter, and draws a corresponding coloured dot on a display screen representing that spot. The intensity of colour of the dot corresponds to how much of the wave was reflected back. The portion of the wave which is transmitted through the interface continues till it hits another interface and is partially reflected back, and so on till the wave dissipates. It is for this reason that pelvic ultrasound examinations are performed with a full bladder. The fluid in the bladder transmits the wave with fewer reflections, allowing it to penetrate the deep pelvic structures. These numerous reflections along a single line of sight form a picture of the object along a single axis. To form an image of a plane within the subject, many waves are sent out from the emitter along different lines of sight over a 10 to 20-second period and are saved in the scanner's memory. The computer combines the results to form a 2-D picture of the object on the screen. The more lines of sight that are emitted, the greater the resolution of the picture. Most scanners use between 50 and 200 lines. Loss of resolution can occur if the object moves while being scanned since the information from the individual lines of sight are acquired at different times.[3]

Advances in ultrasound continued with the development of real-time scanners. These scanners use a modification of B-mode. They make a 2-D picture as described above, then rapidly scan over the same area again to make a second picture and so on. These sequential pictures are like the frames of a film, allowing the observer to visualize movement of the object. The more rapid the movement of the object, the quicker the scanner has to take pictures — i.e. the higher must be the frame rate — to keep the motion from appearing jerky on the screen. Scanners are currently available with frame rates from 5 to 40 images per second. Most institutions use real-time scanners for all of their obstetrical imaging. Some advantages of real-time scanning are that it it shows fetal movement, it allows rapid changes in the scan plane, and it reduces total examination time because the operator gets instant feedback about anatomical structures in the field of view.[3]

A recent development is the Duplex scanner, a combination of real-time ultrasound with Doppler ultrasound. Using the Doppler phenomenon, the scanner can determine if an object is moving away from or towards the emitter. Sound waves can be bounced off red blood cells to determine the direction of blood flow in vessels. When colour is added, it helps delineate vessels in the placenta, umbilical cord, and fetus[4]. The hand-held ultrasound stethoscope used by obstetricians for detecting fetal heart sounds uses the Doppler principle to detect heart-wall motion.

How Safe is it?

One of the reasons ultrasound was so quickly adopted into the field of obstetrics and gained such wide use so quickly was its use of sound waves instead of ionizing radiation. At present, there are no confirmed biological effects on fetuses from the use of diagnostic ultrasound.[5] Randomized clinical trials have been performed which showed no difference in developmental, neurological, or psychological outcomes, with as much as 12 years follow-up.[6] Theoretical safety risks from ultrasound energy include viscous stress, thermal damage and cavitation effects. High levels of ultrasound intensity can cause agitation of molecules leading to increases in temperature. Ultrasound-induced cavitation in tissues can result in disruption of molecular

ABOUT THE AUTHOR

Jamie Mangin is a third-year medical student at UWO with a strong interest in diagnostic radiology. He received his BSc in Mechanical Engineering from General Motors Institute in Flint, Michigan.

bonds and free-radical production. Viscous stresses can occur at tissue boundaries leading to disruption of membranes at the interface.[2] The Bioeffects Committee of the American Institute of Ultrasound in Medicine released a statement on current research and concluded that with the judicious use of ultrasound, the benefits outweigh any potential risks.[7]

CURRENT USES IN PREGNANCY

The number of clinical situations in which ultrasound examination is recommended has grown rapidly with the advances in resolution. It's low-risk, non-invasive properties also make it an attractive choice for evaluation of the fetus. The National Institute of Health Consensus Development Conference reviewed the available literature on obstetric ultrasonography in 1984 and produced a list of clinical situations in which ultrasound might be beneficial.[8] They are shown in Table 1[9]. At that time they did not endorse routine ultrasound screening in the US because of a lack of evidence that it benefited the low-risk fetus. Other countries such as Germany, England, Norway and Canada endorse routine screening. In Germany, two routine ultrasound examinations are performed at 18 and 30 weeks of gestation. These are integrated into the maternity-care regulations and are covered by sickness funds. No prospective, randomized study on the effectiveness of this policy has ever been conducted.[10] The Canadian Task Force on Periodic Health Examination reviewed the current literature on prenatal ultrasound screening in 1992 and concluded that there was fair evidence to support the inclusion of a single routine ultrasound examination, usually between 16 and 20 weeks gestational age, in the management of women with no clinical indication for prenatal ultrasonography. They also concluded that there was poor evidence to support routine serial ultrasound screening in women with no clinical indications.[11]

This article will address in further detail the use of ultrasound examination for estimation of gestational age and weight, and for detection of multiple pregnancies and malformations.

Estimation of Fetal Age and Weight

The accurate estimate of fetal age allows the obstetrician to determine the approximate date of spontaneous delivery or plan for the elective delivery of the baby at term (37 to 42 weeks). Accurate dates allow the obstetrician to implement the necessary measures for both preterm deliveries (i.e. RDS prophylaxis) and post-term deliveries (i.e. induction). Comparison of the ultrasound-determined age with the age calculated from the last normal menstrual period allows the obstetrician to evaluate the rate of fetal growth. Ultrasound estimates of fetal age are given in the number of menstrual weeks, thus allowing for quick comparison.

Gestational age can be estimated during the first trimester using crown-rump length or gestational sac size. Crown-rump length is the preferred method and when performed between 7 and 12 weeks is accurate within plus or minus 5 days.[12] The high degree of accuracy at this stage in the pregnancy is thought to be due to the small amount of biological variability in fetal size during the early stages of development, and to the rapid rate of growth. Later on in the pregnancy, genetic and environmental factors play a larger role in fetal size.

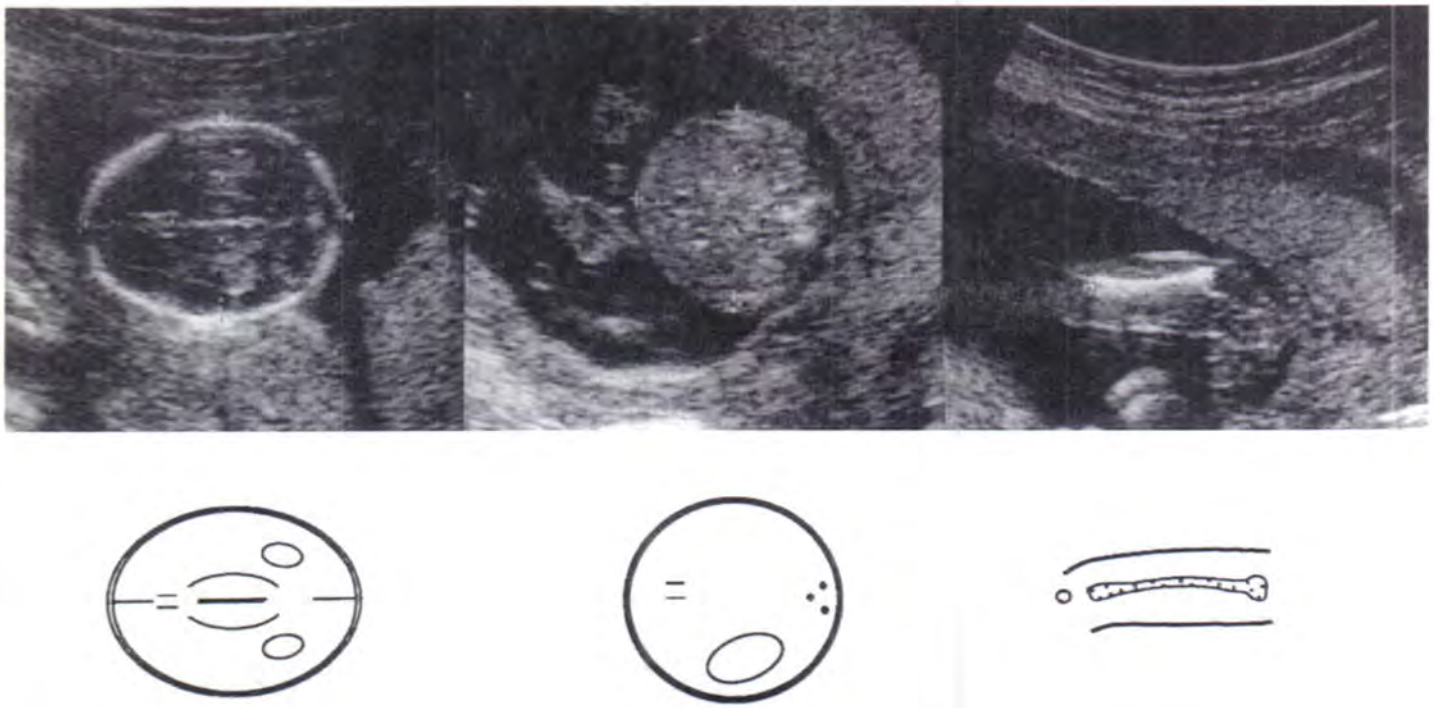

Figure 1. High-resolution, real-time ultrasound images of fetal head on left, the abdomen in middle, and femur on right in a 16-week fetus. Suitable images for age estimation.

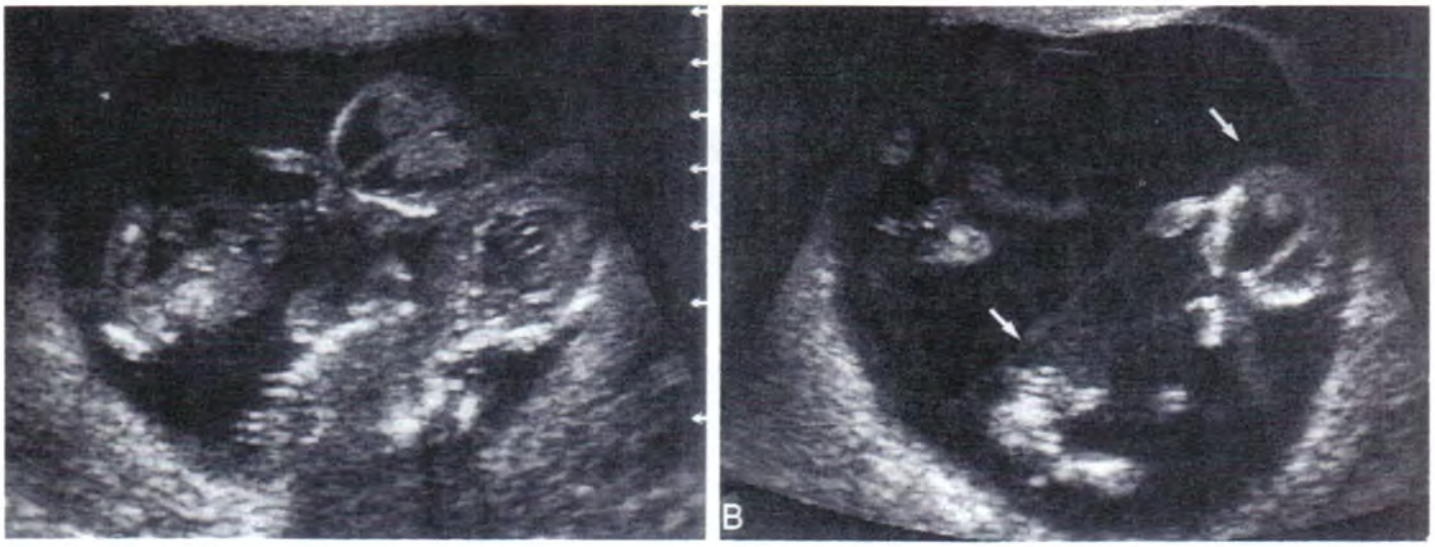

Figure 2. *A. Transvaginal ultrasound image of monochorionic, diamniotic twins in a 12-week pregnancy. B. Arrows indicate diamniotic membrane.*

Determination of age during the second and third trimesters is calculated using a variety of fetal measurements. The four primary measurements used are biparietal diameter, head circumference, abdominal circumference and femur length as shown in Figure 1. Real-time scanning has increased the ease and accuracy of taking these measurements. These measurements are plotted on tables corresponding to menstrual age estimates and an average of the four is calculated. This average can be determined by simply dividing by four, or can be calculated using linear regression equations to increase the accuracy of the estimate. With the use of linear regression equations, the accuracy of the age estimate in one study was quoted as estimated age plus or minus 7% at any time during the pregnancy.[12] For example, a 30-week age estimate would have an accuracy of plus or minus 2.1 weeks.

Fetal weight estimates are calculated in the same manner using combinations of the fetal measurements described above. Fetal weight estimates are quoted from various studies in the range of plus or minus 12 to 25%.[12] In the future, advances in 3-D ultrasonography may allow accurate calculation of fetal volume, thus improving fetal weight estimation.

Multiple Pregnancies

Multiple gestations are at increased risk of perinatal morbidity and mortality from a variety of causes. Early diagnosis of multiple gestations allows close monitoring of the pregnancy and early decision-making regarding

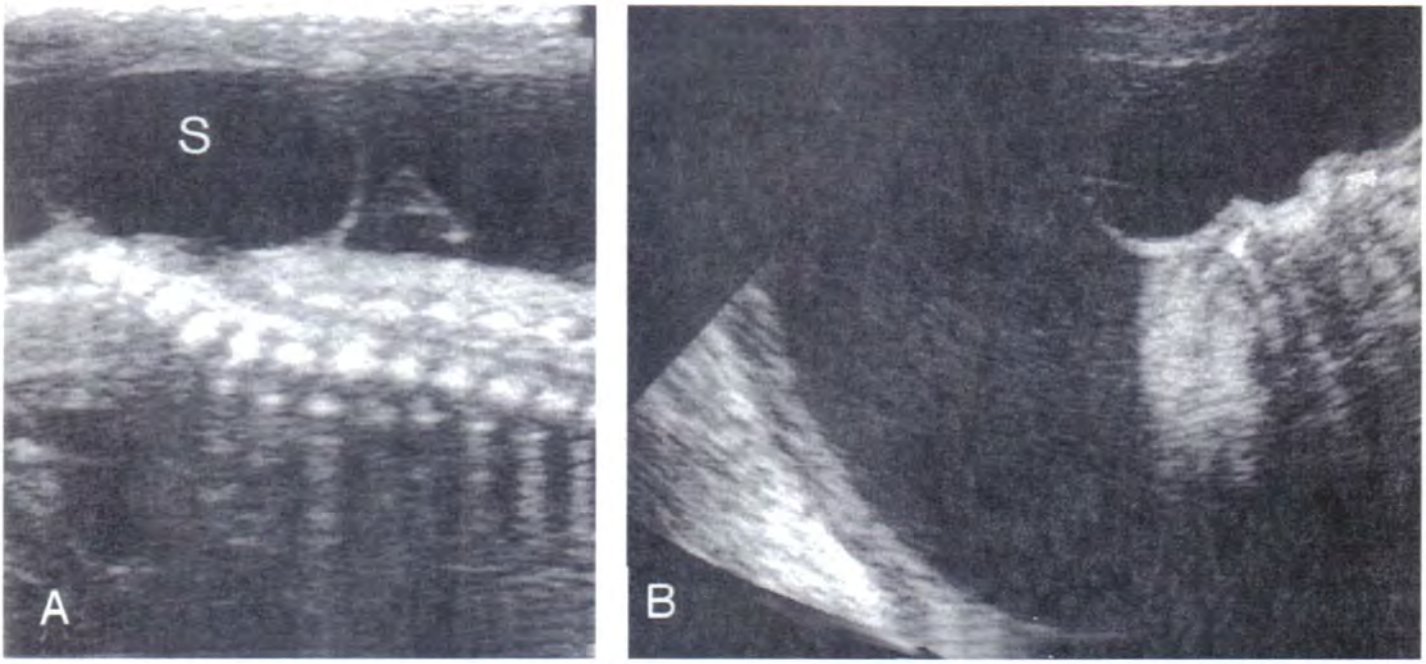

Figure 3. *A. Parasagital ultrasound image of the spine showing a myelomeningocele sac (S) beginning at L5. B. Transverse image shows splayed posterior elements (arrows).*

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management and delivery. Thirty per cent of all unscanned twin pregnancies are clinically missed until birth.[13] An ultrasound scan should be performed between 16 and 18 weeks for size, fetal number, placentation, visualization of the membranes, amniotic-fluid volume and congenital anomalies. Determination of the type of placentation provides prognostic information for the obstetrician as morbidity and mortality rates vary with chorionicity and amnionicity. For example, the mortality rate for monochorionic, monoamniotic twins is 50% compared with 9% for dichorionic, diamniotic twins.[14] A first-trimester ultrasound of monochorionic, diamniotic twins is shown in Figure 2. Serial ultrasound during the pregnancy can monitor growth and screen for anomalies as there is a higher incidence of anomalies and intrauterine growth restriction in multiple gestations.[13] A third-trimester ultrasound can give information on the position of the fetuses and placentae thus aiding in the decision of vaginal versus caesarean delivery.

Congenital Anomalies

With ultrasound, many congenital anomalies can now be diagnosed early in pregnancy. In high-risk populations, the accuracy of diagnosis is over 90%.[9] However, the accuracy is still highly dependent on the type of congenital malformation, the quality of the equipment and the expertise of the sonographer. CNS anomalies are some of the more common anomalies picked up on ultrasound between 16 and 20 weeks. A cross-sectional view through the ventricles can pick up hydrocephalus, which is often the presenting sign of subarachnoid haemorrhages, Dandy-Walker syndrome, spina bifida occulta and aqueductal stenosis. Views of the hemispheres and cerebellum can detect anencephaly and cerebellar agenesis. Spinal anomalies such as spina bifida occulta with associated meningocele or myelomeningocele can be detected by longitudinal and cross-sectional views of the spine. Figure 3 shows an image of a myelomeningocele. Gastrointestinal anomalies commonly detected in the second trimester include omphalocele and gastroschisis. Duodenal atresia can be diagnosed by the characteristic image of an overdistended stomach and enlarged duodenum. This is known as the double-bubble sign. Fetal kidneys can be seen by ultrasound routinely at 18 weeks, thus allowing detection of major abnormalities such as agenesis. [13] Congenital heart disease is one of the most common congenital malformations. A cross-sectional, four-chamber view of the heart after 16 weeks of age has the potential to pick up 50 to 60% of congenital heart malformations. However, it has been shown that only 10% of congenital heart disease is diagnosed prenatally.[9]

Table 1. Indications for Ultrasound Examination*

1. Estimation of Gestational Age: uncertain or verification of dates for caesarian, induction or termination of pregnancy
2. Evaluation of Fetal Growth: uteroplacental insufficiency suspected or pregnancy complication
3. Estimation of Fetal Weight: PROM, premature labour
4. Determine Fetal Presentation: uncertain presenting part
5. Suspected Multiple Gestation: multiple fetal heart beats, increased SF height, fertility drugs
6. Serial Evaluation of Multiple Gestation
7. Discrepancy in size compared to dates
8. Pelvic Mass on clinical exam
9. Suspected Hydatidiform Mole: high BHCG
10. Ovarian Cysts on pelvic exam
11. Suspected Ectopic or screen in high-risk
12. Localize Placenta after prior previa identification
13. Vaginal Bleeding not yet diagnosed
14. Suspected Fetal Death
15. Suspected Uterine Abnormality
16. Localize IUD
17. Monitor ovarian follicle development
18. Biophysical Profile: fetal well-being after 28 weeks, limited prenatal care
19. Assist Delivery: 2nd twin, placenta removal
20. Suspected Polyhydraminos/Oligohydramnios
21. Suspected Abruptio Placentae
22. Follow-up of Congenital Anomaly
23. Previous Congenital Anomaly
24. Abnormal AFP level for age
25. Adjunct to In Utero procedures: fetoscopy, shunt placement, chorionic villous sampling
26. Adjunct to External Version
27. Adjunct to amniocentesis

* adapted from Garmel SH, D=Alton ME. Diagnostic ultrasound in pregnancy: an overview. Seminol Perinatol 1994;18(3):117-32.

FUTURE DEVELOPMENTS

Real-Time Scanning

The resolution and frame speed of real-time scanning continue to increase. This development permits access to the fetus. Procedures such as amniocentesis, chorionic villous sampling and fetal blood sampling have been made possible and safer by ultrasound. Developments in the area of in utero surgery such as fetoscopy are guided by high resolution, real-time ultrasound.[15]

Scanning Techniques

During the last 10 years, ever-smaller probes have led to new techniques such as transvaginal ultrasonography. This technique has improved resolution by allowing the sound waves to be sent directly into the deep pelvic region, thus avoiding transmission through the bladder as in the case of abdominal ultrasound. The addition of Doppler and 3-D ultrasound to these small probes is becoming possible as the miniaturization of electronics continues.[3]

Contrast Agents

The purpose of these agents is to increase image quality by changing the acoustic properties of tissues in which they reside. Agents are being developed which displace air from the path of the sound waves thus allowing deeper penetration and less reflection. Another group of agents is used to increase the echogenic property of the organ being visualized by introducing encapsulated, air-filled microspheres.

3-D Ultrasound

One problem with 2-D ultrasound is the small field of view and the inability to see neighbouring anatomy. Interpretation of the anatomy is accomplished clinically by making many slices. This is made easier and quicker with real-time ultrasound. Sometimes a view through the third axis, the z-axis, is not possible with 2-D ultrasound because of other anatomy blocking the line of sight. 3-D ultrasound is being developed to provide the missing z-axis, thus eliminating the need for many slices to be made by the operator. Currently 3-D ultrasound is in its infancy. It is following much the same course of development as 2-D ultrasound did over the last 20 years, but at a faster rate. At this time in its development, only static views are available. The complex emitter/transducer is quite bulky, and reconstruction of the 3-D view is very time-consuming. A clinical trial performed on an experimental 3-D scanner found that the third axis helped pick out some features not seen in the other 2-D views.[16] Another promising feature is its ability to estimate volume. This can be applied to improving the accuracy of fetal weight and age estimation. With the development of high-speed computers and the miniaturization of complex electronics, 3-D real-time ultrasound may be a reality in the near future.

CONCLUSION

Advances in technology have made ultrasound one of the fastest growing and most exciting areas of diagnostic imaging. Ultrasound has become commonplace in obstetrical practice as a tool for diagnosis and for evaluation of fetal well-being. It continues to establish itself in medical practice as a safe, non-invasive method of imaging. If the past 20 years are any indication, ultrasound imaging will continue to improve and expand in use well into the future.

Acknowledgements: The author would like to thank Dr William Dawson, MD, FRCP(C), Program Director, Department of Diagnostic Radiology, UWO, for his valuable suggestions regarding the preparation of this manuscript.

All figures are from Ultrasonography in Obstetrics and Gynecology, 3rd ed., edited by PW Callen, WB Saunders Co., Philadelphia, USA (1994) with permission from the publisher.

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Ω

Peripheral Nerve Transplantation

by Dariusz Brzozowski

BACKGROUND

Peripheral nerve injuries are a common entity associated with musculoskeletal trauma. Simple axon transection may be repaired by suturing the opposing epineurium or corresponding fascicles of the two opposing neural stumps.[1] This allows sprouting axons to enter the distal nerve stump and regenerate through it to contact and reinnervate peripheral end organs. Such axon regeneration follows the process of Wallerian degeneration which serves to clear the distal stump of axoplasm and myelin in preparation for subsequent axon regeneration.[2] However, in the situation where large gaps exist between the cut axonal ends, they cannot be opposed primarily without tension. In these cases there is the necessity for nerve grafting.[1]

These deficits present a reconstructive challenge for the surgeon. Currently, nerve grafting involves using a sensory autograft acquired from the patient. This clearly is associated with donor-site morbidity such as a loss of sensation, scarring and neuroma pain over the harvested area.[3] A commonly used source is the cutaneous sural nerve, which is located in the posterior aspect of the lower leg.[1] Another consideration is the possibility of inadequate expendable autogenous nerve grafts to allow for optimal reconstruction.[4]

Peripheral nerve allografts present a favourable alternative to autografts. Not only are donor-site complications eliminated, but there is a limitless supply of graft material. Nevertheless, there is a rejection response elicited by the allograft tissue. Consequently, immunosuppression with its associated complications is a necessity when this reconstructive avenue is utilized.[5,6]

The nerve allograft serves only as a temporary scaffold for regenerating host axons. Host Schwann cells eventually replace allograft Schwann cells.[7] Therefore, it is possible to discontinue immunosuppression after the sprouting axons have transversed the allograft.[8,9] Using these principles, the first peripheral nerve allograft was performed by Dr. SE Mackinnon in 1988.[4]

CASE REPORT

An 8-year-old boy sustained several injuries to both legs by a motor boat propeller on May 29, 1988.[4] Among these injuries, he had an extensive left sciatic nerve injury, a 23-cm gap which extended from the proximal gluteal region to the region of the popliteal fossa. Peripheral nerve transplantation was considered as an alternative to limb amputation.

On September 24, 1988, a suitable donor, with respect to blood type and antigen profile, was located in London, Ontario. Ten nerve grafts from both upper and lower limbs of the donor were prepared and microsurgically used for the patient's sciatic nerve reconstruction. Immunosuppression was achieved using 100 mg of oral cyclosporin A twice daily, and 10 mg of oral prednisone once daily. This regimen was begun the evening of surgery and continued until there was evidence of sensation in the peroneal and posterior tibial nerve distribution 26 months after surgery.

Presently, the patient walks unassisted and is free of pain. Although his sensations are quantitatively diminished, he is able to perceive painful stimuli, light touch and vibration in his left foot. He has no evidence of motor recovery.

DISCUSSION AND SUMMARY

The rate of peripheral nerve regeneration witnessed in this case was the same as would be anticipated using autogenous graft material. Nerve regeneration is limited to approximately 1 mm per day.[10] Given the large distance between the most proximal nerve injury and the muscle target in this case report, the lack of motor

ABOUT THE AUTHOR

Dariusz Brzozowski is a fourth-year medical student at UWO with an interest in plastic and reconstructive surgery.

recovery could be anticipated. It is known that muscle must be reinnervated within 18 to 24 months for functional recovery to be possible.[11] In contrast, sensory receptors can be reinnervated even years after a nerve injury to provide reasonable sensation.[12]

With the advent of the first successful peripheral nerve transplantation, the capacity of reconstructive surgery has escalated. As outlined in the case above, this development offers an alternative to limb amputation and can repair at least some of the morbidity associated with peripheral nerve loss. It is in extensive injuries where the sources of expendable donor nerves required for allografting are insufficient for reconstruction that peripheral nerve transplantation is most useful.

Future developments will focus on attempts to reduce graft immunogenicity. Recent investigations have involved graft pretreatment[13] and manipulation of the host's immune system.[14]

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Ω

Virtual Reality and Medicine

by Erik Viirre

For the past two years I have had the great opportunity to work at the Human Interface Technology Laboratory (HIT Lab) at the University of Washington. This facility is unlike any other in the world, as we work on development of fundamental technologies and applications for Virtual Reality (VR) .

WHAT IS VIRTUAL REALITY?

VR is based on active interaction with a computer graphics environment. Many things in our society of the late 1990s are described as "virtual", but few are true VR. In a VR system, a head-mounted display (HMD) presents an image to each eye that is created by a computer graphics engine. The image is of a scene, or "virtual environment", a place that is completely generated by the computer. The key to VR is interactivity with this environment. As the user moves his head and body, sensors detect the changes in position. The computer is fed the new coordinates and the image sent to the HMD is updated to correspond to the new point of view. Other sensors may detect hand gestures or other signals that allow the user to send control commands to the computer. Such commands might include picking up an object or triggering a scene change. If the scene rendered by the computer is compelling enough and the interactivity is fast enough, the user will experience a sense of "presence" or "immersion", which is usually described as the feeling of being in another place. Photorealism of the scene is not essential as even scenes with simple or unusual features can induce presence. This very important quality has prompted such eminent researchers as Dr. Lawrence Stark of Berkeley to identify VR as a key technology of the future. Good virtual environments exist even now, and transfer of the technology to the medical realm is under way.

VR is not limited to visual displays and detection of movement of body parts. 3-D audio environments greatly enhance the sensation of presence and can provide cues to many items out of the immediate field of view of the display. Tactile or "haptic" feedback is becoming more and more compelling. As one picks up, or cuts or touches an object in VR through mechanical implements, motorized feedback through the instrument gives one the sensation of a solid object with weight, or even elastic tissue qualities.

Important technologies related to VR are Augmented Reality (AR) and Telepresence. In augmented reality, the computer graphics images are superimposed onto the real world. This allows such things as data values or graphics showing internal features to be presented on top of objects in the real world. Telepresence is a means of actively interacting with a remote location. Instead of movements of the user being used to drive computer graphics, cameras in the remote location are driven interactively. Thus, turning one's head left or right changes the view from the cameras.

HOW CAN VR BE USED IN MEDICINE?

The sense of presence and the views of information are the features of VR that make it potentially useful in medicine. Furthermore, the user of VR is well instrumented: we can monitor what they are seeing as well as what movements they make.

3-D data sets from imaging modalities already exist in medicine. Instead of viewing slices or 2 1/2-dimensional images on a screen, anatomical objects can be seen in 3-D and the viewer can make natural movements to change the field of view. Relations between surface features and deep objects are readily seen with this type of view. Active research is under way to see if interventional radiology techniques or planning of multiple angles of radiation exposure for cancer can be done more effectively in VR.

Training and simulation are most actively being researched as applications of VR. The VR system can display anatomic relations that cannot be seen in the operating room. This allows a surgeon to safely practice techniques and fully understand the anatomic relations in the site. For example, a simulator of sinus surgery allows the practicing of techniques close to delicate anatomic structures such as the optic nerve. The recent trend in surgery is toward "minimally invasive procedures", where surgery is carried out through instruments while the scene is visualized via a TV camera. Minimally invasive surgery is immediately transferable to simulation through VR technologies. Larger scale scenes can also be simulated in VR. These include an emergency room, where compelling situations that are altered by the user's actions can be created. Handling of trauma, cardiac arrest or anaesthesia protocols may be carried out in VR in the future, where the student will have an impressive level of involvement through "presence".

An interesting use of a virtual environment has been developed by a team at the HIT Lab. The Laboratory for Integrated Medical Interface Technology (LIMIT) was designed to research medical information display. VR was originally developed by the HIT Lab director Dr Thomas A. Furness III to integrate widely dispersed visual information for pilots. Instruments in the cockpit have become so numerous and varied in type that the pilot may be overwhelmed in critical situations, such as landing in bad weather. By integrating the information

ABOUT THE AUTHOR

Erik Viirre received his MD and PhD from UWO in 1988. He is now a Research Scientist at the Human Interface Technology Laboratory, University of Washington, Seattle, Washington.

into a virtual world, aircraft systems, traffic, weather and other necessary information can be presented in a useful, easily recognized manner.

Like a pilot, a modern physician in a critical situation, such as emergency triage, is faced with widely disparate forms and types of information. The LIMIT lab is designed to display information as it might be seen by the physician of the near future. Should radiology images be presented "attached" to the patient's body? Should critical vital signs or alarms be fixed in the physician's field of view (as though they were attached to his head)? These questions and more can be addressed in the virtual environment testbed.

Abstract information such as epidemiological data might be effectively displayed in VR rather than a series of 2-D images. Even 3-D Internet browsers are now being tested where the third dimension is used to represent various relations between data.

VR AS THERAPY

The special characteristics of VR make it potentially useful for certain forms of therapy. The feeling of presence evoked by a virtual environment makes it a promising tool for behaviour-modification therapy. Current modes of therapy for fear of heights, flying, open spaces, spiders etc. involve visualization techniques. The patient is asked to mentally visualize their phobic stimulus. Successive visualization sessions are used to attempt to prepare the patient for an encounter with the real thing. Many centres are now researching the use of a virtual environment instead of mental visualization. Fear of flying is of particular interest because many people are affected and they have a strong desire to travel. Further, the cost of renting a plane to gradually get used to the idea is prohibitive. In contrast, in a virtual environment, the patient's "sticking point" can be approached repeatedly, be it walking up the gate to the plane, or taking off or landing. Ongoing clinical studies will demonstrate efficacy of this method.

VR can also be effectively used to demonstrate neurological defects to patients and others. Rita Addison is a traumatic brain injury survivor. With the help of the Supercomputing Center at University of Illinois, she was able to have a virtual environment created that demonstrates her neurological problems with vision. She has scotomas and intermittent visual blurring as the result of her injury. Her VR experience demonstrates what a scotoma is functionally like and how her condition compares to normal vision. This technique may be extended to other conditions to help patients describe symptoms and help the rest of us understand their problems.

My own research using VR as therapy concerns defects in motion detection from damage to the vestibular apparatus. Patients with long term inner ear damage from Meniere's Disease, infection, surgery or adverse drug reactions are left with defects in detecting motion of the head. This leads to instability of vision and gait. My project is investigating methods of improving residual vestibular function through the use of a custom designed virtual environment. The visual motion of the scene relative to the patient's actual motion will be designed to attempt to drive the vestibular function back toward normal, farther and more rapidly than normal adaptive processes would go.

AUGMENTED REALITY

The superimposition of graphic images onto the real world view of the patient's body may be very useful in a variety of applications such as interventional radiology. If the physician can "see" internal structures that are matched to the appropriate position on the surface of the patient's body then navigation and intervention may be easier. Particularly in fields such as neurosurgery, the navigation information must be precise. Having an integrated view might be more efficacious than switching views from radiology screens back to the surgical field.

CONCLUSION

VR is an emerging technology. Many hurdles have to be crossed before it can effectively be used in real world applications. Yet, the number of situations where 3-D information (real, reconstructed or abstract) appears in medicine is very large. Simple, unobtrusive VR technology may be part of your future training, surgery or information display. Ω

UWO Faculty of Medicine Preclerkship Curriculum Renewal: Paving the Way to the Twenty-First Century

by Alexander L Lee

The Faculty of Medicine at the University of Western Ontario graduated its first class of medical students in 1883. Since then, Western has had a tradition of excellence in medical education; Western graduates have earned a reputation that ranks with the best in the country, and the world.

Throughout the history of the medical school, countless improvements and revisions have been made to the undergraduate medical curriculum, but none as ambitious as the current curriculum renewal process.

The process began in April 1996 with the formation of fourteen Subject Development Groups, the Curriculum Coordinating Team, and four Resource Task Teams. Dr John Howard, Director of Curriculum and Evaluation, is heading the renewal process, and the new MD curriculum will be implemented in September 1997 for the Class of 2001. In all, the process currently involves more than 200 individuals, with representation from the basic and clinical science departments, the medical student body, and the communities of London and Southwestern Ontario.

The Subject Development Groups were formed to evaluate the material currently taught, in an effort to coordinate and integrate basic and clinical sciences within fourteen general subject areas. The Subject Development Groups are Introduction to Medicine; the Life Cycle; Reproduction and Embryology; Blood; Endocrine and Metabolism; Immunology and the Skin; Heart and Circulation; Respiration and Airways; Genitourinary System; Nutrition and the Digestive System; Musculoskeletal; Neurosciences, Eye, and Ear; Psychiatry and the Behavioural Sciences; and Health, Illness, and Society.

The mandate of the Curriculum Coordinating Team is to facilitate the activities of the Subject Development Groups, and to make recommendations on curriculum reform. The four Resource Task Teams were created to provide faculty support in teaching methods, research in education, and faculty and student evaluation. The four Resource Task Teams are Teaching Methods, Educational Research, Evaluation, and Curriculum Resources. Other Task Teams formed include Patient Centred Learning, Oncology, Nutrition, Career Choice, Rural Medicine, and Geriatrics.

The goals of curriculum change are to integrate subject matter between courses and to create a curriculum that is responsive to both student and community needs. The new undergraduate medical curriculum will be "student-centred in its delivery, and patient-centred in its content."

Prior to renewal, the MD curriculum included courses such as anatomy, biochemistry, histology, etc. Each course had been revised and balanced for many years, but each course operated independently of the others, with minimal coordination. The curriculum renewal process will foster integration between basic sciences, between clinical sciences, and between basic and clinical sciences. It is clear that the underlying theme is "integration."

The "patient-centred" curriculum acknowledges that medicine is both a science and an art, reflecting a commitment to individual patients, their families, and the community. Patient-Centred Medicine is a concept that was first developed by the Department of Family Medicine at Western. The six interactive components of the patient-centred process are: exploring the disease and the illness experience, understanding the whole person, finding common ground regarding management, incorporating prevention and health promotion, enhancing the patient-physician relationship, and being realistic in managing time and resources.[1] Physicians must understand the patient's condition from the patient's own unique perspective, and must understand that no two patients are alike. The four dimensions of illness (feelings, ideas, function, and expectations) should also be explored. These principles will be emphasized throughout the undergraduate medical education from the first day, right on through to graduation. Early patient contact and a variety of community experiences will complement these goals.

Medical students have played a significant role throughout the curriculum renewal process, contributing on the Curriculum Coordinating Team, Subject Development Groups, and Resource Task Teams. Student opinions were gathered, and presented at the October 23, 1996 Curriculum Renewal Half-Day by Andy Thompson (Meds '98) and I. Student-centred needs were identified, and included integration within and between basic and clinical sciences, active learning, an approach to symptoms, and techniques of critical appraisal and evidence-based medicine. Students were unanimous in their desire for a unique, innovative, and dynamic

ABOUT THE AUTHOR

Alexander Lee is a second-year medical student at UWO. He received his BSc and MSc from McMaster University. He is currently the Hippocratic Council VP Academic Jr, and a member of the Curriculum Coordinating Team, and the Heart and Circulation Subject Development Group.

curriculum that represented the needs and values of the student body, the Faculty of Medicine, and the community.[2] These issues have subsequently been adopted into the guiding principles and aims of the renewal process.

Learning will be more active, with emphasis on small-group tutorials and problem-oriented learning. Case scenarios will be used extensively to allow students the opportunity to develop clinical approaches to patient presentations and to address disease and illness issues. Other teaching methods that will be used include self-instructional materials, laboratories, large-group discussions, and lectures.

The new preclerkship curriculum will be divided into two halves. Basic sciences and clinical sciences will be integrated, with emphasis on basic sciences in the first half, and emphasis on clinical sciences in the second half. The curriculum will begin with Introduction to Medicine. The remainder of the first year will be made up of Foundation Blocks. Second year will be made up of Clinical Blocks. Subjects (as defined by the Subject Development Groups) will be grouped in Blocks based on regional anatomy. An example is the Thorax Block which will include Respiration and Airways, Heart and Circulation, and Blood. Each subject will be divided in half; the first half will be taught in the Thorax Foundation Block, and the second half in the Thorax Clinical Block. This "double block" system is a student initiative.

The new undergraduate medical curriculum will take Western into the next millennium. The entire renewal process has occurred through cooperation from all those involved. New and innovative learning, teaching, and evaluation techniques will be employed. It is our hope that Western's new MD curriculum will be a model for others to follow. The tradition of excellence upon which the Faculty of Medicine is built will undoubtedly continue.

Acknowledgements: I wish to thank Dr John Howard, Director of Curriculum and Evaluation, Faculty of Medicine, UWO, and Andy Thompson, Meds '98, Hippocratic Council VP Academic Sr, Faculty of Medicine, UWO.

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Ω

Periampullary Tumour in an Elderly Gentleman

by Paul J Collins

A 70-year-old gentleman presents to his family physician complaining that over the past few weeks his skin has turned yellow and his urine has turned brown in colour.

PLEASE STOP AND ANSWER THE FOLLOWING QUESTIONS

1. Name the condition.
2. Define the condition.
3. Classify the etiologies of the condition.
4. List possible causes under each classification.

The gentleman is referred to a general surgeon. On history, the patient's symptoms include jaundice, dark urine, weight loss (40 lb. over the past few months) and abdominal pain (diffuse, worse at night, radiates to back). He also mentions intermittent episodes of weakness, nausea, vomiting and diarrhea. He is a 50-pack-year smoker and a heavy drinker. Medical history reveals cholecystectomy at the age of 40. Family history is negative. On examination, the man has a temperature of 37.5°C, BP 110/60, HR 65, height 5'11", weight 130 lb. There is diffuse abdominal tenderness. The liver is palpable 2 cm below the costal margin. The remainder of the physical examination is normal. Lab tests and imaging studies are ordered.

PLEASE STOP AND ANSWER THE FOLLOWING QUESTIONS

5. What diagnosis does the clinical picture suggest? Why?
6. List the most common symptoms of this disease.
7. List the most common signs of this disease.
8. List the risk factors for this disease.
9. What is the importance of early diagnosis?

ABOUT THE AUTHOR

Paul Collins is a second-year medical student at UWO with a BSc from McMaster University. He is interested in general surgery.

Lab tests revealed elevated conjugated bilirubin and alkaline phosphatase, characteristic of extrahepatic biliary obstruction. Ultrasound demonstrated dilated common bile duct, dilated intrahepatic bile ducts, and a mass in the region of the pancreas. CT scan demonstrated a mass in the area of the head of the pancreas with extension to the duodenum, bile ducts and stomach. There was no vascular invasion, lymph-node involvement outside the boundary of resection, or distant metastases. Pathological examination of a CT-guided fine needle aspiration biopsy showed ductal adenocarcinoma of the pancreas.

PLEASE STOP AND ANSWER THE FOLLOWING QUESTIONS

10. What is the differential diagnosis for a tumour in the periampullary region? Why is tissue diagnosis important?
11. What is the most common histopathological type of pancreatic carcinoma? What is its pathogenesis?
12. Describe the staging of pancreatic carcinoma? What stage is this patient?

The patient arrives at the office to discuss the options for treatment and the prognosis of his condition.

PLEASE STOP AND ANSWER THE FOLLOWING QUESTIONS

13. What potentially curative therapy is available?
14. Name and briefly describe the procedure.
15. Comment on the risks involved in the procedure.
16. Comment on the efficacy of the procedure.

The gentleman underwent standard pancreaticoduodenectomy with adjuvant radio-chemotherapy. He is still fighting a year after his operation.

ANSWERS

1. Jaundice (=icterus).

2. Jaundice (=icterus) refers to the yellow pigmentation of skin, sclerae, mucous membranes and excretions due to hyperbilirubinaemia (>35 (mol/l) and deposition of bile pigments. Examine the sclerae in a good light (they are the most sensitive indicator).

3. (a) Prehepatic (acholuric) jaundice. Bilirubin is formed from the breakdown of haemoglobin and is usually all conjugated by hepatocytes. If there is excess bilirubin or an inborn error of uptake or conjugation, some bilirubin is unconjugated and remains in the circulation. Being water insoluble, it does not appear in the urine.

   (b) Posthepatic (obstructive or cholestatic) jaundice. Normally, conjugated bilirubin flows out into the gut, where intestinal bacteria convert it to urobilinogen, some of which is reabsorbed and appears in the urine. The rest is converted to stercobilin, which colours faeces brown. If the biliary system is blocked, plasma conjugated bilirubin rises. Being water soluble, some is excreted in the urine, making it dark. By contrast, less bilirubin passes into the bowel; the faeces now have less stercobilin and so are pale.

   (c) Hepatocellular jaundice. This implies diminished hepatocyte function (usually with varying degrees of cholestasis) and results in conjugated and unconjugated hyperbilirubinaemia.

4. (a) Prehepatic (acholuric) jaundice. Haemolysis (excess bilirubin), Gilbert's syndrome (failure of uptake), Crigler-Najjar syndrome (failure of conjugation).

   (b) Posthepatic (obstructive or cholestatic) jaundice. Obstruction anywhere in bile duct system caused by gallstones, tumours, congenital anomalies, strictures, primary biliary sclerosis, primary sclerosing cholangitis.

   (c) Hepatocellular jaundice. Viruses (hepatitis A, B, C, E, EBV), drugs, toxins, cirrhosis.

5. In persons over 60 years of age, the combination of jaundice and significant weight loss usually means carcinoma of the head of the pancreas or periampullary region. Pain, dark urine, weakness, nausea, vomiting, diarrhea, and palpable liver also contribute to the diagnosis.

6. The most common presenting symptom of carcinoma of the head of the pancreas include weight loss, jaundice, pain, anorexia, dark urine, light stools, nausea, vomiting, weakness, pruritis, diarrhea, melena, constipation, fever, haematemesis.

7. The most common presenting signs of carcinoma of the head of the pancreas include jaundice, palpable liver, palpable gallbladder, tenderness, ascites, abdominal mass.

8. Pancreatic cancer is more common in men than in women and develops most often in the seventh decade of life. Environmental etiologic factors include smoking, dietary fat and chemical carcinogens. There is no compelling evidence to support a role of coffee or alcohol. Host etiologic factors include abnormal glucose tolerance and genetic factors. There is no compelling evidence to support a role of chronic pancreatitis.

9. Many of the problems in the treatment of pancreatic cancer can be traced to our inability to diagnose the disease in its early stages. The vague early symptoms of pancreatic cancer are often minimized by both patient and physician, typically leading to a delay of months in making the diagnosis. It is usually not until the patient develops jaundice or extreme weight loss that the diagnosis is made, and by this time the pancreatic tumour is typically large and has grown beyond the confines of the pancreas.

10. Lesions in the periampullary region may originate from the duodenum, ampulla of Vater, distal common bile duct, or the head of the pancreas. The first three sites are associated with a reasonable chance of cure following complete removal of the tumour.

11. Despite the fact that ductal cells make up less that 5% of exocrine tissue, they appear to be the cell of origin of over 90% of pancreatic carcinomas. Ductal adenocarcinoma of the exocrine pancreas is by far the most common form of pancreatic cancer. It probably arises as a progressive process beginning with ductal hyperplasia, followed by dysplasia, carcinoma in situ and finally invasive carcinoma, as is the case for many neoplasms.

12. The current staging system for cancer of the pancreas is based on the TNM definitions: T = primary tumour, N = regional lymph node involvement, M = distant metastases. This patient is Stage I (T1-2, N0, M0); there is limited direct extension to adjacent viscera, with no regional node extension and no distant metastases. Limited direct extension is defined as involvement of organs adjacent to the pancreas that could be removed en bloc with the pancreas if a curative resection were attempted. Normally, patients presenting with jaundice already have extension and metastasis. However, this patient's tumour was so localized to the ampullary region that jaundice occurred when the tumour was still small enough to be resectable.

13. Surgery is the only potentially curative therapy for pancreatic cancer. Unfortunately, few patients are actually cured of the disease; fewer than 1% of patients survive 5 years after the diagnosis of pancreatic cancer. Typically, only 10-20% of pancreatic cancer patients can undergo attempted resection for cure.

14. Pancreaticoduodenectomy (Whipple procedure). During this procedure, the antrum of the stomach, duodenum, proximal jejunum, head of the pancreas, gallbladder and distal common bile duct are removed en bloc. Continuity is reestablished by anastomosing the distal pancreas to the proximal jejunum. Sequentially then the transected common bile duct is reimplanted into the jejunal limb and the transected stomach is implanted distal to the other 2 anastomoses into the jejunal limb.

15. Pancreaticoduodenectomy is a formidable operation with historically high morbidity and mortality rates. Until recently, the average operative mortality was approximately 20%. However, operative mortality rates have declined to 5-10% recently owing to improved management of seriously ill patients. The most dreaded complication is disruption of the pancreaticojejunostomy with consequent necrotizing infection, disruption of major vessels and intraperitoneal haemorrhage. Other complications include upper gastrointestinal haemorrhage, marginal ulceration, biliary fistula, and delayed gastric emptying.

16. In terms of cure, the results are discouraging. On one hand, most known cures of pancreatic cancer have been achieved by pancreaticoduodenectomy. On the other hand, only 5% of patients undergoing that operation are alive and disease-free 5 years later. Average survival after standard pancreaticoduodenectomy is about one year and reflects the inability to render patients disease-free with standard surgery alone. Additional approaches include increasing the extent of surgery to prevent local recurrence, using adjuvant radiotherapy to improve local control, and using adjuvant chemotherapy to control systemic disease. Ω

The Skin Game

by Dr. Colby

My clerkship rotation in Dermatology was one of the most pleasant. Clinics did not begin until the civilized hour of 9 a.m., which by University of Toronto convention, means 9:10 a.m. I was thus able to revert to my preferred nocturnal activity schedule without fear of the sleep deprivation fugue state so common during surgical rotations.

Dermatology, like neurology, is a specialty in which the physical examination assumes a central importance in diagnosis. To be honest, I have never found that the physical examination contributed much to the final medical assessment of most patients. Once in a while, the diagnosis is clinched by physical findings but in most cases the history and laboratory tests are sufficient to make the diagnosis and formulate a treatment plan. Dermatologists, on the other hand, like to perform the physical examination first and use the history (sometimes with lab tests) to provide confirmatory information. This makes sense because the appearance of a cutaneous eruption is everything and questions like "How long have you had this?" and "Does it itch?" are of secondary importance.

In many countries the diagnosis and treatment of sexually transmitted diseases is the responsibility of the dermatologist. I suspect this is because of the protean presentations of syphilis, which in its secondary stage, often presents as a rash. My rotation supervisor, Dr Gasher (name changed to protect the innocent), told me during one of my first clinics that there was nothing he found so unpleasant in the entire sphere of medical practice as pelvic examinations. He went on to tell me that he became an expert at this procedure in order to minimize the trauma to his psyche. I have found this to be excellent advice over the years which is broadly applicable to the areas of medicine which are less than pleasant. Let's face it, everybody has certain aspects of medical practice which they find unpleasant, unless they are so riddled with psychopathology that they can no longer discern the good from the bad.

It had been a long, long night, I had not been able to obtain a wink of sleep. I felt like the bottom of a parrot's cage. It seemed like I had to make critical decisions every moment. In other words, I had been at another all-night card game, playing for money. I have always been intrigued by people who say they don't gamble. To me life is a gamble and it is hard for me to imagine that gambling could not be entertaining (particularly if you are on a winning streak). Nevertheless, some folks don't like it and I respect that. I just don't understand it. The game broke up just before 8 a.m. The pot leader bid up a questionable hand and promptly blew his entire hoard. I grabbed a shower and made some coffee amid the wreckage of the evenings activities. I arrived late for dermatology clinic by about 20 minutes but luckily met Dr Gasher in the foyer of the hospital, hurrying in just as tardily as myself. It is hard to chastise another person for being late when you are just as late yourself. Nevertheless, my initial euphoria turned to fear when I saw him heading for the stairwell instead of the elevator. The dermatology clinic was on the 12th floor. He beckoned me to follow and proceeded up the stairs double time, two steps per stride. By the time we got to the 12th floor I was a florid example of dyspnea, cyanosis, chest pain and a feeling of impending doom. Most of the patients that morning had what is called in the trade a "Don't do anything rash". I survived the day despite my incredible fatigue and did not perk up until I quaffed a few ales at the Brunswick House that evening, that being a Friday-night ritual for University of Toronto medical students.

The next day, I headed up to a friend's cottage at Jackson Point where I ran into a number of my classmates. One of them asked me what rotation I was doing and after I told him he showed me the sole of his foot. There was the largest plantar wart I have ever seen, being a full 2 inches long, 1/2 inch wide and 1 inch thick. I said "Rob, why don't you come around to clinic on Tuesday and we will take care of that for you?"

"Will it hurt?" he asked.

"Na", I said. When Tuesday rolled around I told Dr Gasher that I had asked a buddy of mine to stop by so we could treat his plantar wart.

"No problem" said Dr Gasher. Sure enough, Rob turned up. Dr Gasher surveyed the bottom of his foot, put his ankle in a front headlock, grabbed a paring blade and immediately started carving the wart off the bottom of his foot.

Rob said "I can feel that, Dr Gasher." Dr Gasher continued his work. Rob said "Dr Gasher, that is starting to hurt a little bit." Dr Gasher continued his work. Rob started breaking out in a sweat and said "Dr Gasher, that is really starting to hurt." Dr Gasher continued his work. Rob said "Holy Mackerel! This is really hurting!"

Dr Gasher said "It won't be long now." and put down the curette. Rob breathed a sigh of relief, but this was premature. Dr Gasher removed the largest Q-tip I have ever seen, something that is normally used to swab out rigid sigmoidoscopes, from a boiling pot of liquid nitrogen. Tightening his headlock on Rob's ankle he jammed the liquid nitrogen swab onto the remnant of his wart with all the strength he could muster. Rob's foot plantar-flexed so much that he was almost touching his toes to his calcaneum. He actually lost the ability to speak momentarily. Dr Gasher said "There."

Rob said "Gee, thank you, Dr Gasher."

"No problem," said Dr Gasher as he walked away. "Come back one week from today and we will finish the job." Rob looked at me, started to put on his shoes and limped out. He never returned. As far as I know, he still has his remarkable plantar wart. Through this I learned another valuable lesson. People in general don't go back for a second round unless the experience was a pleasant one. One of the only exceptions to this rule is postgraduate medical training. Ω

LIPITOR*

ATORVASTATIN CALCIUM

LIPITOR*
(Atorvastatin Calcium)
10 mg, 20 mg and 40 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-methylglutaryl-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, and lowers Very Low Density Lipoprotein-Cholesterol (VLDL-C) and serum triglycerides (TG), as well as the number of apolipoprotein B (apo B) containing particles.
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 565 liters. Atorvastatin is ≥98% bound to plasma proteins.
Atorvastatin is extensively metabolized by cytochrome P450 3A4 to ortho- and para-hydroxylated derivatives and various beta-oxidation products. Approximately 70% of circulating inhibitory activity for HMG-Co A 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 diet, at least equivalent to the American Heart Association (AHA) Step 1 diet, for the reduction of elevated total cholesterol, LDL-C, triglycerides (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, and
- Heterozygous familial hypercholesterolemia.

In clinical trials, LIPITOR (10-80 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 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 (TG>350 mg/dL), LIPITOR lowered TG levels by 27-42%.
Limited data is available in homozygous familial hypercholesterolemia (FH). An open-label study with atorvastatin 80 mg/day in homozygote FH patients showed a LDL-C lowering of 30% for patients not on plasmapheresis and of 31% for patients who continued plasmapheresis. A 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-C (mmol/L) = total cholesterol - [(0.37 x (TG) + HDL-C)]
LDL-C (mg/dL) = total cholesterol - [(0.2 x (TG) + HDL-C)][1]

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

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

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.

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 during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin (nicotinic acid) or azole antifungals. Although there is no experience to date with the use of LIPITOR given concurrently with these drugs, with the exception of a pharmacokinetic study with erythromycin (see PRECAUTIONS, Drug Interactions), the benefits and risks of such combined therapy should be carefully considered.
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

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 (CoQ_{10}) 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).

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) levels. Until further experience is obtained, it is suggested, where feasible, that measurements of serum Lp(a) be followed up in patients placed on atorvastatin therapy (see SELECTED BIBLIOGRAPHY).

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 child-bearing 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; and SELECTED BIBLIOGRAPHY).

Renal Insufficiency

Plasma concentrations and LDL-C lowering efficacy of LIPITOR are similar in patients with moderate renal insufficiency compared with patients with normal renal function. In patients with severe renal insufficiency (creatinine clearance <30 mL/min), the lowest dosage should be used and implemented cautiously (see WARNINGS, Muscle Effects).

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.

Drug Interactions

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 with that of 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.

[1] Friedewald, WT et al. *Clin Chem* 1972; 18(6):489-502.

LIPITOR*
ATORVASTATIN CALCIUM

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 no 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 is increased with concurrent administration (see WARNINGS, Muscle Effects).
Erythromycin: In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of LIPITOR and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, Muscle Effects).
Coumarin Anticoagulants: LIPITOR had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.
Digoxin: Coadministration of multiple doses of LIPITOR and digoxin increased steady-state plasma digoxin concentrations by approximately 20%. Patients taking digoxin should be monitored closely and appropriately.
Antipyrine: Antipyrine was used as a 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.
Oral Contraceptives: Coadministration of LIPITOR with an oral contraceptive, containing 1 mg 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.
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%.
Other Concomitant Therapy: Caution should be exercised with concomitant use of immunosuppressive agents and azole antifungals (see WARNINGS, Muscle Effects).
In clinical studies, LIPITOR was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted.
Cytochrome P-450 Inhibitors: Atorvastatin is metabolized by the microsomal hepatic enzyme system (cytochrome P-450 system) as are most other HMG-CoA reductase inhibitors. While atorvastatin did not interact with antipyrine, it did interact with erythromycin, a known inhibitor of cytochrome P450 3A4. Grapefruit juice has also been shown to inhibit cytochrome P450 3A4. There may be a potential for increased plasma concentrations of HMG-CoA reductase inhibitors upon coadministration with grapefruit juice, and other compounds which affect this enzyme system (see SELECTED BIBLIOGRAPHY).

Patients with Severe Hypercholesterolemia:

Higher drug dosages (80 mg/day) required for some patients with heterozygous familial hypercholesterolemia or severe 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 erythromycin (see WARNINGS, Muscle Effects; and PRECAUTIONS, Drug Interactions).**

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.
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 American Heart Association (AHA) Step 1 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 levels, the desired LDL-C target (such as that recommended by the US National Cholesterol Education Program [NCEP] and/or the Canadian Consensus Conference Guidelines), 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).

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of LIPITOR if cholesterol falls below the targeted range such as that 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 Hypercholesterolemia

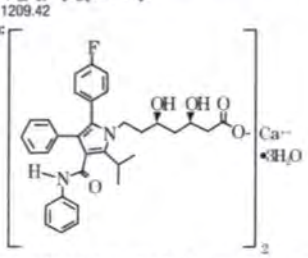
In patients with severe hypercholesterolemia, including heterozygous familial hypercholesterolemia, higher dosages (up to 80 mg/day) may be required (see WARNINGS, Muscle Effects and PRECAUTIONS, Drug Interactions).

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)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate
Empirical Formula: $(C_{33}H_{35}FN_2O_5)_2Ca \cdot 3H_2O$
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 or 40 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 25°C.

AVAILABILITY OF DOSAGE FORMS

LIPITOR (atorvastatin calcium) is available in dosage strengths of 10 mg, 20 mg and 40 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.

1. LIPITOR (atorvastatin calcium) Product Monograph, Parke-Davis Div., Warner-Lambert Canada Inc., February 1997. 2. Dart A, Jerums G et al. A multicentre, double-blind, 1-year study comparing the safety and efficacy of once-daily atorvastatin with that of simvastatin patients with hypercholesterolemia. *Am J Cardiol* 1997; in press. 3. Bertolini S, Bitollo Bon G, et al. The efficacy and safety of atorvastatin compared to pravastatin in patients with hypercholesterolemia. *Atherosclerosis* 1997; 130:191-197. 4. Davidson MM, McKenney JM, Stein EA, et al. Long term efficacy and safety of atorvastatin compared to lovastatin in hypercholesterolemic patients. *Am J Cardiol* 1997; in press. 5. Heinonen TM et al. Atorvastatin, a new HMG-CoA reductase inhibitor as monotherapy and combined with colestipol. *J Cardiovasc Pharmacol Therapeut* 1996; 1(2):117-22. 8. Parke-Davis 1997 catalogue and ODB Formulary 1996.

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

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ZITHROMAX

(azithromycin dihydrate† / pfizer)

NAME OF DRUG

ZITHROMAX

(azithromycin dihydrate)

- Capsules 250 mg USP
- Tablets 250 mg
- Powder for Oral Suspension 100 mg/5 mL and 200 mg/5 mL
- One gram single dose packet

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION AND CLINICAL PHARMACOLOGY

Azithromycin dihydrate, a macrolide antibiotic of the azalide subclass, exerts its antibacterial action by binding to the 50s ribosomal subunits of susceptible bacteria and suppressing protein synthesis. Following oral administration, azithromycin is rapidly absorbed (T_{max} = 2-3 hours) and distributed widely throughout the body. Rapid movement of azithromycin from blood into tissue results in significantly higher azithromycin concentrations in tissue than in plasma (up to 50 times the maximum observed concentration in plasma). The absolute bioavailability is approximately 37%.

When azithromycin capsules were administered with food to 11 healthy adult male subjects, the rate of absorption (C_{max}) of azithromycin from the capsule formulation was reduced by 52% and the extent of absorption (AUC) by 43%. However, when azithromycin suspension was administered with food to 28 healthy adult male subjects, the rate of absorption (C_{max}) was increased by 56% while the extent of absorption (AUC) was unchanged. Therefore, azithromycin capsules and powder for oral suspension should be given one hour before or two hours after a meal.

Food does not affect the absorption of azithromycin in the tablet and the one gram single dose packet dosage forms. Unlike the capsule and powder for oral suspension, azithromycin tablets and the one gram single dose packet can be taken without regard to meals. Azithromycin tablets are bioequivalent to the capsule formulation; the oral suspension as a one gram single dose packet is bioequivalent to four 250 mg capsules or tablets

Adult Pharmacokinetics:

Plasma concentrations of azithromycin decline in a polyphasic pattern, resulting in an average terminal half-life of 68 hours. The prolonged half-life is likely due to extensive uptake and subsequent release of drug from tissues. Over the dose range of 250 to 1000 mg orally, the serum concentrations are related to dose. The long tissue half-life and large volume of distribution result from intracytoplasmic uptake and storage in lysosomal phospholipid complexes.

In adults, the following pharmacokinetic data have been reported:

DOSE/DOSAGE FORM	Subjects	C_{max} (µg/mL)	T_{max} (hr)	AUC 0-24 (µg•hr/mL)	$T_{1/2}$ (hr)
500 mg/250 mg capsule	16;fasted	0.40	2.4	3.69[a]	-
500 mg/250 mg tablet	12;fasted	0.34	2.1	2.49[a]	-
500 mg/250 mg tablet	12; fed	0.41	2.3	2.40[a]	-
1 g/250 capsule	33; fasted	0.84	2.0	10.5[c]	43.9
1g/Single Dose*	33; fasted	0.95	1.4	10.2[c]	43.9
1g/Single Dose*	12; fasted	0.75	1.5	6.49[b]	-
1g/Single Dose*	12; fed	1.05	2.0	7.37[b]	-
2 g/250 capsule	15; fasted	1.69	1.3	18.8[d]	59.8

* One gram single dose packet

[a] 0-48 hr; [b] 0-72 hr; [c] 0-120 hr; [d] 0-144 hr.

When studied in healthy elderly subjects from age 65 to 85 years, the pharmacokinetic parameters of azithromycin capsules in elderly men were similar to those in young adults; however, in elderly women, although higher peak concentrations (increased by 30 to 50%) were observed, no significant accumulation occurred. There are no pharmacokinetic data available from studies in hepatically- or renally-impaired individuals.

Biliary excretion of azithromycin, predominantly as unchanged drug, is a main route of elimination.

Pediatric Pharmacokinetics:

The table below shows mean pharmacokinetic parameters on day 5 in children 1 to 5 years and 5 to 15 years of age when azithromycin oral suspension was dosed in the absence of food at 10 mg/kg on day 1 and 5 mg/kg on days 2-5.

Pharmacokinetic parameters on day 5 at dosage 10 mg/kg (day 1) and 5 mg/kg (days 2-5)					
Age 1-5			Age 5-15		
C_{max} (µg/mL)	T_{max} (hrs)	AUC 0-24 (µg•hr/mL)	C_{max} (µg/mL)	T_{max} (hrs)	AUC 0-24 (µg•hr/mL)
0.216	1.9	1.822	0.383	2.4	3.109

There are no pharmacokinetic data on azithromycin suspension when administered at a dose of 12 mg/kg/day in the presence or absence of food.

INDICATIONS AND CLINICAL USES

ZITHROMAX (azithromycin dihydrate) is indicated for treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the following diseases and specific conditions. As recommended dosages, durations of therapy, and applicable patient populations vary among these infections, see **DOSAGE AND ADMINISTRATION** for specific dosing recommendations.

ADULTS

Upper Respiratory Tract

Pharyngitis and tonsillitis caused by *Streptococcus pyogenes* (group A ß-hemolytic streptococci) occurring in individuals who cannot use first line therapy.

NOTE: Penicillin is the usual drug of choice in the treatment of *S. pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. **ZITHROMAX** is often effective in the eradication of susceptible strains of streptococci from the oropharynx. However, data establishing the efficacy of **ZITHROMAX** in the subsequent prevention of rheumatic fever are not available at present.

Lower Respiratory Tract

Acute bacterial exacerbations of chronic obstructive pulmonary diseases caused by *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae.* Community-acquired pneumonia caused by *S. pneumoniae* or *H. influenzae* in patients for whom oral therapy is appropriate.

Skin and Skin Structure

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus, S. pyogenes* or *Streptococcus agalactiae.*

Genitourinary Tract

Urethritis and cervicitis due to *Neisseria gonorrhoeae* or *Chlamydia trachomatis.* Genital ulcer disease in men due to *Haemophilus ducreyi* (chancroid). Due to the small number of women included in clinical trials, the efficacy of azithromycin in the treatment of chancroid in women has not been established. Patients should have a serologic test for syphilis and appropriate cultures for gonorrhea performed at the time of diagnosis. Appropriate antimicrobial therapy and follow-up tests should be initiated if infection is confirmed.

Appropriate culture and susceptibility tests should be initiated before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with **ZITHROMAX** may be initiated before results of these tests are known; once the results become available, antibiotic treatment should be adjusted accordingly.

CHILDREN (see **DOSAGE AND ADMINISTRATION; Use in Children, PRECAUTIONS** section).

Acute otitis media caused by *H. influenzae* (ß-lactamase positive and negative strains), *M. catarrhalis* or *S. pneumoniae.* (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION** section).

Pharyngitis and tonsillitis caused by *S. pyogenes* (group A ß-hemolytic streptococci) occuring in individuals who cannot use first line therapy. (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION** section).

NOTE: Penicillin is the usual drug of choice in the treatment of *S. pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. **ZITHROMAX** is often effective in the eradication of susceptible strains of streptococci from the oropharynx. However, data establishing the efficacy of **ZITHROMAX** in the subsequent prevention of rheumatic fever are not available at present.

CLINICAL STUDIES IN PEDIATRIC PATIENTS

From the perspective of evaluating pediatric clinical trials, because of the extended half-life of azithromycin, days 11-14 were considered on-therapy evaluations and are provided for clinical guidance. Day 30 evaluations were considered the primary test of cure endpoint.

Otitis Media

Efficacy Protocol 1

In a double-blind, controlled clinical study of acute otitis media performed in North America, azithromycin (10 mg/kg on day 1 followed by 5 mg/kg on days 2-5) was compared to an antimicrobial/ß-lactamase inhibitor. For the 553 patients who were evaluated for clinical efficacy, the clinical success rate (i.e., cure plus improvement) at the day 11 visit was 88% for azithromycin and 88% for the control agent. For the 528 patients who were evaluated at the day 30 visit, the clinical success rate was 76% for azithromycin and 76% for the control agent.

Efficacy Protocol 2

In a non-comparative clinical and microbiologic trial performed in North America, and in which significant numbers of ß-lactamase producing organisms were identified (35%), the combined clinical success rate (i.e. cure plus improvement) was 84% at the day 11 visit (n=131) and 70% at the day 30 visit (n=122).

Microbiologic determinations were made at the pre-treatment visit. Microbiology was not reassessed at later visits. The following presumptive bacterial/clinical cure outcomes (i.e., clinical success) were obtained from the evaluable group:

Bacteriologic Eradication	Day 11	Day 30
	Azithromycin	Azithromycin
S. pneumoniae	61/74 (82%)	40/56 (71%)
H. influenzae	43/54 (80%)	30/47 (64%)
M. catarrhalis	28/35 (80%)	19/26 (73%)
S. pyogenes	11/11 (100%)	7/7 (100%)
Overall	177/217 (82%)	97/137 (73%)

Pharyngitis and Tonsillitis

In three double-blind North American controlled studies, azithromycin (12 mg/kg once a day for 5 days) was compared to penicillin V (250 mg three times a day for 10 days) in the treatment of pharyngitis due to documented group A ß-hemolytic streptococci (GABHS or *S. pyogenes*). Azithromycin was clinically and microbiologically statistically superior to penicillin at day 14 and day 30 with the following clinical success (i.e., cure and improvement) and bacteriologic efficacy rates (for the combined evaluable patients with documented GABHS):

Three North American Streptococcal Pharyngitis Studies
Azithromycin vs. Penicillin V
EFFICACY RESULTS

	Day 14	Day 30
Bacteriologic Eradication		
Azithromycin	323/340 (95%)	261/329 (79%)
Penicillin V	242/332 (73%)	214/304 (71%)
Clinical Success (cure plus improvement)		
Azithromycin	336/343 (98%)	313/328 (95%)
Penicillin V	284/338 (84%)	240/303 (79%)

Approximately 1% of azithromycin-susceptible *S. pyogenes* isolates were resistant to azithromycin following therapy.

NOTE: Penicillin is the usual drug of choice in the treatment of *S. pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. **ZITHROMAX** is often effective in the eradication of susceptible strains of streptococci from the oropharynx. However, data establishing the efficacy of **ZITHROMAX** in the subsequent prevention of rheumatic fever are not available at present.

Appropriate culture and susceptibility tests should be initiated before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with **ZITHROMAX** may be initiated before results of these tests are known; once the results become available, antibiotic treatment should be adjusted accordingly.

CONTRAINDICATIONS

ZITHROMAX (azithromycin dihydrate) is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, or other macrolide antibacterial agents.

WARNINGS

Rare serious allergic reactions, including angioedema and anaphylaxis, have been reported in patients on **ZITHROMAX (azithromycin dihydrate)** therapy (see **CONTRAINDICATIONS** section). Allergic reactions may occur during and soon after treatment with **ZITHROMAX**. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

ZITHROMAX should not be used in patients with community-acquired pneumonia who are judged to be inappropriate for oral therapy because of the presence of severe illness or because of accompanying risk factors.

Pseudomembranous colitis has been reported with nearly all antibacterial agents including **ZITHROMAX** and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis". After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile.*

In the absence of data on the metabolism and pharmacokinetics in patients with lysosomal lipid storage diseases (e.g., Tay-Sachs disease, Niemann-Pick disease) the use of **ZITHROMAX** in these patients is not recommended.

PRECAUTIONS

General:

Since liver is the major route of elimination for **ZITHROMAX (azithromycin dihydrate)**, the use of **ZITHROMAX** should be undertaken with caution in patients with significant hepatic disease.

No dose adjustment is needed in patients with mild renal impairment (creatinine clearance > 40 mL/min), but there are no data regarding **ZITHROMAX** usage in patients with more severe renal impairment. Thus caution should be exercised before prescribing **ZITHROMAX** in these patients.

The following adverse events have been reported with macrolide products: ventricular arrhythmias, including ventricular tachycardia and *torsades de pointes*, in individuals with prolonged QT intervals. Although these adverse events have not been reported in clinical trials with azithromycin, one AIDS patient dosed at 750 mg to 1 g daily experienced prolonged QT interval and *torsades de pointes*.

Use in Pregnancy:

Animal studies have demonstrated that azithromycin crosses the placenta. Safety of **ZITHROMAX** for use in human pregnancy has not been established.

Use in Nursing Mothers:

There are no data on secretion in breast milk. Safety of **ZITHROMAX** for use in human lactation has not been established.

Use in Children:

Acute Otitis Media: Safety and efficacy of **ZITHROMAX** in the treatment of children with acute otitis media (dosage regimen: 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5) under 6 months of age have not been established.

Pharyngitis and tonsillitis: Safety and efficacy of **ZITHROMAX** in the treatment of children with pharyngitis and tonsillitis (dosage regimen: 12 mg/kg on days 1-5) under 2 years of age have not been established.

Studies evaluating the use of repeated courses of therapy have not been conducted. Safety data with the use of ZITHROMAX at doses higher than proposed and for durations longer than recommended are limited to a small number of immunocompromised children who underwent chronic treatment.

In animal studies, treatment with azithromycin is associated with accumulation in various tissues, including the extra-cranial neural ganglia (i.e., retina and sympathetic nervous system). Tissue accumulation is both dose and time dependent, and is associated microscopically with the development of phospholipidosis (intra-lysosomal drug phospholipid complexes). The only evidence in animals that azithromycin is associated with alterations of intracellular phospholipid metabolism has been the documentation of small increases in phospholipid content after prolonged treatment (6 months) or exaggerated doses. Phospholipidosis has been observed at total cumulative doses only 2 multiples of the clinical dose. One month after withdrawal of treatment the concentration of azithromycin and the presence of phospholipidosis in tissue, including the retina, is at or near predose levels.

No data exist in humans in regard to the extent of accumulation, duration of exposure, metabolism or excretory mechanisms of azithromycin in neural tissue such as the retina and the cochlea.

Rare cases of hearing loss have been reported (see **ADVERSE REACTIONS** section).

No data are available on the metabolism and pharmacokinetics of azithromycin in children with lysosomal lipid storage diseases (see **WARNINGS** section).

Use in Elderly:

In elderly subjects (age 65 to 85) the pharmacokinetics are substantially the same as in younger subjects and no dosage adjustment is necessary for elderly patients with normal renal and hepatic functions.

Drug Interactions:

Antacids

Aluminum and magnesium containing antacids (Maalox®) reduce the peak serum levels but not the extent of azithromycin absorption. These drugs should not be taken simultaneously.

Cimetidine

Administration of cimetidine (800 mg) two hours prior to **ZITHROMAX** had no effect on azithromycin absorption.

Theophylline

Concurrent use of macrolides and theophylline has been associated with increases in the serum concentrations of theophylline. **ZITHROMAX** did not affect the pharmacokinetics of theophylline administered either as a single intravenous infusion or multiple oral doses at a recommended dose of 300 mg every 12 hours. There is one post-marketing report of supraventricular tachycardia associated with an elevated theophylline serum level that developed soon after initiation of treatment with **ZITHROMAX**. Until further data are available, prudent medical practice dictates careful monitoring of plasma theophylline levels in patients receiving **ZITHROMAX** and theophylline concomitantly.

Warfarin

ZITHROMAX did not affect the prothrombin time response to a single dose of warfarin.

However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with **ZITHROMAX** and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

Carbamazepine

In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant **ZITHROMAX**.

Concomitant Therapy

The following drug interactions have not been reported in clinical trials with **ZITHROMAX** and no specific drug interaction studies have been performed to evaluate potential drug-drug interactions. Nonetheless, they have been observed with macrolide products, and there have been rare spontaneously reported cases with **ZITHROMAX** and some of these drugs, in postmarketing experience. Until further data are developed regarding drug interactions, when **ZITHROMAX** and these drugs are used concomitantly, careful monitoring of patients is advised both during and for a short period following therapy:

Digoxin: Elevation of digoxin levels.

Disopyramide: Increase in pharmacological effects.

Ergotamine or dihydroergotamine: Acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

Triazolam: Decreases in the clearance of triazolam and increases in the pharmacologic effect of triazolam.

Drugs metabolized by the cytochrome P450 system: Elevations of serum cyclosporine, hexobarbital, cisapride, and phenytoin levels.

Antihistamines: Prolongation of QT intervals, palpitations or cardiac arrhythmias with concomitant administration of astemizole or terfenadine.

No data are available on the concomitant clinical use of **ZITHROMAX** and gentamicin or other amphiphilic drugs which have been reported to alter intracellular lipid metabolism.

ADVERSE REACTIONS

The majority of side effects observed in controlled clinical trials involving patients (adults and children) treated with **ZITHROMAX (azithromycin dihydrate)** were of a mild and transient nature.

Approximately 0.7% of both adult patients (n=3812) and children (n=2878) who had multiple doses of **ZITHROMAX** discontinued therapy because of drug related side effects. Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea or abdominal pain. Rare but potentially serious side effects were angioedema and cholestatic jaundice.

Clinical:

Multiple-dose regimen (adults and children):

In adult patients, the most common side effects in patients receiving the multiple-dose regimen of **ZITHROMAX** were related to the gastrointestinal system with diarrhea (4.3%), abdominal pain (2.6%), vomiting (1.3%) and nausea (3.5%). In children (n=1944) enrolled in North American controlled clinical trials in acute otitis media and *S. pyogenes* pharyngitis, the type of side effects was comparable to that seen in adults, with diarrhea/loose stools (5.3%), vomiting (3.6%), abdominal pain (2.6%), nausea (1.0%), rash (1.0%) and headache (1.0%) the most frequently reported.

Different side effect incidence rates for the two dosage regimens recommended in children were observed:

Acute Otitis Media: For the recommended dosage regimen of 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the most frequent side effects were diarrhea/loose stools (2%), abdominal pain (2%), vomiting (1%) and nausea (1%).

Pharyngitis/tonsillitis: For the recommended dosage regimen of 12 mg/kg on days 1-5, the most frequent side effects were diarrhea/loose stools (6%), vomiting (5%), abdominal pain (3%), nausea (2%) and headache (1%). Side effects that occurred with a frequency of 1% or less in patients included the following:

Cardiovascular: palpitations, chest pain;

Gastrointestinal: dyspepsia, flatulence, vomiting, melena, cholestatic jaundice, constipation, anorexia and gastritis;

Genitourinary: monilia, vaginitis and nephritis;

Nervous System: dizziness, headache, vertigo, somnolence, agitation, nervousness, insomnia and hyperkinesia;

General: fatigue, fever and malaise;

Allergic: rash, photosensitivity, angioedema, erythema multiforme, pruritus and urticaria

Single 1-gram dose regimen (adults):

In adult patients (n=904), side effects that occurred on the single one-gram dosing regimen of **ZITHROMAX** with a frequency greater than 1% included diarrhea (6.1%), nausea (4.9%), abdominal pain (4.9%), vomiting (1.7%), vaginitis (1.3%), loose stools (1.2%) and dyspepsia (1.1%).

Single 2-gram dose regimen (adults):

Overall, the most common side effects in patients receiving a single 2-gram dose of **ZITHROMAX** were related to the gastrointestinal system. Side effects that occurred in patients in this study with a frequency of a 1% or greater included nausea (18.2%), diarrhea/loose stools (13.8%), vomiting (6.7%), abdominal pain (6.7%), vaginitis (2.2%), dyspepsia (1.1%) and dizziness (1.3%). The majority of these complaints were mild in nature.

The following adverse experiences have been reported in patients under conditions (e.g., open trials, marketing experience) where a causal relationship is uncertain or in patients treated with significantly higher than the recommended doses for prolonged periods:

Cardiovascular: cardiac arrhythmia;

Gastrointestinal: pancreatitis, hepatic necrosis, drug induced hepatitis, pseudomembranous colitis;

Genitourinary: interstitial nephritis, acute renal failure, nephrotic syndrome;

Nervous System: hearing loss‡, seizure, loss of taste, tinnitus;

General: muscle pain;

Allergic: serum sickness, Stevens-Johnson syndrome, anaphylaxis, toxic epidermal necrolysis, exfoliative dermatitis, vasculitis.

‡ Hearing loss has been reported rarely in adult and pediatric patients treated with **ZITHROMAX**. Hearing loss is generally reversible and associated with the use of higher than recommended doses for prolonged periods.

Laboratory Abnormalities:

Adults:

Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials in patients were reported as follows:

With an incidence of 1-2%, elevated serum creatine phosphokinase, potassium, ALT (SGPT), GGT and AST (SGOT).

With an incidence of less than 1%, leukopenia, neutropenia, decreased platelet count, elevated serum alkaline phosphatase, bilirubin, BUN, creatinine, blood glucose, LDH and phosphate.

When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 3000 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities and 1 because of a renal function abnormality.

Children:

Significant abnormalities (irrespective of drug relationship) occurring during clinical trials were all reported at a frequency of less than 1%, but were similar in type to the adult pattern.

In multiple-dose clinical trials involving almost 3000 pediatric patients, no patients discontinued therapy because of treatment-related abnormalities.

OVERDOSAGE

Symptoms:

There are no data on overdosage.

Treatment:

Gastric lavage and general supportive measures are indicated.

Up to 15 grams cumulative dose of **ZITHROMAX (azithromycin dihydrate)** over 10 days has been administered in clinical trials without apparent adverse effect.

DOSAGE AND ADMINISTRATION

Adults:

CAPSULES: ZITHROMAX (azithromycin dihydrate) Capsules should be given as a single daily dose at least 1 hour before or 2 hours after a meal.

TABLETS: ZITHROMAX Tablets can be taken with or without food.

ONE GRAM SINGLE DOSE PACKET: ZITHROMAX powder for oral suspension as one gram single dose packet can be taken with or without food after reconstitution.

Mixing Directions:

Directions for administration of the powder for oral suspension as a one gram single dose packet: The entire contents of the one gram single dose packet should be mixed thoroughly with 60 mL (two ounces) of water. Drink the entire contents immediately, add an additional 60 mL (two ounces) of water, mix, and drink to assure complete consumption of dosage.

For skin and skin structure infections, upper and lower respiratory tract infections: The recommended dose of **ZITHROMAX** for the treatment of individuals 16 years of age and older is 500 mg as a single dose on the first day followed by 250 mg once daily on days 2 through 5 for a total dose of 1.5 grams.

Genitourinary: The recommended dose of **ZITHROMAX** for the treatment of genital ulcer disease due to *Haemophilus ducreyi* (chancroid) and non-gonococcal urethritis and cervicitis due to *C. trachomatis* is: a single 1 gram (1000 mg) oral dose of **ZITHROMAX**. This dose can be administered as four 250 mg capsules, four 250 mg tablets, or as a one gram single dose packet.

The recommended dose of **ZITHROMAX** for the treatment of urethritis and cervicitis due to *Neisseria gonorrhoeae* is: a single 2 gram (2000 mg) dose of **ZITHROMAX**. This dose can be administered as eight 250 mg capsules, eight 250 mg tablets, or as two single dose packets (1 g each).

In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of **ZITHROMAX** compared to those with normal hepatic function. In these patients urinary recovery of azithromycin appears to increase. Hence no dose adjustment is recommended for patients with mild to moderate hepatic impairment. Nonetheless, since the liver is the principal route of elimination for azithromycin, the use of **ZITHROMAX** should be undertaken with caution in patients with significant hepatic disease.

Children:

POWDER FOR ORAL SUSPENSION: ZITHROMAX Powder for Oral Suspension should be given as a single daily dose at least 1 hour before or 2 hours after a meal.

Mixing Directions:

ZITHROMAX Powder for Oral Suspension:

Tap bottle to loosen powder. Add the directed volume of water. Shake well before each use. Oversized bottle provides shake space. Keep tightly closed. The table below indicates the volume of water to be used for reconstitution:

Amount of Water to be added	Nominal Volume after reconstitution (azithromycin content)	Azithromycin concentration after reconstitution
9 mL (300 mg bottle)	15 mL (300 mg bottle)	100 mg/5 mL
9 mL (600 mg bottle)	15 mL (600 mg bottle)	200 mg/5 mL
12 mL (900 mg bottle)	22.5 mL (900 mg bottle)	200 mg/5 mL

For upper respiratory tract infections:

Acute Otitis Media:

The recommended dose of **ZITHROMAX** oral suspension for the treatment of children with acute otitis media is 10 mg/kg as a single-dose on the first day (not to exceed 500 mg/day) followed by 5 mg/kg on days 2 through 5 (not to exceed 250 mg/day), for a total dose of 30 mg/kg of **ZITHROMAX** (see chart below).

PEDIATRIC DOSAGE GUIDELINES FOR ACUTE OTITIS MEDIA
(Age 6 months and above)
Based on Body Weight

ACUTE OTITIS MEDIA

Dosing Calculated on 10 mg/kg on Day 1 dose, followed by 5 mg/kg on Days 2 to 5.

Weight		100 mg/5 mL Suspension		200 mg/5 mL Suspension		Total mL per Treatment Course
Kg	lbs	Day 1	Days 2-5	Day 1	Days 2-5	
5	11	2.5 mL (1/2 tsp)	1.25 mL (1/4 tsp)			7.5 mL
10	22	5 mL (1 tsp)	2.5 mL (1/2 tsp)			15 mL
20	44			5 mL (1 tsp)	2.5 mL (1/2 tsp)	15 mL
30	66			7.5 mL (1 1/2 tsp)	3.75 mL (3/4 tsp)	22.5 mL
40	88			10 mL (2 tsp)	5 mL (1 tsp)	30 mL

Pharyngitis and Tonsillitis:

The recommended dose for children with pharyngitis and tonsillitis is 12 mg/kg once a day (not to exceed 500 mg/day) for 5 days for a total dose of 60 mg/kg of **ZITHROMAX** (see chart below).

PEDIATRIC DOSAGE GUIDELINES FOR PHARYNGITIS AND TONSILLITIS
(Age 2 years and above)
Based on Body Weight

PHARYNGITIS AND TONSILLITIS

Dosing Calculated on 12 mg/kg once daily Days 1 to 5.

Weight		200 mg/5 mL Suspension	Total mL per Treatment Course
Kg	lbs	Day 1-5	
8	18	2.5 mL (1/2 tsp)	12.5 mL
17	37	5 mL (1 tsp)	25 mL
25	55	7.5 mL (1 1/2 tsp)	37.5 mL
33	73	10 mL (2 tsp)	50 mL
40	88	12.5 mL (2 1/2 tsp)	62.5 mL

PHARMACEUTICAL INFORMATION

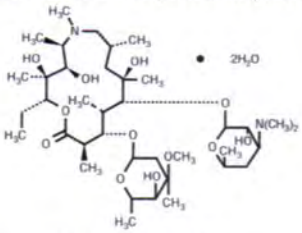
DRUG SUBSTANCE

Trade Name: **ZITHROMAX**

Proper Name: azithromycin dihydrate

Chemical Name: 9-deoxo-9α-aza-9α-methyl-9α-homoerythromycin A dihydrate.

Structural Formula:



Azithromycin dihydrate

Molecular Formula: $C_{38}H_{76}N_2O_{14}$

Molecular Weight: 785.0

Description: Azithromycin dihydrate is a white to off-white crystalline powder of uniform appearance. The aqueous solubility at pH 7.4 at 37°C is 39 mg/mL. The powder is non-hygroscopic.

pK_a: 8.48

Composition: **ZITHROMAX (azithromycin dihydrate) Capsules** contain the following non-medicinal ingredients: lactose; corn starch; magnesium stearate and sodium lauryl sulphate. The capsule shells contain gelatin, FD&C Red #40 and titanium dioxide.

ZITHROMAX Tablets are supplied for oral administration as engraved, film-coated, modified capsular-shaped tablets, containing azithromycin dihydrate equivalent to 250 mg azithromycin and the following inactive ingredients: pregelatinized starch, anhydrous calcium phosphate dibasic, sodium croscarmellose, magnesium stearate, sodium lauryl sulphate, hydroxypropyl methylcellulose, lactose, titanium dioxide, triacetin and D&C Red # 30 aluminum lake.

ZITHROMAX Powder for Oral Suspension contains azithromycin dihydrate equivalent to: 300 mg; 600 mg; and 900 mg of azithromycin per bottle. The non-medicinal ingredients include: sucrose; sodium phosphate, tribasic hydroxypropyl cellulose; xanthan gum; FD&C Red #40 and artificial flavours. After reconstitution, the 300 mg strength contains 100 mg/5 mL and the 600 and 900 mg each contain 200 mg/5 mL (see **DOSAGE AND ADMINISTRATION, Mixing Directions** section).

ZITHROMAX one gram single dose packet contains azithromycin dihydrate equivalent to 1000 mg of azithromycin in a mixture of: sucrose, sodium phosphate tribasic, colloidal silicon dioxide, artificial banana and artificial cherry flavours (see **DOSAGE AND ADMINISTRATION, Mixing Directions** section).

Storage Recommendations:

Store **ZITHROMAX (azithromycin dihydrate)** Capsules, Film-Coated Tablets and the One gram single dose packet at controlled room temperature (15-30°C).

Powder for Oral Suspension:

Dry powder: Store at controlled room temperature (15-30°C).

Reconstituted suspension: Store between 5°C and 30°C. Discard unused portion after 5 days.

AVAILABILITY OF DOSAGE FORMS

CAPSULES: ZITHROMAX (azithromycin dihydrate) Capsules each contain azithromycin dihydrate equivalent to 250 mg of azithromycin. The red, No. 0 hard gelatin capsules imprinted with "Pfizer" and **"ZITHROMAX"** in black ink, are packaged in white plastic (high density polyethylene) bottles of 30 and 100 or in a single treatment package (Z-PAK) of 6 blister packaged capsules per box.

TABLETS: Each pink, film-coated, modified capsular-shaped **ZITHROMAX** tablet, engraved "Pfizer" on the upper face, and scored on the lower face, contains azithromycin dihydrate equivalent to 250 mg of azithromycin. The tablets are packaged in white plastic (high density polyethylene) bottles of 30 and 100 or in a single treatment package (Z-PAK) of 6 blister packaged tablets per box.

POWDER FOR ORAL SUSPENSION: ZITHROMAX Powder for Oral Suspension, after reconstitution, contains a cherry flavoured suspension. Each bottle (high density polyethylene) provides azithromycin dihydrate equivalent to: 300 mg per 15 mL (100 mg/5 mL); 600 mg per 15 mL (200 mg/5 mL); 900 mg per 22.5 mL (200 mg/5 mL). Dropper is included in the package.

ONE GRAM SINGLE DOSE PACKET: ZITHROMAX powder for oral suspension as a one gram single dose packet contains azithromycin dihydrate equivalent to 1000 mg of azithromycin in a sealed, laminated aluminum foil and polyethylene pouch.

Product Monograph Available Upon Request.

† Product licensed from Pliva, Zagreb, Croatia.

References: R.T.I.

1. Zithromax* Product Monograph, Pfizer Canada Inc.
2. Drew RH, Gallis HA, Azythromicin-Spectrum of activity, pharmacokinetics, and clinical applications. Pharmacotherapy 1992;12(3):161-173.
3. Felstead SJ, Daniel R, European Azithromycin Study Group. Short-course treatment of sinusitis and other upper respiratory tract infections with azithromycin: a comparison with erythromycin and amoxycillin. J Int Med Res 1991;19:363-372.
4. Dard D. Multicenter evaluation of azithromycin and cefaclor in acute lower respiratory tract infections. Am J Med 1991;91(Suppl3A):31S-35S.
5. Pozzi E, Grossi E, Pecori A and the Azithromycin Research Group. Azithromycin versus clarithromycin in the t..atment of acute exacerbations of chronic bronchitis. Curr Ther Res 1994;55(7).
6. Hooton TM. A comparison of azithromycin and penicillin V for the treatment of streptococcal pharyngitis. Am J Med 1991;91(Suppl 3A):23S-26S.
7. Hopkins S. Clinical toleration and safety of azithromycin. Am J Med 1991;91(Suppl 3A):40S-45S

References: Pediatric

1. Zithromax* Product Monograph, Pfizer Canada Inc.
2. Khurana CM. Issues concerning antibiotic use in child care setting. Pediatr Infect Dis J 1995;14(4):S34-8.

PALTACE® ramipril

PHARMACOLOGIC CLASSIFICATION:
Angiotensin Converting Enzyme Inhibitor

INDICATIONS AND CLINICAL USE: *Essential Hypertension.* Treatment of essential hypertension. It may be used alone or in association with thiazide diuretics.

ALTACE should normally be used in patients in whom treatment with a diuretic or a beta blocker was found ineffective or has been associated with unacceptable adverse effects.

ALTACE can also be tried as an initial agent in those patients in whom use of diuretics and/or beta blockers are contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

The safety and efficacy of ALTACE in renovascular hypertension have not been established and therefore, its use in this condition is not recommended.

The safety and efficacy of concurrent use of ALTACE with antihypertensive agents other than thiazide diuretics have not been established.

Treatment Following Acute Myocardial Infarction

ALTACE is indicated following acute myocardial infarction in clinically stable patients with signs of left ventricular dysfunction to improve survival and reduce hospitalizations for heart failure.

Sufficient experience in the treatment of patients with severe (NYHA class IV) heart failure immediately after myocardial infarction is not yet available. (See WARNINGS - Hypotension.)

GENERAL: In using ALTACE consideration should be given to the risk of angioedema (see WARNINGS).

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected ALTACE should be discontinued as soon as possible (see WARNINGS – Use in Pregnancy).

CONTRAINDICATIONS: ALTACE (ramipril) is contraindicated in patients who are hypersensitive to this drug, or to any ingredient in the formulation, or in those patients who have a history of angioedema.

WARNINGS: Angioedema: Angioedema has been reported in patients with ACE inhibitors, including ALTACE (ramipril). Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, ALTACE should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is involvement of tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy (including, but not limited to 0.3 to 0.5 mL of subcutaneous epinephrine solution 1:1000) should be administered promptly (see ADVERSE REACTIONS).

The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black than in non-black patients.

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

Hypotension: Symptomatic hypotension has occurred after administration of ALTACE, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (see ADVERSE REACTIONS). Because of the potential fall in blood pressure in these patients, therapy with ALTACE should be started under close medical supervision. Such patients should be followed closely for the first weeks of treatment and whenever the dose of ALTACE is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension and has been associated with oliguria, and/or progressive azotemia, and rarely, with acute renal failure and/or death.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of 0.9% sodium chloride. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion *in hypertensive patients.* However, lower doses of ALTACE and/or reduced concomitant diuretic therapy should be considered. *In patients receiving treatment following acute myocardial infarction, consideration should be given to discontinuation of ALTACE (see ADVERSE REACTIONS - Treatment Following Acute Myocardial Infarction, DOSING & ADMINISTRATION - Treatment Following Acute Myocardial Infarction).*

Neutropenia/Agranulocytosis: Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Several cases of agranulocytosis, neutropenia or leukopenia have been reported in which a causal relationship to ALTACE cannot be excluded. Current experience with the drug shows the incidence to be rare. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and/or renal disease.

Use in Pregnancy: ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ALTACE should be discontinued as soon as possible.

PRECAUTIONS: Renal Impairment: *As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.*

Use of Altace should include appropriate assessment of renal function.

ALTACE should be used with caution in patients with renal insufficiency as they may require reduced or less frequent doses (see DOSAGE AND ADMINISTRATION). Close monitoring of renal function during therapy should be performed as deemed appropriate in patients with renal insufficiency.

Anaphylactoid Reactions during Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g. polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agents.

Anaphylactoid Reactions during Desensitization: There have been isolated reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitization treatment with hymenoptera (bees, wasps) venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they have reappeared upon inadvertent rechallenge.

Hyperkalemia and Potassium-Sparing Diuretics: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials treated with ALTACE. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was not a cause of discontinuation of therapy in any hypertensive patient. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia or other drugs associated with increases in serum potassium (see PRECAUTIONS – Drug Interactions).

Surgery/Anesthesia: In patients undergoing surgery or anesthesia with agents producing hypotension, ALTACE may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it may be corrected by volume repletion.

Aortic Stenosis: There is concern, on theoretical grounds, that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Patients with Impaired Liver Function: Hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with ACE inhibitors in patients with or without pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug.

Elevations of liver enzymes and/or serum bilirubin have been reported with ALTACE (see ADVERSE REACTIONS). Should the patient receiving ALTACE experience any unexplained symptoms particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigations be carried out. Discontinuation of ALTACE should be considered when appropriate. There are no adequate studies in patients with cirrhosis and/or liver dysfunction. ALTACE should be used with particular caution in patients with pre-existing liver abnormalities. In such patients baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

Nursing Mothers: Ingestion of a single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, ALTACE should not be administered to nursing mothers.

Pediatric Use: The safety and effectiveness of ALTACE in children have not been established; therefore use in this age group is not recommended.

Use in Elderly: Although clinical experience has not identified differences in response between the elderly (>65 years) and younger patients, greater sensitivity of some older individuals cannot be ruled out (see *ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).*

Patient Alertness: ALTACE may lower the state of patient alertness and/or reactivity, particularly at the start of treatment (see ADVERSE REACTIONS).

Cough: A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of ALTACE, has been reported. Such possibility should be considered as part of the differential diagnosis of cough.

Drug Interactions: Diuretic therapy: Hypotension may result but can be minimized by discontinuing diuretic or increasing salt intake prior to ramipril treatment and/or reducing initial dose. Agents increasing serum potassium: Use potassium sparing diuretics with caution and monitor frequently. Agents causing renin release: ALTACE antihypertensive effect increased. Lithium: Lithium levels may be increased. Administer lithium with caution and monitor levels frequently. Antacids: The bioavailability of ALTACE and the pharmacokinetics of ramiprilat were not affected. Digoxin: No change in ramipril, ramiprilat or digoxin serum levels. Warfarin: The co-administration of Altace with warfarin did not alter the anticoagulant effects. Acenocoumarol: No significant changes. Non-steroidal anti-inflammatory agents (NSAID): The antihypertensive effects of ACE inhibitors may be reduced with concomitant administration of NSAIDs *(e.g. indomethacin).*

ADVERSE REACTIONS: *Essential Hypertension.* Serious adverse events occurring in North American placebo-controlled clinical trials with ALTACE monotherapy in hypertension (n=972) were: hypotension (0.1%); myocardial infarction (0.3%); cerebrovascular accident (0.1%); edema (0.2%); syncope (0.1%). Among all North American ALTACE patients (n=1244), angioedema occurred in patients treated with ALTACE and a diuretic (0.1%).

The most frequent adverse events occurring in these trials with ALTACE monotherapy in hypertensive patients (n=651) were: headache (15.1%); dizziness (3.7%); asthenia (3.7%); chest pain (2.0%); nausea (1.8%); peripheral edema (1.8%); somnolence (1.7%); impotence (1.5%); rash (1.4%); arthritis (1.1%); dyspnea (1.1%). Discontinuation of therapy due to clinical adverse events was required in 5 patients (0.8%).

In placebo-controlled trials, an excess of upper respiratory infection and flu syndrome was seen in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ALTACE patients, with about 4% of these patients requiring discontinuation of treatment. Approximately 1% of patients treated with ALTACE monotherapy in North American controlled clinical trials (n=972) have required discontinuation because of cough.

Treatment Following Acute Myocardial Infarction

Adverse events (except laboratory abnormalities) in a controlled clinical trial of post-AMI patients with clinical signs of heart failure considered possibly/probably related to ALTACE and occurring in more than 1% of stabilized patients (n=1004) were: hypotension (10.7%); increased cough (7.6%); dizziness/vertigo (5.6%); nausea/vomiting (3.8%); angina pectoris (2.9%); postural hypotension (2.2%); syncope (2.1%); heart failure (2.0); severe/resistant heart failure (2.0%); myocardial infarct (1.7%); vomiting (1.6%); headache (1.2%); abnormal kidney function (1.2%); abnormal chest pain (1.1%); diarrhea (1.1%).

Isolated cases of death have been reported with the use of ramipril that appear to be related to hypotension (including first dose effects), but many of these are difficult to differentiate from progression of underlying disease (see WARNINGS - Hypotension). Discontinuation of therapy due to adverse reactions was required in 368/1004 post-AMI patients taking ramipril (36.7%), compared to 401/982 patients receiving placebo (40.8%).

Clinical Laboratory Test Findings: increased creatinine; increases in blood urea nitrogen (BUN); decreases in hemoglobin or hematocrit; hyponatraemia; elevations of liver enzymes, serum bilirubin, uric acid, blood glucose; proteinuria and significant increases in serum potassium.

DOSAGE AND ADMINISTRATION: *Essential Hypertension* Dosage of ALTACE (ramipril) must be individualized. Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation and salt restriction. The dosage of other antihypertensive agents being used with ALTACE may need to be adjusted.

Monotherapy: The recommended initial dosage of ALTACE in patients not on diuretics is 2.5 mg once daily. Dosage should be adjusted according to blood pressure response, generally, at intervals of at least two weeks. The usual dose range is 2.5 to 10 mg once daily. A daily dose of 20 mg should not be exceeded. In some patients treated once daily, the antihypertensive effect may diminish towards the end of the dosing interval. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dose, or an increase in dose should be considered. If blood pressure is not controlled with ALTACE alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of ALTACE.

Concomitant Diuretic Therapy: Symptomatic hypotension occasionally may occur following the initial dose of ALTACE and is more likely in patients who are currently being treated with a diuretic. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with ALTACE to reduce the likelihood of hypotension (see WARNINGS). If the diuretic cannot be discontinued, an initial dose of 1.25 mg ALTACE should be used with careful medical supervision for several hours and until blood pressure has stabilized. The dosage of ALTACE should subsequently be titrated (as described above) to the optimal response.

Use in Renal Impairment: For patients with a creatinine clearance below 40 mL/min/1.75m² (serum creatinine above 2.5 mg/dL), the recommended initial dose is 1.25 mg ALTACE once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 5 mg. In patients with severe renal impairment (creatinine clearance below 10 mL/min/1.75m²) the maximum total daily dose of 2.5 mg ALTACE should not be exceeded.

Treatment Following Acute Myocardial Infarction

Initiation of therapy requires consideration of concomitant medication and baseline blood pressure and should be instituted under close medical supervision, usually in a hospital, three to ten days following an acute myocardial infarction in haemodynamically stable patients with clinical signs of heart failure.

The recommended initial dosage of ALTACE is 2.5 mg given twice a day (b.i.d.), one in the morning and one in the evening. If tolerated, and depending on the patient's response, dosage may be increased by doubling at intervals of one to three days. The maximum daily dose of ALTACE should not exceed 5 mg twice daily (b.i.d). After the initial dose of ALTACE, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. If the patient becomes hypotensive at this dosage, it is recommended that the dosage be lowered to 1.25 mg b.i.d. following effective management of the hypotension. (see WARNINGS - Hypotension).

Patients who have been fluid or salt depleted, or treated with diuretics are at an increased risk of hypotension (see WARNINGS -Hypotension). An excessive fall in blood pressure may occur particularly in the following: after the initial dose of ALTACE, after every first increase of dose of ALTACE, after the first dose of a concomitant diuretic and/or when increasing the dose of the concomitant diuretic. If appropriate, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension (see PRECAUTIONS - Drug Interactions). Consideration should be given to reducing the initial dose to 1.25 mg of ALTACE in these patients.

Use in Renal Impairment: In patients with impaired renal function (creatinine clearance of 20-50mL/min/1.73m² body surface area), the initial recommended dosage is generally 1.25 mg of ALTACE once daily. This dosage may be increased with caution up to 1.25 mg of ALTACE twice daily, depending upon clinical response and tolerability.

Insufficient data is available concerning the use of ramipril following acute myocardial infarction in patients with heart failure and severe renal failure. (see ACTION & CLINICAL PHARMACOLOGY - Pharmacokinetics & Metabolism, PRECAUTIONS - Renal Impairment).

Use in Hepatic Impairment: Insufficient data is available concerning the use of ramipril following acute myocardial infarction in patients with heart failure and hepatic dysfunction. Dose reduction and careful monitoring of these patients is required (see ACTIONS & CLINICAL PHARMACOLOGY - Pharmacokinetics & Metabolism, PRECAUTIONS -Patients with Impaired Liver Function).

AVAILABILITY: No. 4 hard gelatin capsules:

- 1.25 mg (white/yellow);
- 2.5 mg (white/orange);
- 5 mg (white/red);
- 10 mg (white/blue).

ALTACE capsules 1.25 mg, 2.5 mg, 5 mg and 10 mg are packaged in cartons of 30 (2 x 15 blister-packed) capsules.

Product monograph available upon request.

References:

1. Altace (ramipril) Product Monograph, Hoechst Marion Roussel Canada Inc. **2.** Todd PA, Benfield P. *Drugs* 1990; 39 (1): 1-27. **3.** Kanedo Y, *Am J Cardiol* 1987; 59: 86D-91D. **4.** The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. *Lancet* 1993; 342: 821-828. **5.** Bender N, *Clin Physiol Biochem* 1990 8 (Suppl 1): 44-52.

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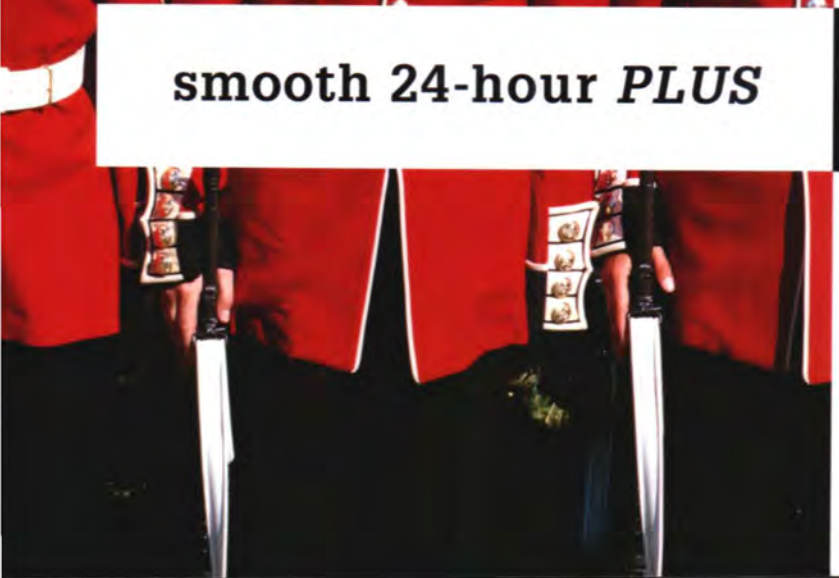

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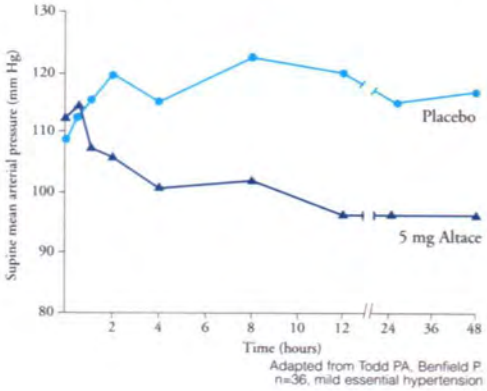

Adapted from Todd PA, Benfield P. n=36, mild essential hypertension

- **Effective blood pressure control even during the last stages of the dosing period[2]**

More than 80% of patients respond to ≤5 mg once daily[3]

† Altace is indicated in the treatment of essential hypertension, normally when beta-blockers and diuretics are inappropriate. Like other ACE inhibitors, Altace is not recommended for pregnant or lactating women and should be used with caution in patients with renal insufficiency.

Product monograph available to physicians and pharmacists upon request.

References: 1. Todd PA, Benfield P. *Drugs* 1990; 39: 1-27. **2.** Altace (ramipril) Product Monograph, Hoechst Marion Roussel Canada Inc. **3.** Carré A, et al. *Clin Physiol Biochem* 1992; 9: 105-112.

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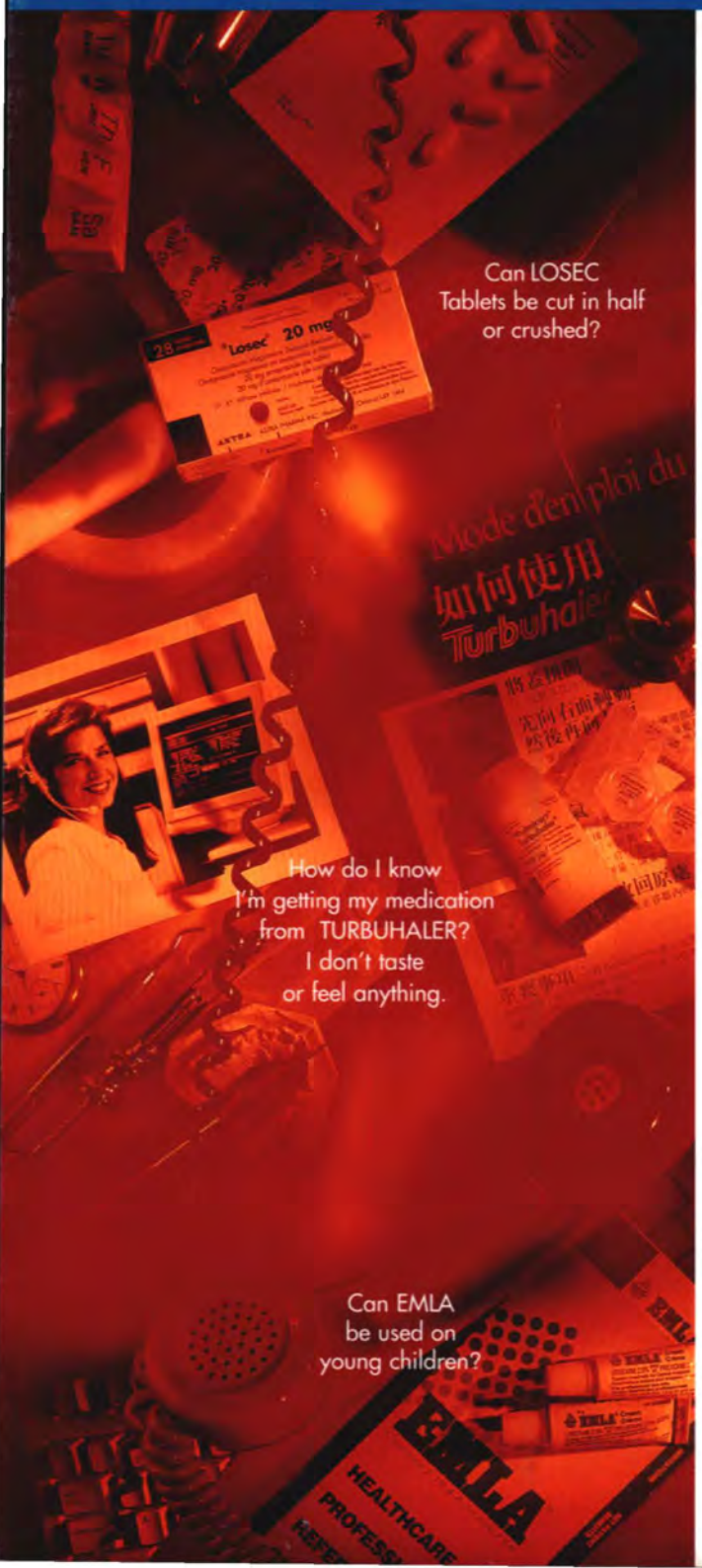

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