PROCEEDINGS

ST VINCENT'S CLINIC, SYDNEY

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Editorial

The Sandra David Orations

Dr John H. O'Neill MD, FRACP

EDITOR, PROCEEDINGS

FOLLOWING her death in 1994, annual scientific orations have been held at St Vincent's Clinic to commemorate the life of Sandra David, beloved eldest daughter of Joe and Edith David, a member of the Congregation of the Sisters of Charity and for some time a missionary in the Highlands of New Guinea. Published in this issue of *Proceedings* are abridged versions of the 1997 and 1998 Sandra David Orations.

Although time has marched on since the 1997 oration entitled "Crisis in Health Care" by Professor Douglas Tracy, it is generally conceded that the health crisis has, in fact, worsened and Professor Tracy's clear analysis of the crisis and message to those involved in formulation of health policy is even more relevant today than at the time he wrote the manuscript.

Ethics Committees have become increasingly involved in medical research but at times have been viewed by researchers as a negative rather than a positive influence to scientific and medical advancement. Dr Gerald Gleeson, graduate of the Universities of Cambridge and Leuven (Belgium), is a priest who teaches Philosophy and Christian Ethics at the Catholic Institute of Sydney. He is a research associate in Bioethics at the John Plunkett Centre for Ethics in Health Care. The abridged version of his 1998 oration provides insight into the principles of ethics and, in particular, their application to the rapid advances which are occurring daily in the field of medical genetics. It is my personal view that ethics principles, as espoused by Dr Gleeson, are essential to the practice of Medicine.

A state of the art Medical Resonance Imaging (MRI) scanner was installed at St Vincent's Clinic in 1994. With time and improved software MRI scanning has seen increasing applications. The article by Dr Sharyn Rothwell, radiologist, outlines the value of MRI scanning in the diagnosis and management of diseases of the pancreas and biliary tree. MRI scanning can sometimes be of diagnostic value in the management of difficult ankle sprains, a common injury of particular concern to elite athletes. The modern management of difficult ankle sprains is capably dealt with in the article by Dr Martin Sullivan, Orthopaedic Surgeon.

The three interlocking triangles forming the emblem of St Vincent's Clinic emphasise its aims of excellence in patient care, medical teaching and clinical research. The highly successful fundraising work of the Ladies Committee of St Vincent's Private Hospital (SVPH) and Clinic Foundation is vital to the support of clinical research at the Clinic. The original work by Dr Christopher Hayward which forms part of his article on Women and Heart disease together with the scientific research work on human atherosclerotic lesions (published in *Cardiovascular Research, 1998*) by Dr Bobryshev were partly funded in this way. The Committee fully supported the important studies by Dr Henshall et al on head and neck squamous cell carcinoma. Future issues of *Proceedings* will continue to feature a selection of completed research projects which were approved by the St Vincent's Clinic Foundation and monetarily supported by the Ladies Committee of SVPH and Clinic Foundation.

St Vincent's Clinic Foundation Sandra David Oration

"The Crisis in Health Care"

By Emeritus Professor G. Douglas Tracy, AO

Outline Of The Crisis

IT is not hard to find media headlines appropriate to the title "Crisis in Healthcare", for it is now almost a weekly news item (Figures 1 and 2). Why is there a health crisis? **Paradoxically it is the very success of modern medicine that has given rise to the current problems, because our potential for diagnostic and therapeutic interventions has outgrown our capacity to pay for them.**

Through the 20th Century there has been proliferation of new therapies, multiplying technological advances in diagnosis and treatment, and a swelling tide of new pharmacological agents. The monthly MIMS which arrives on doctors' desks lists more than 4,000 prescribable medications – most of which were unknown when I was a medical student.

The rapid expansion of clinical knowledge can be seen from the proliferation of specialties in the last 25 years. When I graduated from medical school in 1948, the teaching hospitals were staffed by general physicians, general surgeons, and just a few surgical specialists like eye, ear, nose and throat. Now the list includes 33 named specialties with new ones accruing every year.

Surgical advances, employing ever more costly technology, include:

1. Implant surgery for replacement of joints, arteries, corneas, etc.
2. Transplant surgery for new kidneys, heart, lungs, liver and other organs.
3. Microsurgery, first in ear operations but now for brain surgery and reconstruction of other parts of the body.
4. Cardiopulmonary bypass surgery.
5. Image guided surgery using an image intensifier or steriotactic localisation in orthopaedic or brain surgery.
6. Endoscopic surgery for minimally invasive operations through narrow tubes with robotic instruments and video magnification.

Technological advances include costly imaging methods such as the CT scan, ultrasonic imaging, magnetic

This is an abridged version of the Sandra David Memorial Lecture, "The Crisis in Health Care" delivered in 1997 by Emeritus Professor G. Douglas Tracy AO, FRCS, FRACS, FACS (Hon), FCSSA (Hon), FRCSED (Hon), FRCPS (Glasg) (Hon), Professor of Surgery, St Vincent's Clinic

resonance imaging, radionuclide imaging- all of which increase greatly the precision of clinical diagnosis and the accurate localisation of pathology, unimaginable 20 years ago.

All these advances occur first in our teaching centres – hospitals where the full range of medical specialties are found. As each new technology is introduced the gap grows between teaching centres and smaller hospitals, which are losing the struggle to keep up with technological advance.

Advancing technology is a global phenomenon escalating health expenditure that creates cost pressures in all countries, as seen in cost comparisons with countries which share a common tradition in health education and clinical practice. (Figures 3 and 4). One can see the escalating costs in dollars per head of population, with the USA easily at the top, Australia well below with New Zealand lower again. As a percentage of gross domestic product, the USA is still highest and the slope for the USA continues to go upwards through 14.5% of GDP, causing such problems that the US has now entered a period of convulsive change in their predominantly private health care system.

In Australia health care expenditure has actually been held to a steady 8.5% of GDP since the mid 1980s. This control of expenditure in Australia for 15 years has had uneven repercussions because some sectors have grown irresistibly, causing severe compression of other sectors of the expenditure pie, as global expenditure is constrained. The rapid increase in expenditure on new pharmaceuticals (which shows no sign of levelling off) and in Medicare payouts, have only been contained within constant global expenditure by disproportionate compression of allocation to hospitals – especially teaching hospitals, which are seen as the most expensive. **However, teaching hospitals should be seen as the living heart of our healthcare system, providing the education and training of the medical, nursing and other health professions, and the factory for new advances in health care.**

Figure 1. *The crisis in health care*

Figure 2. *The crisis in health care*

Study of the sources of health revenue (Figure 5) shows that the Medicare levy contributes less than 10% of health funding, which dispels another government promoted misconception. The contributions from State and Federal funding are locked in a struggle called "cost shifting", while the large unheralded contribution from the private sector continues to grow.

Most teaching hospitals are suffering from the cost containment with

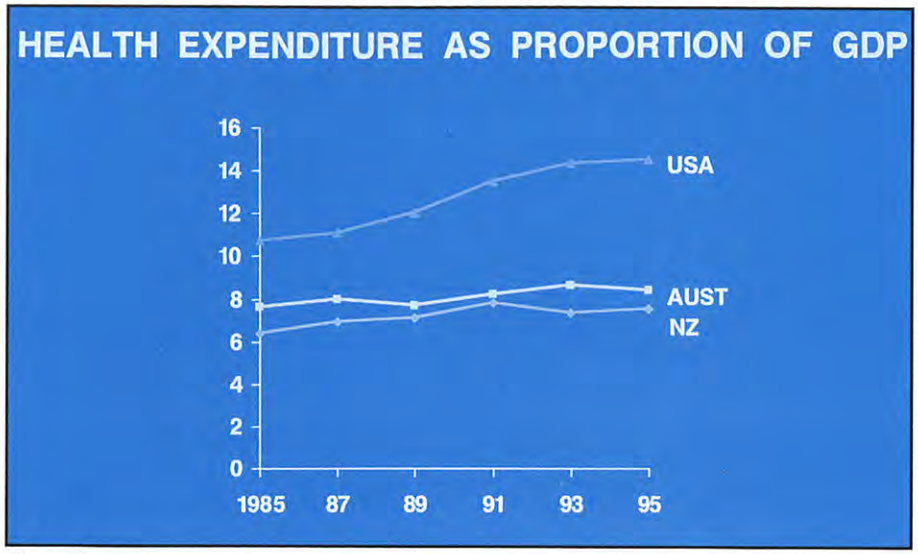


Figure 3.

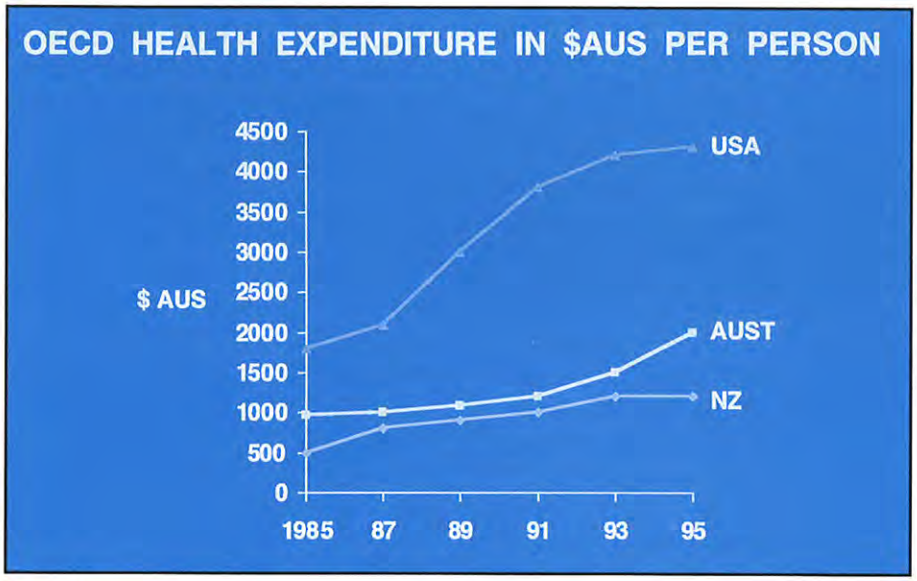


Figure 4.

significant impact on staff morale, as the hospitals experience the following depressing restrictions: bed closures, staff shortages, technology lag, rationed operating sessions, "low activity days", reduced intensive care capacity, outpatient clinic closures, deferment of booked admissions and waiting lists.

Health Policy Misinformation

Instead of admitting to the public that rationing is firmly in place, a statement that would be honest but electorally unpalatable, governments try to persuade us that their cost saving objectives are actually beneficial. Health platitudes uncritically accepted by a long suffering public include the following: "Australia still has the best health service in the world". This assertion, not surprisingly well received by my profession, is not only unprovable but almost certainly untrue.

Another campaign widely propagated is to criticise teaching hospitals for unwarranted zeal to acquire the latest technology and, further, even to question whether the latest advances are worthwhile in health outcomes. For example, Federal Health Minister Michael Woolridge has made the following statement, "In the 19th Century we built cathedrals, but in the 20th Century we have built large teaching hospitals – as technological shrines to immortality", an oblique criticism of high cost procedures like transplantation to extend human life.

When doctors complain about the effects of cost cutting, they are likely to encounter multipronged criticism of the medical profession, for such things as : excessive incomes, maldistribution of doctors (causing inadequate rural services), inappropriate clinical priorities with too little preventative medicine, and the deplorable state of aboriginal health.

The principal reason for much "maldistribution" of the medical workforce is the lack of resources in small country hospitals. The reluctance of specialists to practice in remote regions is not because of aversion to country living, but because of reluctance to work without the aid of supporting specialists and diagnostic technology. Why would an orthopaedic surgeon seek to operate without an image intensifier (necessary to safely guide the insertion of orthopaedic nails and wires) and without the capacity to employ modern developments in his specialty like joint replacements, or without the supporting specialists upon which safe surgery depends?

The issue of preventive medicine – or alleged lack of it – should be viewed in the context that 80% of the causes of premature death in our society can squarely be attributed to social behaviour that is either self indulgent or self destructive: too much food causing obesity, too little exercise causing reduced cardiovascular fitness, tobacco consumption, alcohol abuse, drug abuse, road trauma and suicide. Huge health benefits would follow improvements in these behaviours, but how much have they to do with the medical profession?

The sad state of health of our aboriginal people is due to poverty, social isolation and deprivation with its diffuse sequelae, including: unemployment, lack of housing, lack of education, inadequate nutrition, inadequate clean water, lack of hygiene and alcohol and substance abuse. Once again it must be asked how these matters can be countered by the medical profession?

The Benefits Of Advance In Health Care

What of the widely canvassed notion that all of this specialisation and advanced technology has made no real difference to the outcomes of illness?

There is plenty of evidence of improvements in outcomes of treatment throughout this century. For surgical examples consider the mortality of war wounds. In World War I a quarter of all wounds were fatal. This mortality was halved by World War II with improvements in the management of tissue injury and infection. Blood transfusion and antibiotics reduced the mortality by another quantum leap in the Korean War to about a 5% mortality. In the Vietnam War wound mortality had halved again notwithstanding the increased killing power of rapid fire weapons of higher muzzle velocity. This improvement was directly attributable to rapid evacuation by helicopters, so that the median time between wounding in the battle field and reception in the evacuation hospitals was 27 minutes! This shows that time alone can make the difference between life and death in cases of severe injury.

Time is crucial also in arterial injuries, where restoring the circulation in less than three hours might mean a normal limb, while after six hours the rate of amputation becomes high. Amputation rates after gun shot wounds to the popliteal artery, the main artery behind the knee, were 30% in the World War II. With the new techniques of artery repair in the Korean War this fell to 8%. In the Royal Victoria Hospital in Belfast – where popliteal artery injuries are common from the infamous practice of "knee capping", the amputation rate is 0%. The reason for this is that all were treated in the Royal Victoria Hospital in Falls Road in Belfast, with the average time between the injury and treatment a mere 17 minutes, so that in every case the leg was saved. I wonder if any major injury could be treated in an Australian Hospital within 17 minutes! **We still need to learn in civilian injuries that major artery bleeding or blockage should be monitored by stop watch, so vital is the influence of time in survival of life or limb.**

Improvement in treatment outcomes can also be seen in the mortalities of some common operations during my own surgical career. In such things as gallbladder removal, colon removal and major artery operations, there has been almost a 10 fold improvement in survival, not only from better technique

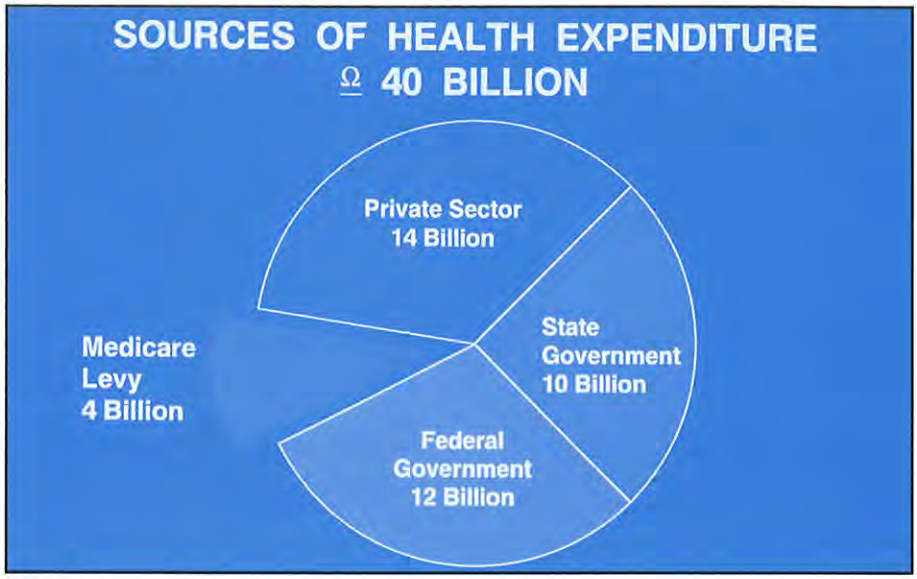


Figure 5.

but from the huge improvements in anaesthesia, intensive care, supportive therapy with support of breathing, body temperature, fluid balance and cardio-vascular homeostasis – supplied by the combined skills of all the specialties brought to bear in the multi-disciplinary teams that teaching centres provide.

Cost Benefit Of Transplant Surgery

Australia is famous for its success with transplants, most of which show better than 80% 5 year survival for the treatment of organ failures which would otherwise be fatal (Figure 6). These excellent results are obtained by costly multi-disciplinary effort, so that critics are quick to point out that the money expended would save more lives if instead it were used to clean water supply for an outback community. Where is the evidence that if we spent nothing on transplant surgery, funding for a water supply to such communities would thereby occur? The same argument could well be made when the government buys a new submarine or F18 fighterbomber. Surely health professions cannot be taxed with these expenditure priorities. More lives could be saved by transplantation if Australians were more generous with organ donation. We have one of the lowest rates of OECD countries for organ donation at about 10 per million of population. In the USA the figure is twice as high and in Spain three times higher.

Why Teaching Hospital Cutbacks Have Negative Impact On Health Care

Criticisms of teaching hospitals are misplaced for that is where better standard medical care is found. Although there is not much data from small hospitals to make comparisons, when such studies have been made (e.g. by Matheson in the United Kingdom and by Luft in the USA) the results of treatment in the teaching centre is superior. Studies show that even in such things as stroke, a specialised stroke unit obtains better results with regard to mortality, extent of residual disability, hospital stay and rehabilitation than is achieved by stroke victims admitted to an ordinary hospital. A recent study reported in the Journal of American Medical Association showed a 20% better survival from major illness in teaching centres when compared with non teaching hospitals.

Sir William Osler, one time Professor of Medicine at Oxford and Magill Universities and one of the famous four who founded the John Hopkins School of Medicine, stated, "The work of an institution in which there is no teaching is rarely first class". I think further that a hospital that does not do research is rarely first class. Teaching and research provide unrelenting stimulus to be abreast of everything known about the subject of research or teaching, as gaps in knowledge will be quickly uncovered.

Teaching centres have been cut back in New South Wales and we have now too few. Political imperatives have dominated hospital planning in our state for years resulting in the building of small hospitals in new electorates or growth areas justified on the theme of "distributional equity". This is always a popular vote winning promise for every new Health Minister. So we have repeatedly missed the opportunity to strengthen existing hospitals by instead building new small ones. "Beds for the West" has been the popular slogan for the last 25 years and has provided an excuse for closing many hospitals in older Sydney – but without matching development in the western growth areas which are still under supplied. Even at Westmead, a teaching centre built to fill a crucial need, 150 beds in that institution have never been opened. Liverpool and Nepean have finally become teaching hospitals, which will lift their standard, but are still under resourced in favour of new smaller hospital developments. Government policy for a new hospital in every electorate means now that we have too many acute beds – mostly in small hospitals. At the same time it is acknowledged that we have too few beds for the care of the elderly and chronically infirm, for which many of these small hospitals would better be dedicated. We have more than twice as many acute general hospitals in Sydney as Melbourne, and nearly three times as many country hospitals in New South Wales as in Victoria. So our health system flounders from lack of vision and inadequate understanding of the needs.

Health Planning For The Future

George Washington, in his farewell address, gave warning to the American people of the frailty of democratic government with the following statement, "In proportion as the structure of government gives forth to public opinion, it is essential that public opinion should be enlightened".

We are so far along the wrong track there should be a commission of inquiry like the Murray Commission for education at the end of World War II. Lack of cohesion between State and Federal authorities and between departments of health and education in our teaching hospitals leaves us with little hope for reform until the health system is guided by a health advisory commission which has predominant membership not of politicians and bureaucrats, but of leaders in the health care faculties and health professions conversant with the issues of health care and its delivery. What could they do? They could first define and publish objectives that inform the general population and as well encourage community involvement and response. Too many present developments seem to be conceived in secrecy and thrust upon a surprised constituency before there is time to respond.

1996 STATISTICS
TRANSPLANTS SURGERY IN AUSTRALIA

ORGAN	YEAR STARTED	TOTAL	5 YEAR SURVIVAL
Kidney	1963	10,368	87%
Liver	1968	1,113	73%
Heart	1968	922	70%
Bone Marrow	1975	4,907	50%

Figure 6.

I have had the opportunity to work in countries, including the United Kingdom, the United States, Hong Kong, New Zealand and South Africa. I was struck by the substantial differences in the hospital systems in each of these countries – as there is between the systems in Victoria and New South Wales – differences which seem to have earned little attention from health authorities. The reasons for this are explicable by a phenomenon encountered in every country where, despite copious criticisms, all felt that their own health service was the best available. It is said that familiarity breeds contempt, but in fact it breeds loyalty – a noble virtue, but loyalty, like love, is blind. This explains why there are more than three million people living in Melbourne who would not prefer to be living in Sydney. Only loyalty could give rise to this inexplicable preference!

The concept of "distributional equity" which led to the widest possible dispersion of hospitals in Sydney and New South Wales, is given no priority in countries like the United States or even New Zealand. In Houston, Texas – a relatively new city which has grown since the discovery of the oil riches of Texas – almost all of their hospitals share a common location, with 15 hospitals and about 12,000 beds. These include many leading world centres including the M.D. Anderson Tumour Clinic, the Texas Heart Centre and the Methodist Hospital made famous by the world's most famous living surgeon, Dr Michael de Bakey.

A more relevant comparison might be with New Zealand, where health expenditure is about one third less than in our country. In the province of Waikato with a population of about one quarter of a million, there is a single hospital at Hamilton with 1200 beds, a teaching centre offering heart surgery, radiotherapy and all the medical care available in a major teaching centre. This is, however, the only hospital in the province. In comparison the Riverina District of New South Wales which also has about one quarter of a million people has 46 hospitals none of which is a teaching hospital and from where many patients still have to be sent to a metropolitan centre for such common procedures as coronary bypass surgery or radiotherapy for the treatment of cancer.

In New South Wales the principle of "distributional equity" does not apply to paediatric hospitals for the treatment of sick children. There are just two for New South Wales and only one in Victoria, The Royal Children's Hospital. This is sited in the immediate environment of Melbourne University, the Royal Melbourne Hospital and the Walter and Eliza Institute for Medical Research, proximity which offers incalculable advantage to the linked hospitals, which

I think would be oblivious to health planners in New South Wales. Rational hospital planning calls for consolidation of health resources rather than dispersal. Expensive technological facilities can only be afforded in large centres where they will be fully utilised by the required critical mass of referred patients.

The acknowledged shortage of teaching resources in New South Wales would be relieved if we followed the New Zealand Model and created teaching centres in rural regions such as the Riverina, New England, Hunter, Illawarra, Central West, Canberra, which would only be affordable by closing small acute hospitals which clutter our health system, diluting the financial resources but able to provide only second rate service, hampered by all things that they complain about such as lack of doctors, lack of specialists, and lack of technology, all unaffordable in a multiplicity of small hospitals. There cannot be a centre for the optimum care of, for instance, heart attack in every hamlet in the nation.

The Effect Of The Health Crisis On St Vincent's

Despite a need unmet for teaching resources and growing patient demand, St Vincent's position in the eastern sector of Sydney has been targeted for cut-backs. Our crisis reached its climax with the surprise announcement to close St Vincent's General Hospital and amalgamate with St George. Because of predictable strong reaction from St George – a secular institution with its own 100 year history and traditions – this move had to be abandoned and we apparently have been given a reprieve which may yet save St Vincent's General as a teaching centre. There is quite a long way to go to recover that status, however, because of progressive cost cutting which has impacted on our teaching role in the following ways: reduction in beds from 650 to less than 300, closure of outpatients clinics, staff reductions, closure of operating theatres, reduced intensive care beds, planned "low activity days", repetitive deferment of booked admissions, and attempts to deflect "out of area patients" whose presence in teaching centres is possibly the best reflection of the reputation of that centre. These measures hit hardest the surgical services because most booked admissions are surgical and because rationing of operating rooms and shortage of intensive care beds creates further blocks. Cutting services to save expenditure would be self-defeating in the state of Victoria, because financial allocations there are linked to clinical productivity by their case mix formula, which has so far been resisted in the state of New South Wales.

Every young clinician appointed to a teaching hospital hopes to develop his or her career, and grow his or her skills and reputation, by experience in outpatient teaching clinics and from both teaching and research opportunities. If these ambitions are realised, he or she will look forward to admitting all patients to the hospital, which will be serviced best if he or she is geographically full time. To be diverted from this by having to admit patients to other hospitals, or by having rooms in other locations in a sort of urban itinerant practice, frustrates these aims, and retards potential academic contributions.

At this time in our history government exercises complete control, but what new clinical advance, new specialty or new technology was every introduced by government or its health department in any teaching hospital? At St Vincent's we have a history of many developments initially blocked by government, but which have come into being by the irrepressible energy of visionary people. The Sacred Heart Hospital owes its existence to Sister Dorothea and her public appeal for funding and to Sister Bernice we owe the Private Hospital and St Vincent's Clinic. Future historians might read the brass plate commemorating the opening of these institutions to gain the impression that they were opened by health ministers of supportive governments, but in truth these brass plates should read, "Opened in spite of government reticence and bureaucratic obfuscation through indomitable inspiration of Sisters of Charity, urged on by Christ's love", as well as by those visionary doctors like Harry Windsor and Douglas Miller with whom they shared a cohesive partnership.

Redefining Our Future Mission

Our Mission Statement describing the goals of St Vincent's Hospital includes one to achieve excellence in clinical care, teaching and research. Such excellence can only be attained by the achievement of recognisable attributes of first class clinical services. A teaching clinical service should exhibit most of the following attributes:

1. Ward units dedicated to a specialty with specialised nursing staff and allied health professionals.
2. Private and public beds which allows patient numbers adequate for clinical research.
3. Clinic offices, research labs and teaching rooms.
4. Daily access to operating theatres to minimise delays in treatment.
5. Teaching outpatient facilities for pre-admission workup, post operative follow-up and ambulant care.
6. Day surgery facility.
7. A home care program integrated with home nursing and local medical officers.
8. Staff numbers adequate for continuous research programs, clinical care, emergency and teaching rosters.
9. Secretarial staff for medical records, audit and publications.

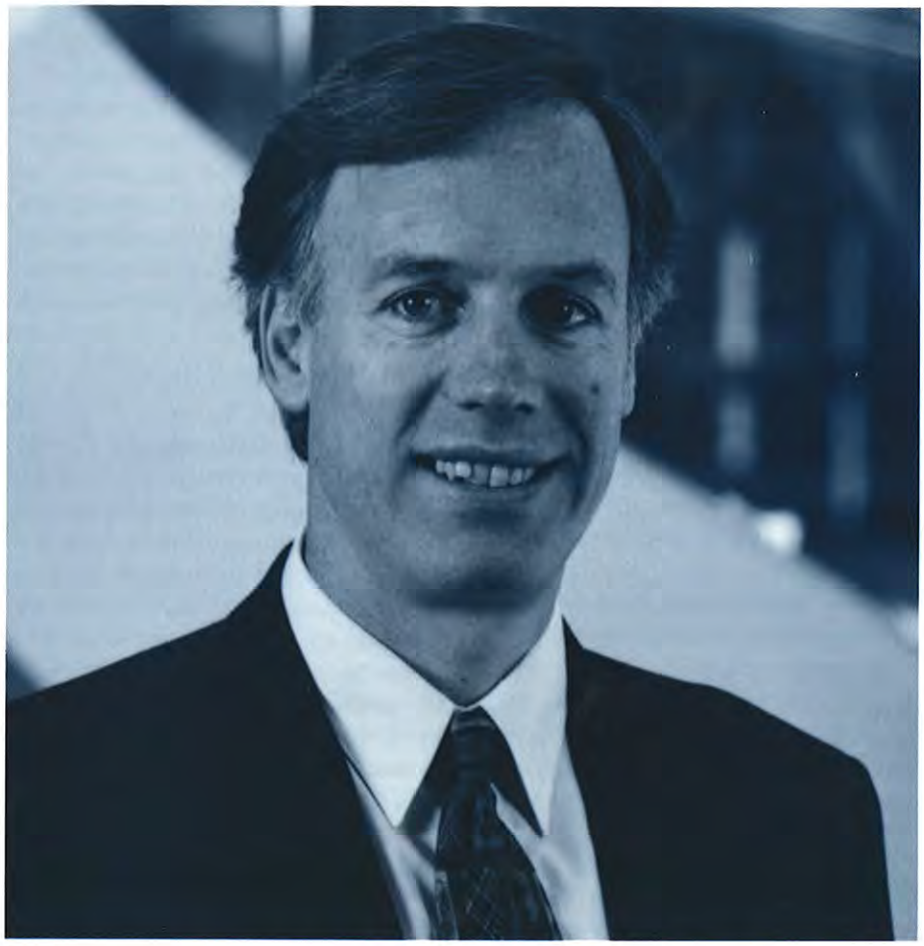
I must say that despite the disheartening developments of an era where cost containment has been the pre-emptive initiative in healthcare, I still feel optimistic for the future of the St Vincent's Hospital campus, a feeling reinforced as I look at the new vista of Victoria Street – the magnificent new Garvan Institute with its double helix staircase rising like a symbolic chrysalis out of a skeleton of two old buildings, the buildings named after the founding nuns – the restored dignity of the Cahill Building and the modern facade of the Aikenhead Building (to where I hope outpatient teaching clinics might one day return), then to the beautiful design of the Private Hospital and St Vincent's Clinic and finally to the serene elegance of the Sacred Heart Hospice.

Surely any enlightened government of the future will recognise the irreplaceable value of these institutions to the wider community of our state and realise that the future strength of health education, research and healthcare in New South Wales will to a large degree depend upon fostering such institutions, whose success will lead to inevitable growth, rather than planned reduction.

Ethics and the Advances in Genetic Medicine

By Rev. Dr. Gerald Gleeson

Introduction



WHEN there is discussion of the current advances in medical science, and especially in genetics, we often hear it said that "science is running ahead of ethics". There are at least three ways of interpreting this remark, each with different implications:

1. There is the rather crude interpretation that *ethics needs to catch up with science*. In relation to medical practice, this view holds that whatever can be done should be permitted, subject only to informed consent and autonomous decision making. So, for example, in the recent case of a woman who obtained sperm from the body of her dead husband (killed in an accident), Helga Kuhse the well-known Monash University bioethicist argued that no laws or rules of practice should prevent the woman using her dead husband's sperm to conceive a child artificially, if that was her considered and autonomous decision.

   This view assumes that ethical reasoning should give priority to individual rights and autonomous choice; the good outcome – e.g. a healthy child – is able to justify whatever means are needed to bring it about. On this view of ethics, known as utilitarianism, the rightness or wrongness of an action is determined by the judgment that its good consequences outweigh its bad consequences.

2. The remark that science is ahead of ethics may be intended to strike a cautionary note, suggesting that *contemporary science should slow down*; perhaps there should even be a moratorium on certain forms of research and experimentation, until all the ethical issues have been resolved. In this vein we may recall those few scientists who, in the wake of World War II and the use of atomic weapons, refused to engage in further nuclear research on the grounds that their results would inevitably be put to evil and destructive uses.

   Not all would agree with the judgment those few scientists made. Some argue that simply because knowledge is good in itself, it would wrong to put a stop to any form of research. How the research is used, they say, is a quite separate ethical issue. Others argue that because some scientists somewhere will continue research in controversial areas, it is better "we" do it with our ethical

This is an abridged version of the Sandra David Memorial Lecture, "Ethics and the Advances in Genetic Medicine" delivered in 1998 by Rev. Dr Gerald Gleeson, Catholic Institute of Sydney and Plunkett Centre for Ethics in Health Care

safeguards in place, rather than leave it to those working secretly in dubious places. (Few doubt that somewhere at present, some scientists are attempting to clone a human being.)

This debate highlights the truth that moral reasoning must consider more than just the consequences of action (assuming these can be reliably determined). Moral reasoning also bears upon *the moral character* of the human agent. Those scientists who discontinued their research were concerned about the kind of people they would become if they contributed to the development of nuclear weapons. Their sense of their own moral integrity required them not to cooperate, even from the safe distance of theoretical research.

3. Falling between these views is a less contentious and more helpful understanding of the relative progress of science and ethics. This view recognises that our ethical beliefs were formed in previous times, when we had only a limited ability to cure disease and improve the human condition. To say that "science is ahead of ethics" is to suggest that traditional ethical beliefs may not be sufficiently refined to enable us to evaluate the new possibilities generated by scientific progress. The implication is that *changed circumstances challenge us to clarify and refine our received moral wisdom.*

An example of the refinement and deepening of traditional understanding in changed circumstances is provided by the case of live organ donation. When a procedure like kidney donation by a live donor was first mooted, many ethicists argued that it could not be justified because it involved "mutilation", i.e. deliberate damage to the bodily integrity of a healthy person. Further reflection and debate, however, have led to a new understanding of what constitutes "mutilation", such that personal integrity and "wholeness" involves not merely one's physical body, but also one's experience of oneself in relationship. Some people cannot be "whole" persons, if they are prevented from being generous persons, and their generosity may even extend to the gift of bodily tissue or organs whose loss does compromise their functional integrity.

This example contains another important insight into the nature of ethics. Ethics is not only about outcomes and moral character, it is also about *the kinds of action* we take to achieve those outcomes. Intentionally harming a person by an act of mutilation is an inherently wrong kind of action, no matter what good it might be thought to serve. That's why torture and genital mutilation are never permissible. Nonetheless, our understanding of what constitutes inherently bad actions like mutilation is open to some further development, and this is why it has been possible for us to come to see why the removal of some organs and tissues (e.g. kidney or bone marrow) need not constitute mutilation in the morally reprehensible sense.

The different attitudes (1 to 3 above) to progress in science and ethics which I have noted, along with the different views about what is involved in thinking ethically, are all at work in contemporary debates about the Human Genome Project and about the uses of genetic manipulation in medicine. Attitudes range from enthusiasm to caution to fear.

One of the current headline issues is human cloning. In the space of a year or two, changes of attitude are already apparent. In the first reports of the successful cloning of the sheep named "Dolly", eminent scientists said, "Of course, human cloning would never be undertaken. This technique is only for breeding animals". Reports of further successful cloning were accompanied by comments that, "Human cloning should not be undertaken yet, because there is so much popular opposition to it." A little later one US scientist, a Dr. Seed, announced that he was planning to establish a centre for human cloning as soon as possible. More recently still, in a "Hypothetical" debate on national television, our own Professor John Shine agreed that the cloning of a human being would inevitably be attempted before too long. In short, the move from rejection of a procedure to openness to its use to actual acceptance, however reluctant, is well under way in relation to human cloning, just as the same pattern has been seen in relation to contraception, abortion, euthanasia, and other issues.

How then should we think ethically about advances in genetic medicine? Is it simply a matter of ethics needing to catch up or should the scientists be asked to slow down? What are the basic goods at stake in genetic research and its application? What counts as benefit and harm in this area? How can we determine what would be appropriate and what would be inappropriate kinds of research and treatment? If further refinement in our ethical thinking is needed, what form should this refinement take?

In order to highlight these questions, we need to reflect on the nature of ethics and then on what constitutes advance and decline in moral matters (refer to the boxed text). We will then be in a position to consider the relationships between technology, ethics, and the good of the human person. My purpose is not to resolve the many ethical puzzles we face today, but to make some of the philosophical distinctions which I believe will help us to approach these questions in a clearer light.

Science, Medicine and Ethics: Tensions between different spheres of human endeavour

Ethical progress requires deeper insight into the significance of *what we do* in relation to *who we are* as human beings. It involves refining our thinking about the right and wrong ways to feel, judge and act, and so to advance in respect for others, especially the most vulnerable, and in regard for the world we jointly inhabit. What then are the distinctive challenges which recent advances in medical science, especially in genetics, make to our received ethical understanding?

In order to bring this question into focus it is important once more to distinguish between different spheres of human activity, each with their proper goals and values. As we will see, our most difficult ethical questions often concern the tensions between the goals of different spheres of activity. Three such spheres are specially relevant to our topic:

1. There is **pure or fundamental science**, whose goal is knowledge for its own sake. The primary value at stake here is *truth*. The criteria for the evaluation of science as good, include the soundness of its methodology, the

elegance of its theoretical basis, and its predictive power. Physics and molecular biology are paradigms of fundamental science.

2. There is **applied science and technology**, whose goals include measurement and manipulation. Technologies are evaluated as good, not so much in themselves, but chiefly insofar as they are instrumental to the attaining of some other good. The primary value at stake here is *effectiveness* in relation to a desired end. Technologies for testing water for contamination, or for gene manipulation, find their value in relation to the goals for which they are undertaken. (One of the most unsatisfactory features of Sydney's recent water troubles arose from uncertainties about the accuracy and the goals of testing, and about the significance of the test results for human health.)
3. There is, of course, clinical medicine itself, whose goals are to cure and alleviate illness, or to maintain satisfactory levels of health. The primary values at stake here are *life* and *health*, as aspects of the good for the human person. Good medicine focuses on the good of the patient as a whole person, and presupposes a rightly ordered relationship between doctor and patient (which means open and sensitive communication, appropriate disclosure of information, and so on.).

Each of these spheres of activity involves ethical judgments in its own right:

- the Pure Scientist has to reflect on the appropriateness of his chosen field and of the uses to which his results may be put.
- the Technologist should be concerned with the rightness or wrongness of the ends to which his techniques will be used.
- the Doctor is obliged by the canons of good practice to neither over-treat nor under-treat the patient, for good medicine always treats the particular person, not a disease in general.

In each case, ethical reflection turns less on technical questions arising within the sphere of activity, and more on deeper questions about one's *human engagement* in the sphere of activity. One must ask: Is this how a fine human being would act? Is this what a just, faithful, and prudent person would do? Would these activities be respectful of the human person or would they "instrumentalise" a person, or treat a fellow human being as an "object" of manipulation?

These ethical questions become even more pressing when tensions arise between the goals of different spheres. In the context of medicine, for example, there is often a tension between the goals of research, pursuing the good of knowledge, and the goals of clinical practice, serving the health of a particular patient. This tension can be especially acute for someone who is both doctor and researcher in relation to the same patient. In the context of advances in genetics, further tensions arise because both genetic information about a patient and treatment by genetic manipulation often have implications for many other people in addition to the original patient. Clearly tensions may arise between what is good for the particular patient and what is good for the wider society and for future generations.

What's new sbout genetic research?

There is something quite new and distinctive about genetic research, as exemplified by the Human Genome Project. Like all medical research, this project aims at the discovery of a truth to be put at the service of human health. Genetic medicine holds out the hope for new kinds of treatment, interventions "from within the evolutionary process", and so the possibility of altering our human make-up, and that of our descendants (Keenan, 1990). Current successes on this very campus, based on the identification of key genetic markers, include the development of insulins for the treatment of diabetes, human growth hormone for treating children of short stature, and the use of genetically engineered protein to prevent genetically determined early emphysema.

It is easy to see that these successes are ethically sound because they directly serve the good of individual patients. In other situations, however, genetic research and treatment options are generating troubling ethical questions.

I believe that the fundamental ethical question with respect to genetic medicine is that of how we can ensure that genetic research and treatment are always in keeping with the respect for the worth and dignity of all human beings, including ourselves. Let us consider some of the key tensions underlying the most frequently debated issues.

Clinical Genetic Testing: Knowledge and the good of the human person

A first set of issues concern genetic testing, both before birth and during one's subsequent life. The questions here concern the use of this information about one's future health and life expectancy. Who should have access to this information? Should it be available to insurance companies, prospective employers, and family members? Should a person be obliged to undergo such testing or is one entitled not to know? Should pre-natal testing be encouraged, given that the results are often used as the basis for selective abortion?

These ethical questions relate to the good of knowledge, the context in which it is obtained, how it is used, and one's readiness for it. These questions can only be answered by reflecting on the relationship between knowledge and the overall or "integral" good of a person's life, along with the claims of others. In terms of the cardinal virtues noted above, we can see how they each bear upon ethical decision making. Genetic information which may be relevant to all human beings raises questions of *justice*. Genetic information relevant to significant others, normally one's blood relations, raises questions of *fidelity*. One's readiness for certain information at a particular time in one's life raises issues of *"self-care"*. *Prudence* or practical moral wisdom is required to discern the resolution of these competing claims of these virtues on one's decision making.

Technology in the context of human reproduction

A second set of issues concern the use of reproductive technologies. It is now possible to bring about conception in non-sexual ways, and with a view to a variety of future parental situations. A federal court in 1998 ordered the return of a child to its birth mother, a woman who had previously agreed to act merely as a "surrogate mother" for a friend. Human cloning and cross-species fertilisation are the more extreme forms

of new reproductive technology, but the basic issues are also raised by IVF techniques which are well established, despite their relatively low success rates. Soon we can expect that genetic interventions prior to birth may benefit both the child and his or her descendants. But in many cases this would require the use of IVF and genetic manipulation prior to implantation of the developing embryo.

These ethical questions relate to the good of human reproduction. The fact that technologies enable us to bring about conception in non-sexual ways does not settle the question whether this is an appropriate context for the coming into existence of a human being. From the ethical viewpoint, we need to reflect on both the prior context out of which a child is conceived and the subsequent context for a child's future upbringing. As many of you would know, the Catholic Church holds that only a committed marriage provides a sound context for human reproduction, and further that a child should be able to look back to its origin in an act of sexual loving between his or her mother and father.

Many will find the Catholic Church's teaching on this point more restrictive than they would wish. But whether restrictive or not, the Church is surely right to bringing this ethical consideration to our attention. What is technically possible is not necessarily ethically sound. We may not avoid the question of whether it is right or wrong to bring about the conception of a human being in a certain way and in a given context. We have no alternative, therefore, but to reflect on what makes for the appropriate context for human conception. Of course, once a child is conceived, no matter by what means, it should be granted unconditional respect. We should never say of any child that it would have been better if he or she had not be born. Nonetheless, I believe we ought not shy away from the proposition that at times it is appropriate to say that it would have been better if a child had not been conceived in the way he or she was conceived, e.g. as a result of a technological procedure rather than as the fruit of an act of marital love.

In addition there are issues of justice to be addressed about how embryos are "used" and to what ends, issues of fidelity between parents and children, issues of self-care in relation to infertility, all of which call for ethically sound judgment.

Knowledge, control and the good of the person

A third set of issues concerns experimentation on human embryos and on the possibilities of genetic manipulation in relation to future generations. Though distinct issues, they both highlight the tension between the goods of knowledge and control, on the one hand, and the good of the human person, on the other. Many of the advances in reproductive technologies (e.g. sperm injection methods of IVF) have involved destructive experimentation on human embryos. The experimentation has been justified by its practitioners on the grounds of the ensuing benefits,.

The ethical questions here relate primarily to justice, and to the unconditional respect owed to every human being, no matter what his or her genetic make-up, or genetically based deficiencies. The rapid growth in the development of reproductive technologies has occurred without any serious engagement with the question of when a human life begins, and of when unconditional respect ought be given the human embryo. Furthermore, the respect we show to other human beings is also the measure of the respect we show to ourselves. How we treat the handicapped unborn child is a measure of our attitude to the handicapped among us now, and of the handicapped person whom any one of us could become through accident or illness in the future.

Designing for the future

Human beings have a shared mortality and shared vulnerability. Advances in genetic medicine proffer the hope of alleviating many of the limitations and defects which mar our lives. There is always the danger, however, that overcoming defects leads

The Nature and

Ethics (or morality) involves a distinctive kind of evaluation, namely, evaluation of the goodness and badness of human actions and characters, and of right and wrong ways to feel, to think, to choose and to act as human beings. There are many other forms of evaluation, e.g. in aesthetics, in etiquette, in taste (be it wine or fashion), and in every field of human endeavour in which there are goals to be achieved, values to be respected, and rules and customs governing the appropriate ways of achieving those goals.

Ethical evaluation is not an optional pastime, for it is concerned not with particular spheres of human activity in their particularity, but with any and every sphere of human activity insofar as it is fitting for human beings so to act. For example, it is the nature of cricket which sets the standard against which a cricketer is evaluated as a good or bad cricketer. But it is a matter for ethical evaluation whether (i) a person should be playing cricket rather than doing something else (such as caring for his child or relaxing at the beach or going to work in an undeveloped country, and so on) and (ii) whether the person is playing cricked in a humanly responsible way (whether fairly or unfairly, with an appropriate degree of competitiveness, selfishly or unselfishly in relation to his team mates, and so on).

Following Aristotle, we can say that in ethical evaluation the standard is set by the nature of what it is to be a fine human being, and that this is best judged by the morally wise or "virtuous" person. Excellence as a human being is about true "happiness", about living a worthwhile and complete human life. Just what it is to be a good human being is best described in terms of the "moral virtues", the stable dispositions of character which underpin a person's life, and which one contemporary author identifies as justice, fidelity, and self-care, as these are integrated by prudence or practical wisdom. Justice is the virtue concerned with our relationships with all other human beings; fidelity is the virtue concerned with our relationships with those special people in our lives to whom we are linked in particular ways; self-care concerns our respect for ourselves and our bodies, and for our sense of self-worth and moral integrity. Prudence is

Progress of Ethics

practical wisdom discerning the particular, and sometimes competing, claims these virtues make on us (Keenan, 1995).

This Aristotelian view of ethics is essentially dynamic and developmental. It outlines an ideal of human development to which we aspire, and it portrays ethical reasoning as a matter of knowing how we should act in order to become to the kind of people we should become. The moral life for each of us as individuals is always one of progress or decline in relation to true excellence as a human being, and one aspect of moral progress consists in our coming to a deeper appreciation of what being human requires in the specific circumstances of the day, in this society given these constraints and opportunities.

Ethical progress

Ethical progress within a society largely consists in the development of laws, customs and social practices which embody a more accurate grasp of the true good for human beings, and of how human beings ought to live and live together in the circumstances in which they find themselves. It is easy to point to some of the moral advances in social practices in recent times. We all welcome the increased tolerance in our society for people with different beliefs and traditions; the increased respect for the equality of men and women; the greater awareness of the impact of our actions on the environment; the new acknowledgment of the prevalence and impact of child abuse; and so on. On the other hand, it is evident that our world is also one of striking moral decline: the wars of our century, the genocide past and present; the growing inequality between rich and poor nations; the ever increasing abortion rate, the AIDS pandemic which in the developing world is so injurious, to women in particular, and so on.

Is our century the most violent ever? In statistical terms, I assume that more have been killed through war and violence in our century than ever before. But are ordinary people more violent now than previously? Probably not. What has changed is the extent to which we are now capable of doing both good and evil, chiefly because of the advances of science and technology.

In warfare, for example, modern weapons of mass destruction can rarely be targeted only at combatants, and the complexity of industrial societies is such that many apparent "non-combatants" are in truth crucial to a war effort. Likewise in guerilla wars the distinction between soldier and civilian is blurred. Who then is a legitimate target, assuming one is engaged in a just war, that is a defensive war? Indeed, is a just war still possible? Are there any morally legitimate forms of defence against urban terrorism?

I use the example of just and unjust warfare to point to another context in which, as with live organ donation, reproductive technology, and genetic manipulation, scientific advances are forcing us to re-consider the adequacy of our traditional moral beliefs. Of course, it does not follow that our traditional beliefs should be overturned completely: killing innocent, non-aggressing people is still wrong, and always will be; mutilating another's bodily integrity is still wrong, and always will be; treating a child as a commodity or as the product of technology is wrong, and always will be. Our uncertainties today arise in relation to those cases in which it is no longer clear just when a person is an innocent non-aggressor, or when the removal of an organ is not a mutilation; or when technology is assisting, rather than substituting for, human reproduction, and so on.

to the goal of "designing" what we suppose would be "superior beings", but who may well cease to be human beings. Philosopher Alasdair MacIntyre asks to reflect on the kind of persons we would want to design for the future, were that possibility open to us. He suggests we would want people who were able to live with the uncertainties of an unpredictable environment; people with a capacity for being at home in a particular place in the world; men and women committed to non-manipulative ways of relating to others, able to find a work that is distinctively theirs, who recognise that there will come a time to die, when life is complete; people with a spirit of hope that goes beyond empirical grounds, and with a willingness and courage to take up arms in the defence of life and civilisation. He then argues that:

> If in designing our descendants we succeeded in designing people who possessed just those traits ... we should have contrived for ourselves descendants who would be unable, by virtue of those very traits, to adopt manipulative, bureaucratic modes of planning. What we would have done is to design descendants whose virtues would be such that they would be quite unwilling in turn to design their descendants (MacIntyre, 1979).

MacIntyre's thought experiment is as stimulating and provocative today, as it was when he proposed it nearly twenty years ago. Till very recently, medicine has simply sought to heal and alleviate human illness without being able to radically alter its biological basis. Modern advances in genetic science are making it possible for us to understand the ultimate bases for both health and illness, so as to intervene from within the genetically structured evolutionary process to alter our physical human nature both in the present and in the future.

This advance presents us with new ethical questions as to who we are as human beings, and who we are becoming as we acquire the ability to alter the genetic bases of life. Our genetic make-up is but one aspect of our humanity, and there is a real danger that people may come to be valued (or disvalued) only in terms of their genetic potential. Our ethical challenge therefore is to deepen and refine our understanding of what it is to be worthwhile human beings, given our new found ability to alter our physical make-up, without abandoning our unconditional respect for every human being, whether born or unborn, able-bodied or disabled. **How we treat others is the true ethical measure of how we are treating ourselves and our own bodies.**

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Dr Sharyn Rothwell

MRI of the Pancreas and Biliary Tree

Introduction

In the past the pancreas and bile ducts were difficult organs to image well with Magnetic Resonance Imaging (MRI). With newer techniques that allow image acquisition in a single breath-hold, dynamic contrast enhancement and selective 3D imaging of fluid filled structures such as pancreatic and bile ducts without the need for injected contrast material, MRI of this area now rivals or surpasses CT scanning.

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Imaging Considerations

1. Biliary and Pancreatic Duct Imaging

This is called Magnetic Resonance Cholangiopancreatography (MRCP). This is a form of MR Hydrography, which is a newly developed technique whereby static or slowly flowing body fluids are viewed as bright structures against a very dark background intensity.

The main advantage over ERCP (endoscopic retrograde cholangiopancreatography) and PTC (percutaneous transhepatic cholangiography) is its non-invasive nature. There is no risk of pancreatitis, haemorrhage, sepsis or hollow viscus perforation. There is no contrast injection and no risk of allergic reaction. There is no ionizing radiation. It is a relatively quick examination at around 30 minutes, with some of the images taking only two seconds. In biliary obstruction the biliary tree is seen both proximal and distal to the stricture with the ability to evaluate the length as well as the location of the stricture for interventional planning. Other organs can be incidentally or actively imaged at the same time with the potential for diagnosis and staging at the one examination.

Studies report visualization of 96% of non-dilated extrahepatic bile ducts. The normal pancreatic duct is visualized on MIP (maximum intensity projection) images in 69% of all the patients and, with review of the source data, 93%. A significant improvement in these figures would be expected for the newer breath-hold techniques. The MRCP reported sensitivities for biliary obstruction are high (91-100%), although determination of the exact cause for obstruction may be difficult to predict on the basis of MRCP sequences alone.

Obtaining good quality MRCP images requires three things: fluid to background contrast, high spatial resolution and suppression of artifacts caused by respiratory motion. Complex methods of respiratory triggered scanning with long scan times (>13mins) have been replaced with a single breath-hold technique with imaging time of under 20 seconds. The FSE (fast spin echo) technique has been modified to a super fast technique that uses a single excitation pulse and half Fourier acquisition and can generate a projected view of the biliary tree (similar in appearance to an ERCP) in about two seconds (Figure 1).

An MRCP study at St Vincents includes four such ERCP like images and slabs of contiguous fine (3mm) slices covering the region of interest in axial, saggital and coronal planes. The super fast two second slabs give an instant overview of the biliary tree evaluating the degree of dilatation and the presence of a stricture. Fine slices give more accurate spatial information for assessment of calculi, the nature of a stricture and the ampulla.

2. Pancreatic Imaging

Several new techniques in pancreatic MR have been developed which have greatly improved image quality and subsequent clinical usefulness. Its main role is in detecting small malignancies and accurate preoperative staging.

Earlier pancreatic imaging suffered from motion artifact, poor lesion to parenchyma contrast and longer scan times. New imaging of the pancreas at high field strength allows for faster imaging and breath-hold imaging rivaling spiral CT. New surface coils are also used to improve the signal to noise ratio allowing finer slices and a smaller field of view.

T1 imaging of the pancreas is useful because of its high lesion to parenchyma contrast. The pancreas has the shortest T1 of the abdominal organs, and is therefore bright. Most lesions of the pancreas lower the signal intensity on T1-weighted imaging and are seen as dark. Imaging is performed with an in-phase breath-hold multisection fast (eg. FMPSPGR) gradient echo sequence (T1-GRE). This sequence provides images that are free of respiratory motion artifacts and that are of sufficient temporal resolution for dynamic contrast-enhanced studies.

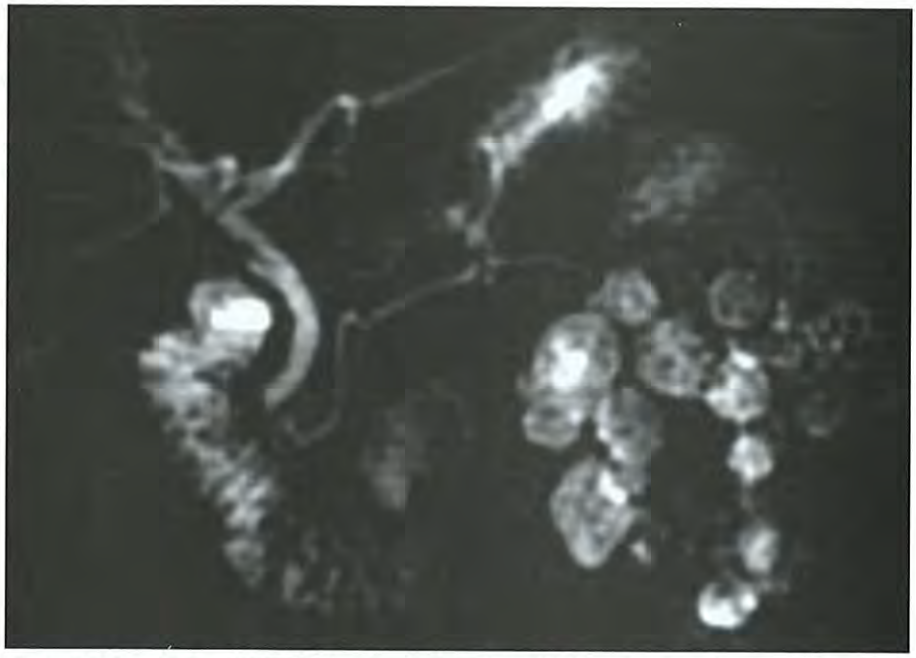


Figure 1. *Normal 5cm slab MRCP study. Each is a breath-hold study acquired in 2 seconds.*

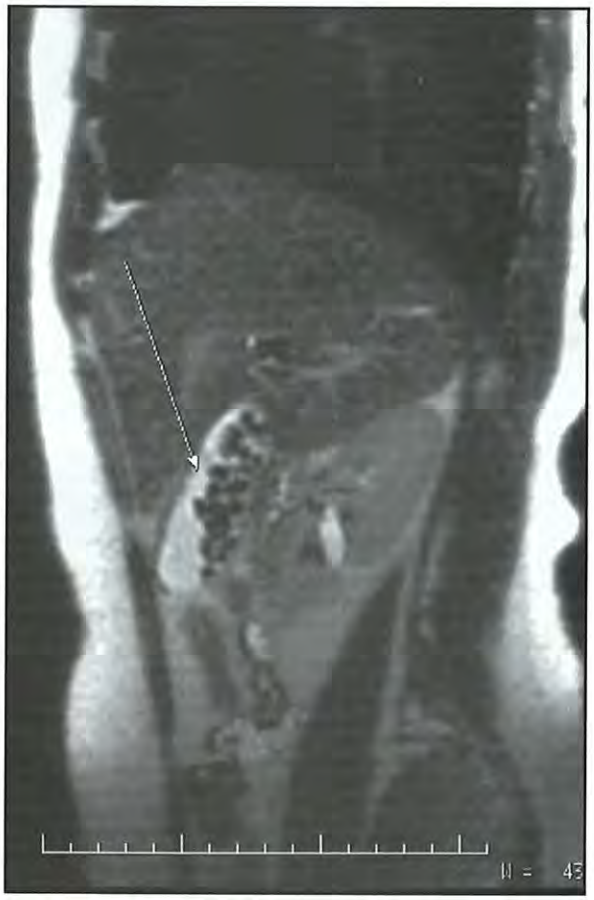


Figure 2. *Gallstones in the gallbladder. A coronal 3mm slice, one of 14 slices acquired in a 27 second breath-hold.*

T2-weighted hybrid rapid acquisition relaxation enhancement (e.g. FSE) techniques offer the advantages of reduced scanning time, better depiction of tissue planes and increased signal to noise. The use of fat suppression techniques will also reduce artifact and improve soft tissue contrast. Other motion compensation techniques include respiratory gating and the use of breath-hold T2 - weighted sequences. T2 - weighted images are important when imaging fluid in pancreatic and bile ducts and islet-cell tumors which have a bright appearance.

Clinical Applications

i. Common Bile Duct Stones

Although Ultrasound is a well-accepted, noninvasive and cheap way of assessing the biliary tree, for common bile duct stones it is of variable sensitivity (generally considered not reliable) but of high specificity. Several studies have shown high accuracy for the diagnosis of choledocholithiasis on MRCP with reported sensitivities of 81% to 95% and specificity of 85% to 98%. It is important to consider when evaluating these figures that they are for MRI techniques that have been generally superceded and when the techniques currently in practice are evaluated they will presumably be

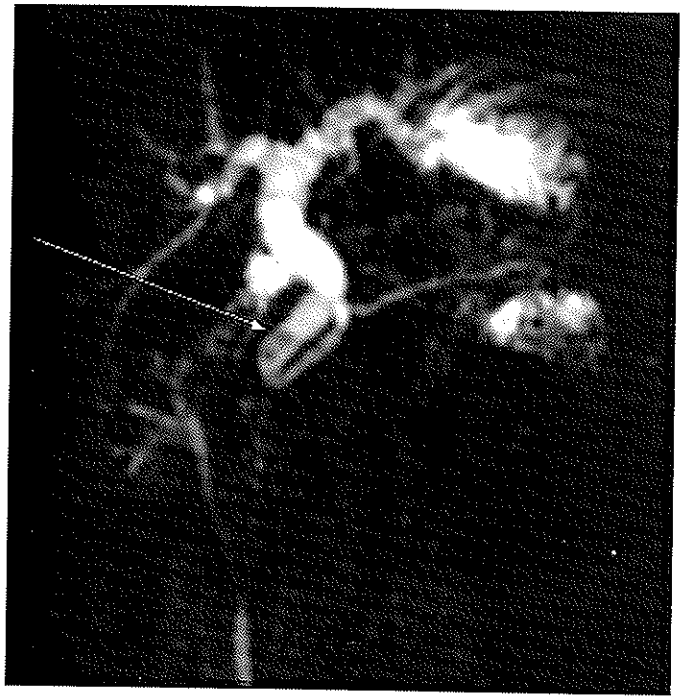


Figure 3a. Two calculi in the distal common bile duct and a dilated biliary tree.

Figure 3b. The two calculi are more easily seen on the fine 3mm slice sequence.

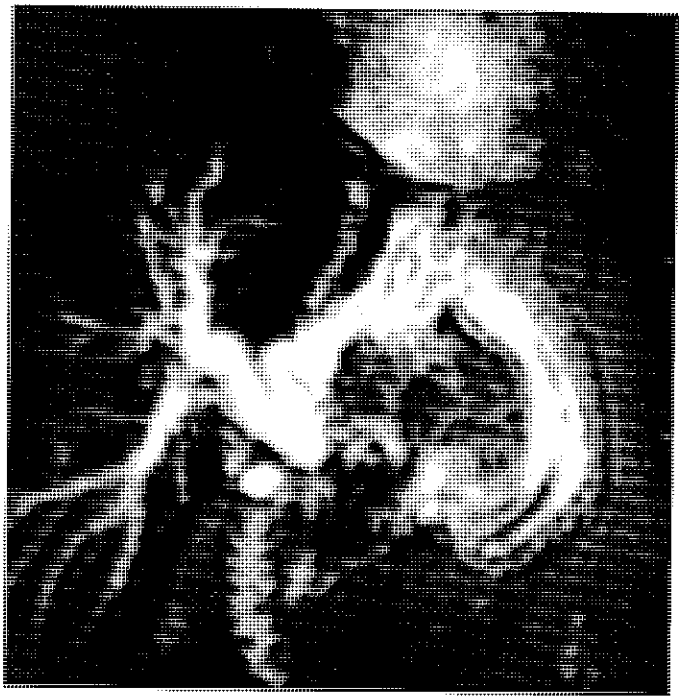
superior. Gall stones, in the gall bladder and common bile duct, are illustrated in Figures 2 and 3.

II. Strictures

Biliary strictures are interpreted looking for the same characteristics as seen on an ERCP or PTC although at this stage MRCP lacks the spatial resolution of these other tests making the characterization less accurate. Benign strictures are more of a tapered or funnel-like narrowed segment and in malignant strictures there is typically an abrupt interruption of the dilated duct with associated asymmetry or irregularity of the strictured segment (Figure 4a and 4b). The presence of the "double duct sign", with dilatation of the pancreatic as well as the common bile duct is also suggestive of malignancy. When evaluating strictures it is useful to have standard MRI imaging in addition to MRCP in order to assess for the presence of an associated mass.

MRCP depicts the common bile duct in its physiological state. The ampullary segment is therefore not depicted directly by MRCP and its location must be inferred. For this reason dilatation of the CBD to the level of the ampulla may represent either calculus impacted in the ampulla, ampullary tumor, benign stricture or spincter of Oddi dysfunction. These entities are difficult to distinguish by MRCP.

Figure 4a. Dilated intrahepatic ducts due to a proximal common bile duct stricture.



III. Pancreatic Neoplasms

The primary goal of imaging is sensitive detection of smaller lesions and accurate preoperative staging so that optimal treatment can be defined for each patient. In routine clinical application CT has been the primary imaging modality in detecting and staging of pancreatic adenocarcinoma. CT and MRI were found to be of similar accuracy with older MRI sequence protocols that did not include fat suppression or dynamic breath-holding techniques. With the new techniques MRI has been shown to be superior in both detection and defining local tumor extension. Dynamic gadolinium-enhanced MRI imaging has a reported sensitivity of 90% in the detection of tumor.

On T1 weighted fat suppressed images, pancreatic adenocarcinoma appears as relatively low signal intensity mass within the high signal of the pancreatic parenchyma (Figure 5). Adenocarcinoma is relatively hypovascular with respect to the normal pancreas. During the arterial phase of dynamic contrast enhancement the

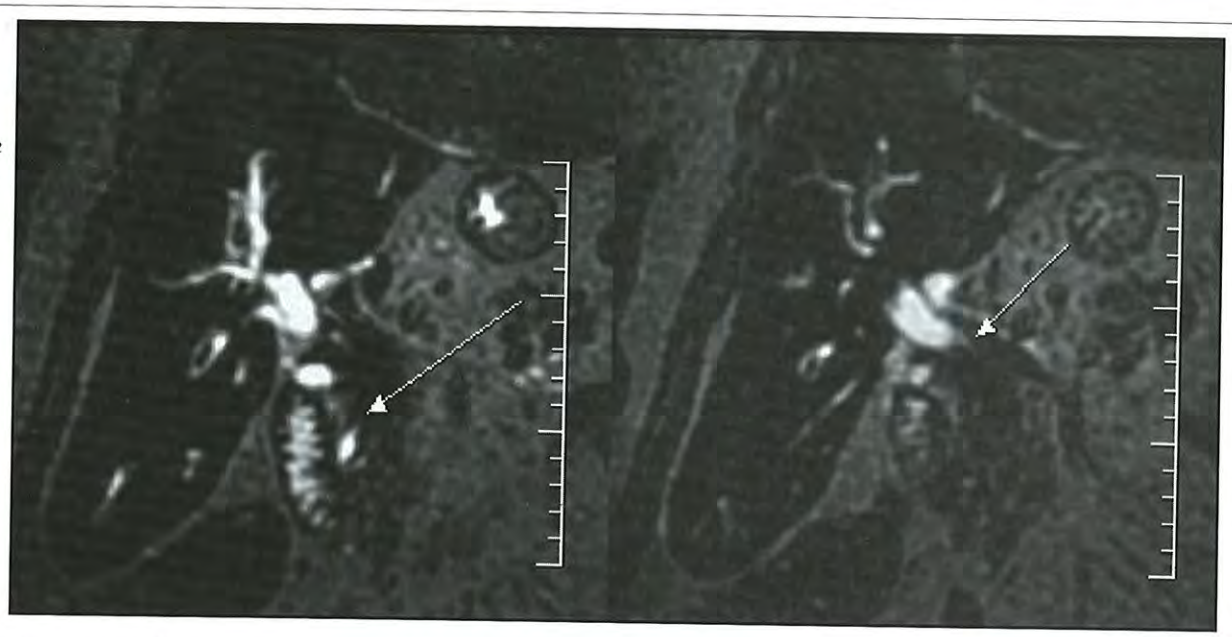


Figure 4b. *The fine slice sequence demonstrates the length of the stricture which was due to cholangio-carcinoma.*

tumor has relatively little contrast enhancement although contrast can diffuse into the mass over time. The increased parenchymal to lesion contrast has been shown to facilitate the detection and characterization of small pancreatic carcinomas that do not alter the contour of the gland (Fig 6a and b). MRI has the potential for direct coronal plane imaging and small ampullary carcinomas are best seen in this plane. Most of the work at St Vincents has been directed toward further evaluation of the pancreas in a situation of high clinical suspicion of a pancreatic adenocarcinoma and a normal or equivocal CT.

There is also the potential for detection of islet cell tumors which have a high lesion to parenchyma tissue contrast which is especially evident on T2 imaging where the tumor exhibits high signal intensity. These tumors are also usually hypervascular and are well depicted despite their small size as high signal following dynamic imaging during the arterial phase of a contrast enhanced scan. MRI appears capable of detecting the smaller lesions not seen on CT.

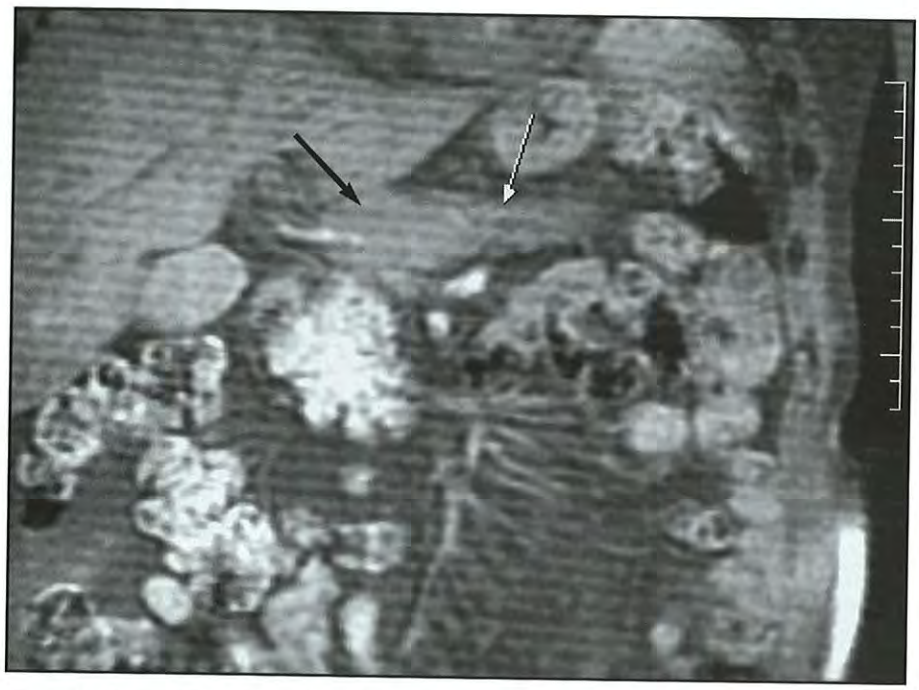


Figure 5. *Tumor of the superior body of the pancreas (bold arrow) not seen on CT despite a relatively large size. The tumor is seen as low intensity compared to the very bright signal of the normal pancreatic head. There is pancreatic tail atrophy and pancreatic duct dilatation (arrowed).*

IV. Chronic Pancreatitis

MRCP is able to detect the ductal abnormalities (strictures, dilatations and calculi) seen in chronic pancreatitis (Figure 7). The dense fibrosis characterising chronic pancreatitis also results in decreased pancreatic signal intensity and decreased contrast enhancement on standard MR imaging. Using the ERCP findings as the standard in patients with chronic pancreatitis MRCP was able to identify filling defects and calculi in 92-100% , duct dilatation in 83-92% and strictures in 70-92%.

V. Variant Anatomy

Anomalies such as low or medial cystic duct insertion, parallel cystic and hepatic ducts and aberrant right hepatic duct are shown with high accuracy. Variants of the cystic and hepatic ducts may be important in planning laparoscopic cholecystectomy.

Pancreas divisum has been associated with a higher incidence of pancreatitis and can be visualized on MRCP reliably, with an incidence similar to that reported in autopsy series (Figure 8).

The exogenous administration of secretin has been suggested to improve the sensitivity for the diagnosis of pancreatic papillary stenosis or dysfunction. This technique is based on an increase in pancreatic fluid flow in response to secretin stimulation although this technique has yet to be used at St Vincents.

Limitations

When compared to ERCP, no functional information about ductal drainage and ampullary function can be obtained. There is also no opportunity for concurrent therapy.

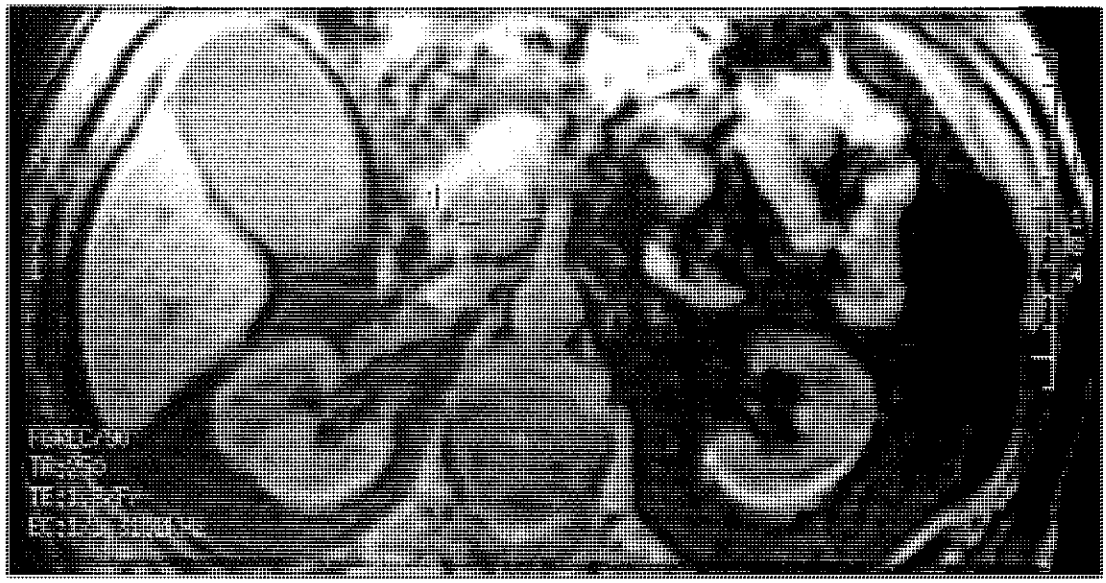


Figure 6a. *A small tumor is seen in the superior head of the pancreas which was not seen on CT.*

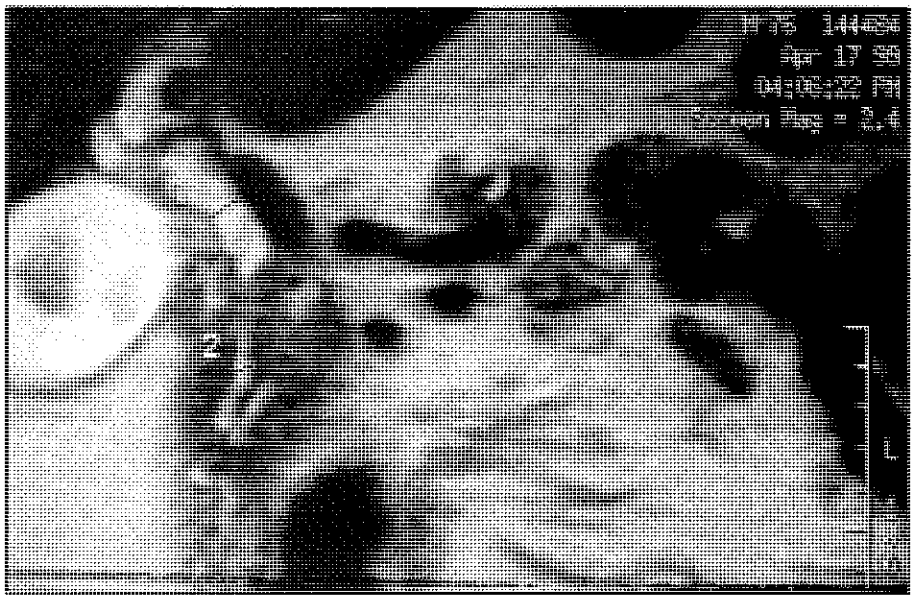


Figure 6b. *There is mild dilatation of the pancreatic duct and common bile ducts proximal to the stricture produced by the tumour which was not appreciated on other modalities.*

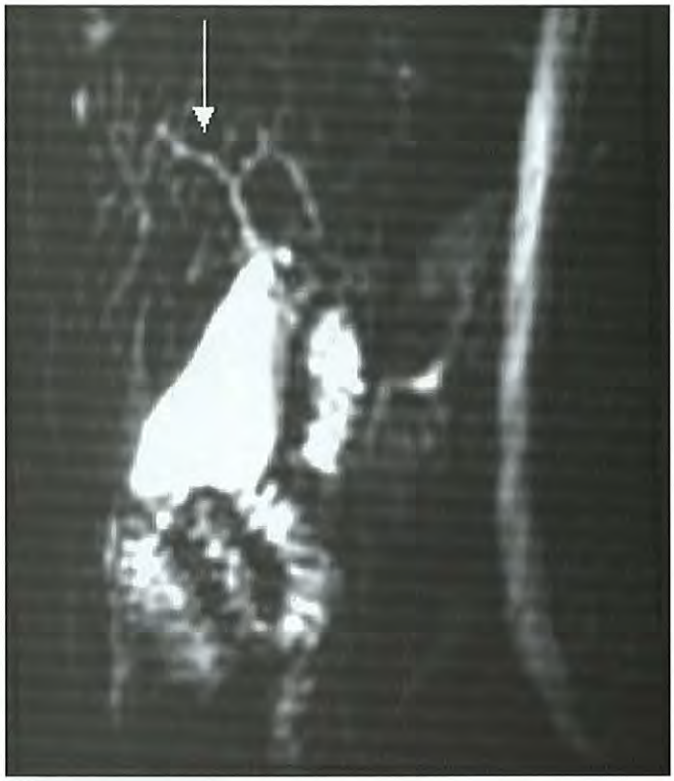
Spatial resolution is not as good as ERCP and a subtle abnormality of ducts may go undetected. Visualization of small calculi and diagnosis of sclerosing cholangitis or chronic pancreatitis, which may require resolution of short segment strictures could be problematic without additional information (Figure 9). The major limitation of all the FSE techniques is that the slices acquired are relatively thick (3mm) limiting the resolution of an image and therefore the minimum size of a structure that can be detected. Therefore multiple slices parallel to the duct of interest or as many as three separate planes may need to be prescribed.

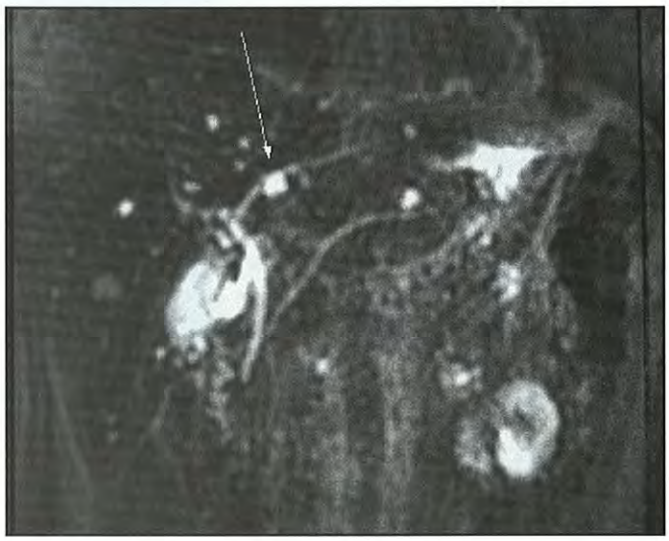
If a filling defect such as a stone is surrounded by fluid it will be obscured on the Maximum Intensity Projection (MIP) image and it is important to view the multislice images. Anything within the ductal system that shortens the T2 relaxation time (blood, protein, air, debri) can cause non-visualization of the duct or a filling defect that can mimic a calculus.

There is not selective depiction of the biliary tree and any fluid such as bowel contents, ascites or strategically located fluid collection can obscure the ducts on MIP images.

There are also the limitations of MRI examinations more generally. There are contraindications to MRI such as pacemakers, difficulties with patient motion and co-operation and the problem of claustrophobia and the possible need for patient sedation. Artifacts from ferro-magnetic clips or inferior vena cava filter adjacent to the biliary tree or pancreas can result in susceptibility artifact which interferes with signal arising from these structures (although this is not always detrimental to diagnostic image quality).

Figure 7. *Dilated and irregular pancreatic duct in chronic pancreatitis*





Suggested Indications For MRCP And MRI Of The Pancreas

1. Failed or incomplete ERCP examination due to anatomic factors such as periampullary diverticula, duodenal stenosis, periampullary masses and ampullary calculi.
2. Known unfavorable anatomy for successful ERCP e.g. previous gastric or biliary bypass surgery
3. Patients requiring diagnostic ERCP for investigation of upper abdominal symptoms where intervention during ERCP is unlikely.
4. Where choledocholithiasis is strongly suspected on clinical grounds but the patient prefers a non-invasive procedure before ERCP.
5. Evaluation of the biliary tree to exclude variant anatomy and choledocholithiasis prior to laparoscopic surgery
6. In obstructive jaundice with suspected malignancy where MRCP may determine the site and length of obstruction and this can be used to decide on the most appropriate approach for decompression i.e. endoscopic, percutaneous transhepatic or surgical.
7. Nature of cystic structures and the relationship to the biliary tree and pancreatic duct (Figure 10)
8. Surgical planning for hepatic tumor resection to establish the relationship and involvement of the biliary tree to the tumor
9. Suspected pancreas divisum in recurrent episodes of pancreatitis
10. Exclude pancreatic malignancy where it is clinically suspected.

Above: Figure 8. *Dominant accessory pancreatic duct.*

Right: Figure 9. *Beaded intrahepatic duct system due to short strictures in sclerosing cholangitis.*

Below right: ***Figure 10.*** *Multiple liver cysts. Normal pancreatic duct and biliary tree.*

Conclusion

In clinical practice MRCP done on a high field magnet with newer software is a fast non-invasive method that is capable of depicting the biliary tree and most causes of biliary obstruction with a high degree of accuracy.

It avoids the invasive risks associated with ERCP. It is clearly indicated in the setting of failed or incomplete ERCP, prior biliary enteric surgery and in patients with relative or absolute contraindications to ERCP. Promising clinical applications include pre-laparoscopic cholecystectomy imaging, imaging of chronic pancreatitis, imaging of pancreas divisum and the diagnosis of stones in the common bile duct in clinically uncertain situations.

Pancreatic MRI is superior to CT scanning for detecting pancreatic malignancy and has the potential to diagnose and stage a lesion in a single investigation.

Reference:

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Dr Martin Sullivan

Advances in the Surgical Treatment of Ankle Pain Following a Sprain

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Introduction

A "SPRAINED ankle" is the most common injury in sport in Australia. It has been reported that 20% of patients treated in the Emergency Department for a sports related injury have an ankle sprain. The overall perception in the medical community (including physiotherapists) is that an ankle sprain is a benign injury that usually gets better. However the literature reports an average of 40% – 50% of patients who develop chronic residual complaints ranging from instability, pain, swelling and/or stiffness. One study has shown that a sprained ankle, (regardless of the severity) interfered in 9% of patient's physical activities and 6% could not return to their previous work level. Athletes have a greater incidence of residual complaints following a sprain, compared with those who undertake less strenuous activities.

Mechanisms Of Chronic Problems After A Sprain

In the majority of ankle sprains the lateral ligaments are torn. The anterior talofibular ligament (ATF) is most often torn followed by the calcaneofibular ligament (CF). Following injury to these ligaments a functional rehabilitation program is started. Some patients however fail to progress with rehabilitation and a diagnosis should be established early, in order to institute a treatment program and prevent secondary problems. Damage to

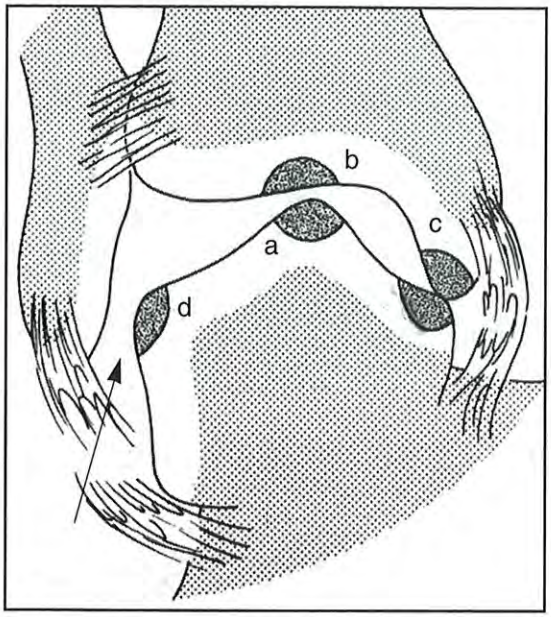

Figure 1. *The medial side of the ankle joint is a common area of articular damage and the various sites are illustrated. Key: a – medial talar dome; b – central tibial plafond; c – medial malleolus; d – lateral talar dome*

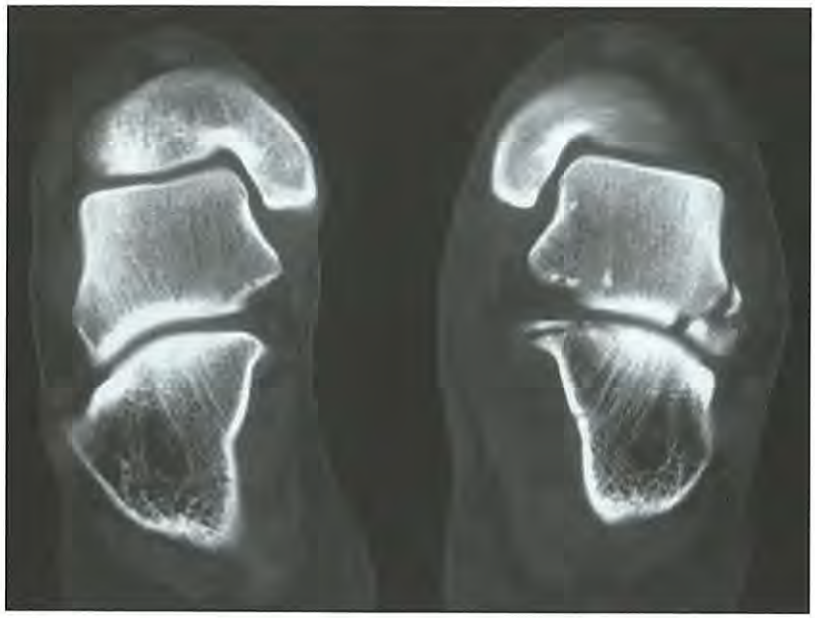

Figure 2. *The "snowboarders' fracture" involves the articular portion of the subtalar joint. If not detected early, degenerative arthritis can rapidly occur in the subtalar joint.*

structures other than the lateral ligaments can occur at the time of the sprain, which can cause ongoing pain and dysfunction.

The usual forces involved in a sprain include inversion and plantar flexion of the ankle and many variations of this are possible. The most common cause for ongoing pain and swelling after a sprain is articular cartilage injury, especially the tibial plafond and talar dome. This is illustrated in Figure 1.

It is possible to have occult fractures after a sprain which do not show on the routine x-ray. Awareness of the possibility of these fractures is extremely important. The anterior process of the calcaneus fracture is often missed initially. It is a bony ligamentous avulsion of the bifurcate ligament. Also the lateral process of the talus fracture can cause subtalar arthritis if not detected early. This fracture is known as the "snowboarders' fracture" and its incidence has increased with the rise in popularity of snowboarding. Figure 2 shows a CT scan of a snowboarding fracture that was not visible on the routine xrays.

Following injury to the lateral ligaments it is possible to initiate an inflammatory synovitis within the ankle which can cause pain and swelling. The ligaments can hypertrophy with healing and cause soft tissue impingement on the talus.

Following a sprain it is possible to awaken congenital disorders such as a fibrous talo-calcaneal coalition. It is also possible to traumatise superficial nerves either by a direct blow, e.g. against the gutter or by blood irritating the nerves. This can trigger a reflex sympathetic dystrophy (RSD). As well as the ligaments, the tendons around the ankle can tear. The most common tendon tear after a sprain is of the peroneus brevis tendon. With an inversion force the peroneus longus tendon forces the peroneus brevis against a sharp ridge on the back of the fibula and can split the tendon. A Magnetic Resonance Imaging (MRI) of a torn peroneal tendon is shown in Figure 3.

Diagnosis

Patients with persistent symptoms should be evaluated with a careful physical examination. A reasonably precise clinical diagnosis is possible with careful palpation of the various structures at risk. MRI can assist the clinician in planning treatment as well as diagnosing unsuspected injuries. It is possible to have multiple pathology following a sprain and MRI can help in this area. For example, following a sprained ankle it is possible to have articular damage on the medial aspect of the ankle joint in association with articular cartilage damage in the subtalar joint, as well as a torn peroneal tendon. None of these injures will show using standard imaging techniques.

One should note that MRI of the foot and ankle is highly specialised and the limitations of the radiologist, as well as the limitations of the MRI technique should be apparent to the doctor ordering the study. For example one should note the MRI cannot detect small areas of articular cartilage damage in the ankle.

Surgical Treatment

The use of ankle arthroscopy for the ankle sprain that has long term symptoms is relatively new. Ankle arthroscopic surgery has a greater risk of complications than arthroscopy of the other joints. It requires the use of a pump irrigation system, as well as meticulous attention to technique. Ankle arthroscopic surgery can lead to a significant improvement in pain relief, particularly in athletes who do not recover from a sprain.

At St Vincent's Clinic we have reviewed the results of ankle arthroscopic surgery in elite athletes under my care. In all cases the surgery was performed in the Day Surgery Unit and the patients were discharged on the day of surgery. The major sports involved were Rugby, Soccer and

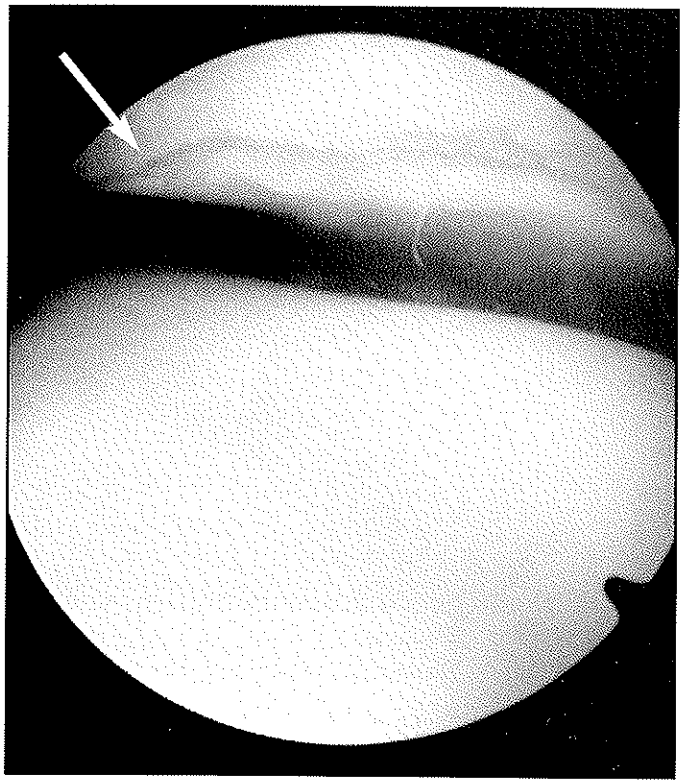

Figure 3. *This photograph illustrates articular cartilage damage seen during an ankle arthroscopic procedure in a soccer player. This was not detected by x-ray, bone scan or MRI.*

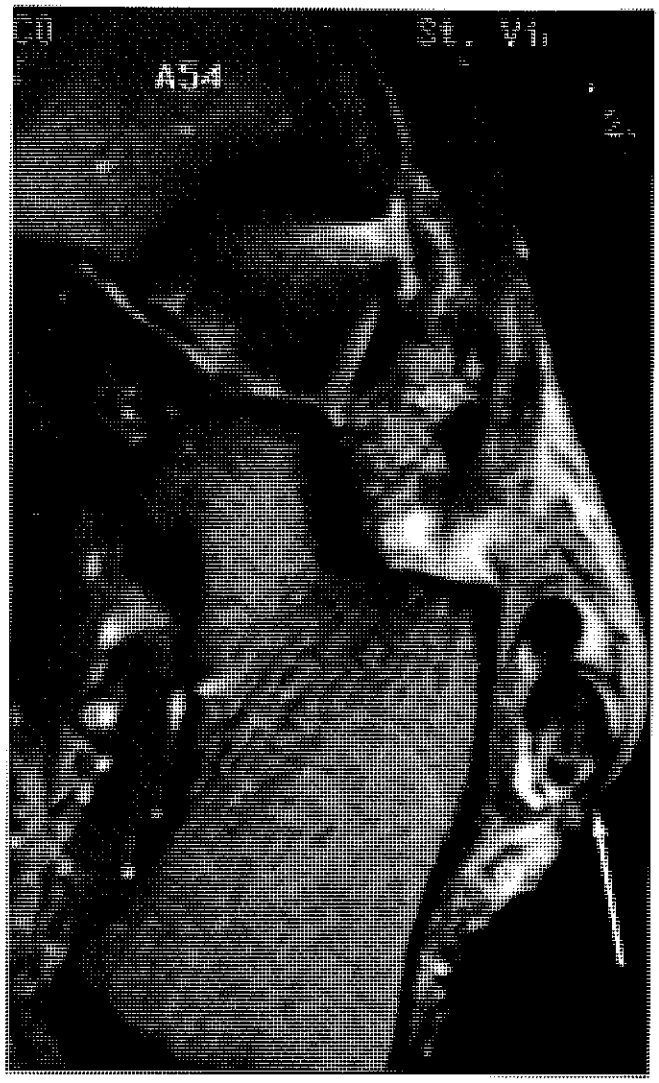

Figure 4. *Peroneus longus tendon tear in an elite long distance runner. MRI is very useful to detect peroneal tendon tears and indicate the site and size of the tear which can aid pre-operative planning. This tear was not detected by ultrasound examination.*

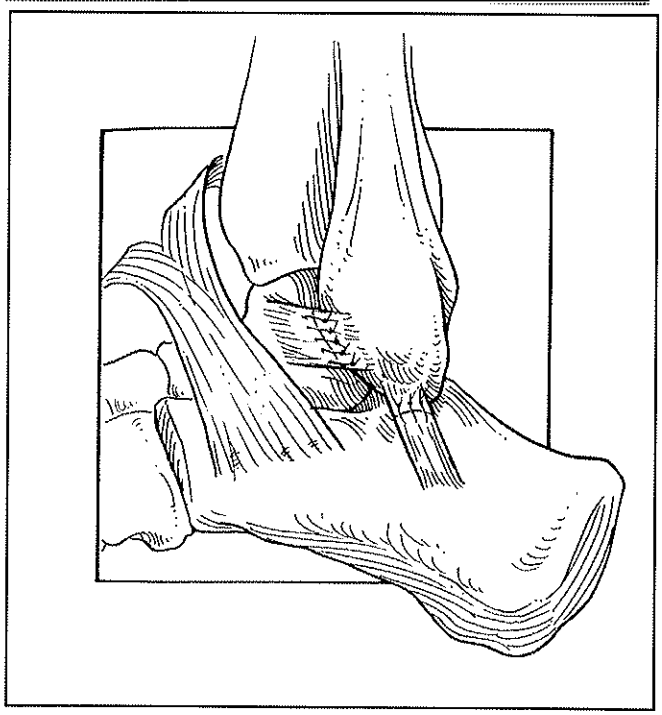

Figure 5. *In an ankle ligament reconstruction the ATF and CF ligaments are shortened and reattached to the distal fibula using a minimally invasive technique and suture anchors in the bone.*

Netball. The predominant site of articular cartilage damage was the central and medial tibial plafond area. The photograph shown in Figure 4 demonstrates the inside of an ankle joint with articular cartilage damage. All the elite athletes in this series returned to sport within weeks of the surgery without complication.

Patients who develop chronic instability symptoms are now able to undergo an ankle ligament reconstruction, which is minimally invasive. A small incision is made to the lateral ligaments, which are identified and reattached to the fibula bone and at the same time the ankle and subtalar joint motion is preserved. The surgical procedure is illustrated in Figure 5. It is now possible to restore full function in elite athletes and ballet dancers. The use of a brace post operatively rather than plaster cast has led to a more rapid return to sport as well as an accelerated rehabilitation program.

SUMMARY:

For health professionals dealing with ankle sprains its imperative that the patients are reassessed at least 6 weeks and/or 3 months post injury for a failure to progress. A careful examination is required to identify the possible cause for any residual symptoms. Minimally invasive surgery can lead to an improvement in patient's symptoms and a return to function in the majority of patients.

Dr Christopher Hayward and Dr Raymond Kelly

Women and Heart Disease

Introduction

WOMEN remain relatively free of cardiovascular disease until later in life compared to men. They do, however, suffer significant morbidity and mortality related to coronary artery disease and may even be more prone to complications once coronary disease is present. The spectrum of disease in female cardiac patients is biased by their higher incidence of diabetes, hypertension and their more advanced age at presentation. Because women tend to present more commonly after the menopause, it has been suggested that hormone replacement therapy may have cardiovascular benefits. While this is based on strong observational data, recent results suggest the issue is far more complex. This review examines gender differences in cardiovascular disease, the role of hormone replacement therapy on management of women with cardiovascular disease, as well as results of research performed at St Vincent's Hospital examining the effect of hormone therapy on certain aspects of cardiovascular physiology.

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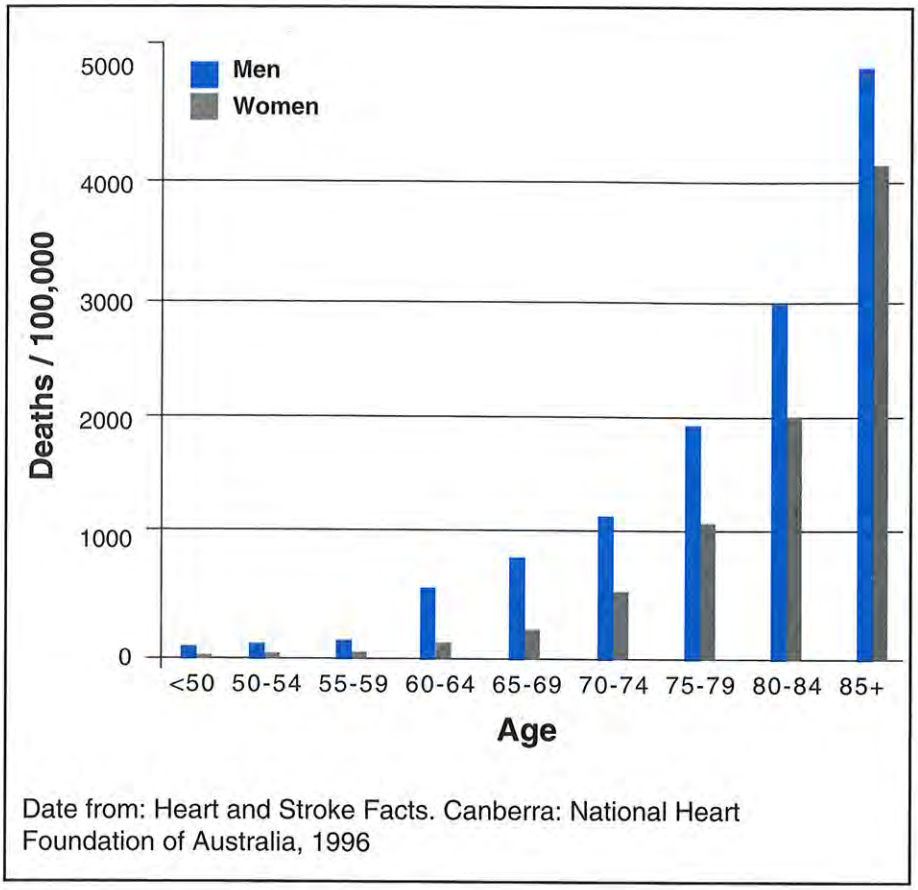
Women and Cardiovascular Disease

Coronary Artery Disease: Because of higher cardiac mortality in men compared to women until late in life, most cardiovascular mortality studies have focussed exclusively on that gender. Women have been excluded from research protocols in youth due to childbearing, as well as in old age because of co-morbidities. There has been somewhat of a reversal in this trend with the realisation that cardiovascular disease remains the most prevalent illness affecting women and remains the commonest cause of female death in developed countries. The mortality rate for women due to cardiovascular disease parallels that of men, delayed by 10-20 years (Figure 1). Part of the turn around in research focus is due to numerous reports that women, once affected by ischaemic heart disease, appear to do worse than their male counterparts. Such a phenomenon has been documented following myocardial infarction, coronary intervention (angioplasty) and coronary artery bypass surgery. This 'gender bias' has been attributed to the excess co-morbidity seen in women because they are older, have less aggressive investigation, or present later in the course of their coronary disease. Procedural difficulties have been attributed to physiologically



Date from: Heart and Stroke Facts. Canberra: National Heart Foundation of Australia, 1996

Figure 1: *Comparison of Male and Female Death Rates, Australia 1990 – 1994*

smaller vascular calibre in women related to their smaller stature. A further consistent finding in gender studies of myocardial infarction is the higher rate of ventricular wall rupture post infarction in women, despite typically smaller myocardial infarctions and a lower rate of transmural infarction.

Cardiovascular Risk Factors in Women

Diabetes mellitus: Diabetes mellitus (DM) has been confirmed as an independent predictor of mortality post AMI in both genders. It has received particular attention in women as premenopausal diabetic women have similar CHD rates to age-matched diabetic men. Hypotheses suggested to account for this sex-diabetes interaction include clustering of other cardiovascular risk factors in diabetic women as well as differences in lipid oxidation in diabetic women compared to men. In terms of risk factors, the marginal detriment due to diabetes is stronger than cigarette smoking in women, but the effects remain cumulative. With the higher rate of diabetes in women, the increasing rate of cigarette smoking among younger women is of major concern.

Hypertension: With increasing age, women are more likely than men to suffer from hypertension. For the age group 45-49 years 10.5% of the Australian female population were hypertensive. In the age group 50-55 years, this had doubled to 21%[1]. By age 75, approximately 45% of women are hypertensive, compared to 30% for men. With regards to treatment for hypertension, a number of early blood pressure trials actually failed to show significant benefit for women. These studies primarily recruited men and may have been underpowered to detect benefit for lower risk groups, such as women. Subsequent larger studies have confirmed significant benefit for women in the treatment of hypertension.

Plasma lipids: In accord with the different risk factors for men and women, different lipid profiles have different significance for each gender. While LDL (low density lipoprotein) cholesterol has been shown to be of primary significance for men, coronary artery disease in women appears more closely related to HDL (high density lipoprotein). While women typically have lower LDL levels, the menopause is associated with a significant increase in LDL in women as well as a decrease in HDL. While the benefit of cholesterol reduction in cardiovascular disease specifically in women has been confirmed in large secondary prevention studies, there are no large primary prevention trials of cholesterol reduction in women.

Women and Cardiac Failure

In the presence of ischaemic heart disease women have higher rates of cardiac failure compared to men, despite typically higher left ventricular ejection fractions[2]. This 'gender paradox' has also been found in large myocardial infarction trials. The higher rate of cardiac failure with better maintained ejection fractions suggests diastolic dysfunction may be a more common cause of the symptoms of congestive cardiac failure in women. The gender difference in cardiac ejection fractions is also present in the absence of heart failure with a number of studies having shown women to have higher ejection fractions at cardiac catheterisation, echocardiography and cardiac nuclear magnetic resonance imaging.

Women and Left Ventricular Hypertrophy

While left ventricular mass remains constant with age in men, it tends to increase in women. In the Framingham population of nearly 5,000 subjects, for each 10 year increment in age, the incidence of left ventricular hypertrophy increased by 67% in women, compared to only 15% for men. Determinants of left ventricular mass are different between men and women. Whereas left ventricular mass in men correlates most strongly with blood pressure, female left ventricular mass is particularly responsive to obesity. A surprising finding is that women develop more marked hypertrophy compared to men in response to similar levels of hypertension or aortic stenosis. These gender differences in ventricular

remodeling and function have been confirmed in experimental models of left ventricular hypertrophy.

Menopause and Cardiovascular Disease

As it is frequently stated that women have less heart disease than men until the age of the menopause, it is assumed that menopause constitutes a significant cardiovascular milestone in terms of physiology, as well as pathology. The role of oestrogen in the genesis of atherosclerosis was first suggested by post-oophorectomy case-control studies and has been maintained by epidemiological studies that have suggested a relationship between age of menopause and cardiovascular mortality. It has been recognised for some time, however, that the incident rate of cardiovascular disease does not accelerate at the age of menopause. While the menopause remains a convenient chronological cutoff in epidemiological studies, the emphasis placed on it cannot be misconstrued to suggest a causal relation between physiology and disease. Studies of menopause are further complicated by interactive effects of smoking, both on vascular disease, as well as induction of earlier menopause. Against popular perception, most studies have *not* found a significant effect of menopause on body weight or blood pressure.

Hormone Replacement Therapy and Cardiovascular Disease

HRT and Cholesterol: A possible role for hormone replacement therapy (HRT) as an adjunctive therapy in postmenopausal women was first suggested by a beneficial oestrogenic effect on lipoprotein levels in the 1950s. Many subsequent epidemiological studies have supported such an action. These findings, using unopposed oestrogen, have been confirmed recently in large randomised trials using combined HRT (oestrogen + progestagen) in the PEPI trial (Postmenopausal Estrogen/Progestin Interventions[3]) and the Heart and Estrogen/progestin Replacement Study (HERS[4]). It is only recently however, that serious consideration has been given to HRT as a combination therapeutic agent in some postmenopausal women with hypercholesterolaemia. HRT may have a unique role in the reduction in lipoprotein (a), which is not seen with other pharmacological agents, including even the HMG-CoA reductase inhibitors.

HRT and Coronary Artery Disease: Initial studies using oestrogen in cardiovascular disease met with disastrous results. In the Coronary Drug Project, a trial attempting to demonstrate a benefit of oestrogen in the peri-infarctional period, the oestrogen arm of the study was abandoned after a preliminary finding of excess mortality due to thrombosis in those subjects. Soon afterwards, analysis of premature cardiac deaths in women were shown to be associated with oral contraceptive use, and hyperoestrogenaemia was suggested to be a risk factor for myocardial infarction in men. These studies most likely failed because of the high doses of oestrogen used.

More recent epidemiological mortality studies have shown that HRT is associated with a marked risk reduction for mortality (relative risk of only 0.56, 95% confidence intervals 0.50-0.61) attributable to HRT[5]. The decrease in relative risk was consistent across different types of studies including healthy case-control, cohort, and prospective controlled studies. While interpretation of these results are clouded by possible selection bias, even studies in patients with defined coronary disease (>70% stenosis) seemed to favour HRT[6]. These studies rekindled optimism that HRT is not only safe, but also beneficial in the management of cardiovascular disease.

Such optimistic benefits may have been overstated because of the unavoidable bias involved in cross-sectional studies of women with differing risk profiles. This uncertainty has been reinforced since the publication of HERS (4). In that study, the first large prospective test of HRT on secondary cardiac protection (2,763 women), no significant benefit for combined continuous HRT on mortality or secondary cardiovascular protection was found, despite confirming a beneficial effect on cholesterol. Indeed, one concerning finding in HERS was the increased incidence of venous thromboembolic events in the first year after randomisation to HRT. The null result, from the cardiac point of view, in the HERS is surprising, given the multiple mechanistic benefits of hormone replacement repeatedly demonstrated in the last few years. These have included alteration in the fibrinolytic balance; induction of prostacyclin; improvement or restoration of endothelial function; induced nitric oxide release; attenuation of endothelin effect; calcium blockade; and smooth muscle relaxation. Blinded clinical studies have also shown acute decreases in exercise induced-ischaemia and angina[7]. Criticisms of HERS include the use of medroxyprogesterone acetate as the sole progestin, given evidence that it may antagonise some beneficial oestrogenic effects , as well as a shorter than planned follow-up period, just when an obvious trend in favour of HRT was apparent. Following HERS, it has been suggested that there is no evidence to support commencing HRT in postmenopausal women from the standpoint of cardiovascular protection. In women who are already receiving HRT, and have not had any significant thromboembolic episodes, it may be reasonable to continue it, as there was a trend to decreased cardiac events becoming evident after year 4.

Hormone Replacement Therapy and Hypertension: Because of the association between the oral contraceptive pill and incidence of hypertension, even with modern low-dose pills, there has been controversy over whether HRT may also increase blood pressure in susceptible individuals. Most studies, however, do not show an increase in blood pressure in response to HRT[3,4]. Early studies of HRT showed occasional patients to have idiosyncratic increases in blood pressure, possibly related to differences in dose or regimen. Initial concerns that progestagens, prescribed as part of combined HRT, may reverse blood pressure lowering in response to oestrogen, appear to be unfounded.

Syndrome X in women

The triad of chest pain, abnormal exercise or perfusion scan despite normal coronary angiography defines Syndrome X. Despite their lower incidence of coronary artery disease, women still commonly suffer with chest pain. Syndrome X is particularly prevalent at the time of the menopause and may be helped by hormone replacement therapy. Various alternate theories attempting to explain this have been provided including altered pain perception, autonomic imbalance, and possibly even the relatively shorter time available for diastolic perfusion due to a combination of faster heart rates and the higher systolic pulsatile load, as discussed below[8]. Unfortunately, therapeutic efforts are often disappointing and empirical treatments including conventional anti-anginal therapy followed by anti-depressants and pain management efforts have been employed.

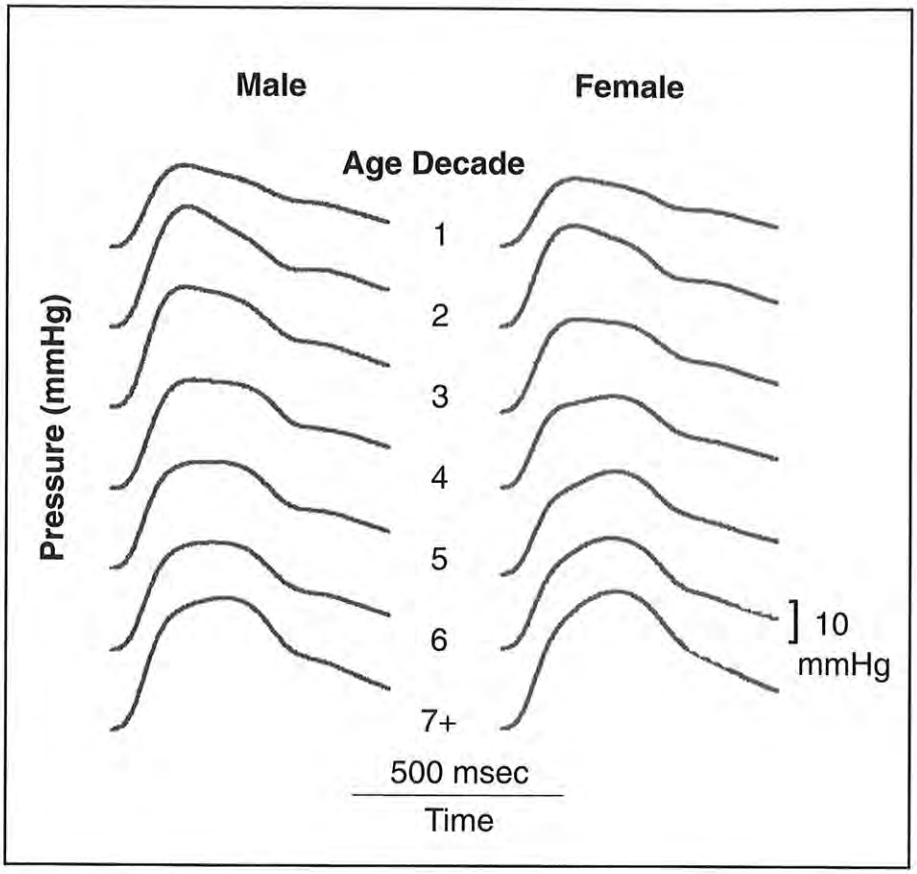


Figure 2: *Averaged central arterial pressure waveforms for men and women across all ages, scaled to average blood pressure.*

Related Research at St Vincent's Hospital

Over the last 5 years we have performed a number of studies examining gender differences in cardiovascular physiology as well as the effect of hormone replacement therapy on haemodynamic indices of both cardiac and arterial function.

The first study involved analysis of the central (carotid) arterial pressure waveform in 350 apparently healthy subjects from a broad spectrum of ages[8]. This project was based on the hypothesis that some of the gender differences in left ventricular hypertrophy may be related to differences in pulsatile loading conditions expressed in the central arterial waveform. This study revealed significant differences in the carotid waveform between men and women starting at a young age. Averaged waveforms for each gender and age decade up to 70 are shown in Figure 2. These waveforms are ensemble averaged for each decade and gender. Women typically have more dominant late systolic pressure peaks, a characteristic that has previously been associated with increased impedance to cardiac ejection and a greater degree of left ventricular hypertrophy. These differences might be explained on the basis of increased wave reflection in women due to a smaller distance to reflecting sites related to their shorter stature. This was supported by a strong relationship between height and degree of late systolic pressure augmentation across the entire adult population. Differences in cardiac function may also be involved in the genesis of the waveform.

The second study examined pressure waveforms and arterial pulse wave velocity in a group of 70 postmenopausal women attending a menopause clinic[9]. This observational study found that those receiving HRT had lower late systolic augmentation than those not. No difference was found in pulse wave velocity. A recent small case control study in normotensive postmenopausal women found lower left ventricular mass in those who had been receiving HRT for more than 10 years[10], a finding consistent with these haemodynamic results. Further randomised studies in diabetic women have confirmed a neutral effect of HRT on blood pressure and haemodynamic function assessed by arterial tonometry or 24-hour blood pressure monitoring in response to HRT[11].

A fourth study examined gender differences in ventricular function in 30 subjects undergoing routine cardiac catheterisation. This found that women tended to have higher blood pressures (indeed the female subjects were marginally more likely to be hypertensive) and smaller cardiac volumes. Measuring simultaneous left ventricular pressure and volume we found that ventricular chamber function tended to be higher in women[12]. This is consistent with other work suggesting higher chamber function in women compared to men. In this study we also found significantly lower passive diastolic ventricular compliance in the female subjects compared to men. The results were essentially unchanged even after indexing to body size or height. Figure 3 shows the averaged pressure-volume loops for men and women and demonstrates the smaller ventricular volumes in women. It can also be appreciated that this group of women tended to have higher resting systolic pressure. The shape of the left ventricular pressure-volume loop is consistent with a higher late systolic peak in women as shown in the earlier non-invasive study of carotid waveforms.

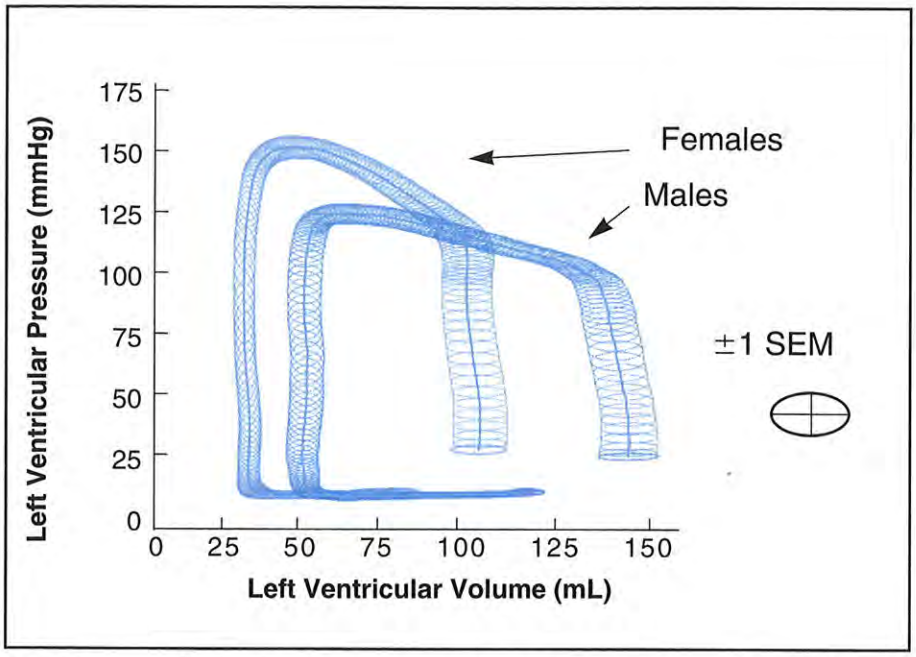


Figure 3: *Averaged Left ventricular pressure-volume loops for men and women. See text for details.*

A final study examined the acute effect of sublingual oestrogen on left ventricular function. As oestrogen exerts some of its vasodilating effect through calcium channel antagonism, it was hypothesised that there may have a negative inotropic effect on the heart. Despite achieving supraphysiological levels of oestrogen during the study, we did not find any significant change in left ventricular systolic or diastolic function[13].

Conclusions:

Women appear to have less ischaemic vascular disease than men until later in life. It cannot be stated, however, that this is due to the protective effect of oestrogen in younger life. While studies examining physiological effects of oestrogen have, in general, shown beneficial effects, prospective studies have yet not confirmed a role for hormone replacement therapy in primary or secondary cardiovascular protection. With respect to risk factors, HRT has been shown to have beneficial effects on serum lipids and appears to have a neutral effect on hypertension. We have found that there are significant gender-related differences in haemodynamics that may be related to differences in body size and possibly cardiac function. Early studies suggest a beneficial effect of hormone replacement therapy on pulsatile arterial function, which need to be confirmed prospectively. We have found no evidence of significant effect of oestrogen on cardiac function.

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Radio-Biologic impact of altered cell cycle regulation in head and neck squamous cell carcinoma

Charles Rees, Susan Henshall, David Quinn, Andrew Biankin, Ronaldo Bova, Robert Smee, Christopher Hughes and Robert Sutherland.

Background: The overall aim of this project was to examine the potential clinical use of aberrantly expressed cell cycle molecules in prognosis and in selection of appropriate treatment of head and neck squamous cell carcinoma (HNSCC) specifically, laryngeal squamous cell carcinoma (LSCC). Considerable evidence now suggests that aberrations in cell cycle regulators occur frequently in several human cancers. Increased expression of the G_1-phase cyclin, cyclin D1, has been described in 30-50% of cases of HNSCC and is associated with decreased survival. Furthermore, recent work suggests that overexpression of cyclin D1 in HNSCC may be a potential predictor of response to radiation therapy. The specific aim of this study was to determine if ectopic expression of cyclin D1 influences the relapse and disease-free interval of a group of patients diagnosed with early stage LSCC and treated by definitive radiotherapy for curative intent. We were also interested in the prognostic potential of other cell cycle regulators thought to play a role in the progression of HNSCC, in particular p53 and p16 INK4A.

Results: We examined $p16^{INK4A}$, p53 and cyclin D1 protein expression by immunohistochemistry in biopsies from 176 patients diagnosed with Tis/T1/T2 stage squamous cell carcinoma of the supraglottic and glottic larynx and treated with radiation therapy. At median follow-up of 68.5 months (range 1.9 to 211 months), 39 of 176 patients (22%) had failed radiation therapy and presented with either persistent or recurrent disease. Analysis was undertaken using Kaplan-Meier method and log-rank test for evaluation of contribution of known patient, tumour and treatment variables to relapse. Primary tumour stage ($p=0.0013$), degree of tumour differentiation ($p<0.0001$), cyclin D1 status ($p<0.0001$) and $p16^{INK4A}$ status ($P<0.0015$) were all highly significant in their association with disease-free survival. Cyclin D1 percentage score delineates two distinct groups of patients with poor prognosis: those with low cyclin D1 (0-30%) and those with high cyclin D1 (>75%). There was also a significant correlation between high $p16^{INK4A}$ expression and recurrence. The total treatment time in days was also significantly associated with disease-free survival. There was no relationship between p53 status and relapse.

Conclusions: The period of funding has resulted in the establishment of an internationally competitive series of early stage laryngeal SCC treated by radiation therapy with a median follow-up of 69 months (range 2 to 21 months). We have demonstrated the potential of using biomarkers associated with progression of cancer of the head and neck, specifically the cell cycle regulatory proteins cyclin D1 and $p16^{INK4A}$ to predict locoregional recurrence of disease. Future work will focus on the prognostic potential of these markers to predict disease-specific survival and their ability to predict response to varying treatment regimes.

The cell adhesion molecule E-Cadherin is widely expressed in human atherosclerotic lesions

Yuri V. Bobryshev, Reginald S.A. Lord, Teruo Watanabe and Tsuyoshi Ikezawa

Objective: Various cell adhesion molecules are expressed in atherogenesis and the significance of their involvement in atherosclerotic lesion formation is well appreciated. In the present work, we examined whether the Ca2+ -dependent cell adhesion molecule E-cadherin is also involved in atherogenesis.

Methods: Specimens of carotid artery and aorta were obtained at operation. Expression of E-cadherin was studied by an immunohistochemical method. The nature of E-cadherin-expressing cells was examined by comparative analysis of consecutive sections and by a double immunostaining procedure. An immunohistochemical approach was also applied to examine how the accumulation of oxidised low density lipoproteins (LDL) by intimal cells is associated with E-cadherin expression.

Results: No E-cadherin+ cells were found in normal non-atherosclerotic intima but E-cadherin+ cells were present in 96% of atherosclerotic lesions. In atherosclerotic intima, E-cadherin was expressed by intimal cells showing varying degrees of transformation into foam cells. These E-cadherin+ cells also contained oxidised LDL in their cytoplasm. Differing numbers of CD68+ foam cells (15% to 60%) expressed E-cadherin but all the CD68+ macrophages without signs of transformation into foam cells were negative for E-cadherin. Neither smooth muscle cells nor foam cells of smooth muscle cell origin (smooth muscle alpha-actin+) were found to be positive for E-cadherin. T-cells (CD3+) and endothelial cells (von Willebrand factor+) were also negative for E-cadherin. Only a few vascular dendritic cells (S-100+) expressed E-cadherin and their expression was weak. We also found that a large proportion (40% to 85%) of E-cadherin+ cells did not stain with any cell-type specific markers.

Conclusions: The finding that E-cadherin is expressed in artherosclerotic lesions expands our knowledge of cell adhesion molecules involved in atherogenesis. That E-cadherin is expressed in intimal cells transforming into foam cells suggests that lipid accumulation might be associated with the alteration and reorganisation of cell-to-cell interactions in atherogenesis. The present observations might assist in understanding the mechanisms associated with intracellular lipid accumulation.

Commentary By Prof. R.S.A. Lord

Dendritic cells comprise a family of members including Langerhans cells in the skin, interdigitating dendritic cells in lymphoid organs, dendritic cells in blood and veiled cells in the lymph. Dendritic cells are currently the focus of intense interest because they capture, process, and present antigen and thus initiate and modulate the immune response mediated by B and T lymphocytes.

The study abstracted above recognises that the cell adhesion molecule E-cadherin is present in atherosclerotic lesions and that E-cadherin is expressed by some vascular dendritic cells. This is the first report of this finding and further characterises dendritic cells.

Until our report dendritic cells were not recognised in the vessel wall and in standard text books of histology and pathology were categorically stated to be absent from the vessel wall. Our research supported by the St Vincent's Clinic Foundation has unequivocally demonstrated the presence of dendritic cells both in apparently normal arteries and in ever greater numbers in arteries affected by atherosclerosis. The role of dendritic cells and their function in plaques is assuming increasing importance.

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Established in 1992, St Vincent's Clinic Foundation strives to provide funds and support for medical research into matters of clinical significance.

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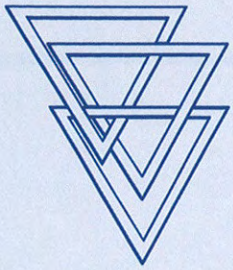

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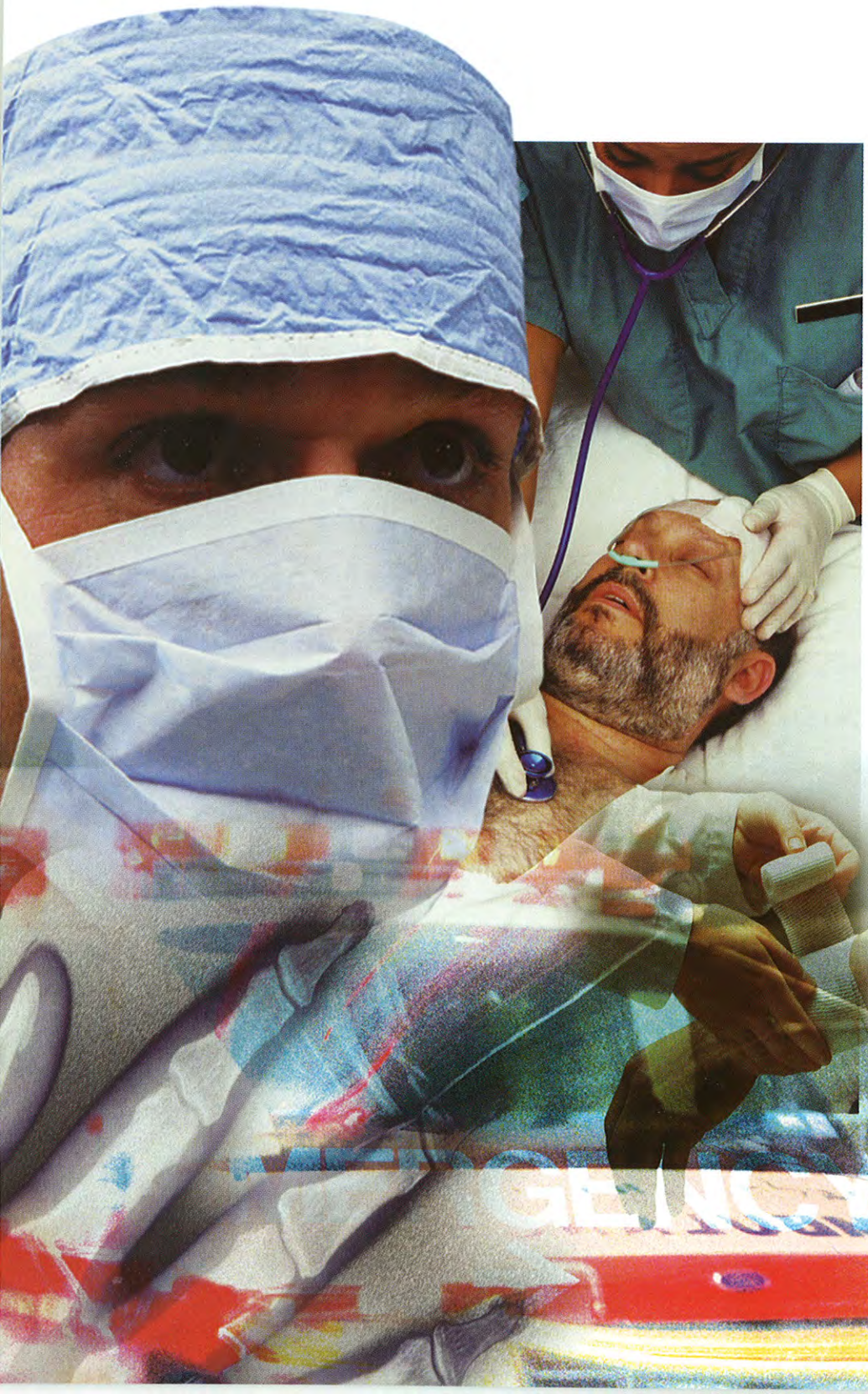

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