JUMMEC

International Conference on Health Sciences

'Partnership in Healthcare : Lessons Learnt and Future Challenges'

Sunway Pyramid Convention Centre,
Subang Jaya, Malaysia
6-8 May 2005

Supplement 1, 2006

ISSN 1823-7339

Journal of the
University of Malaya
Medical Centre

Journal of the University of Malaya Medical Centre

JUMMEC

Supplement 1 **2006**

Correspondence

All manuscripts, general correspondence and enquiries should be addressed to:
The Editor
c/o Dean's Office, University of Malaya Medical Centre
50603 Kuala Lumpur, Malaysia
Tel: (03) 7950-2077 Fax: (03) 7956-8841
E-mail: ZAKIIAH@ummc.edu.my

Publisher

JUMMEC is published twice a year by the University of Malaya Medical Centre, 50603 Kuala Lumpur, Malaysia

Printed by

Millennia Comms, Petaling Jaya, Selangor Darul Ehsan, Malaysia

CLINICAL IMPLICATIONS OF AGEING (OR LONGEVITY) IN MODERN WOMEN: AN INSIGHT BASED ON A NEW 5-YEAR LONGITUDINAL MULTIDISCIPLINARY STUDY

Khoo SK
The Betty Byrne Henderson Women's Health Research Centre, University of Queensland and Royal Brisbane and Women's Hospital, Brisbane, Australia

Introduction

There is a pressing need to know more, and to understand in depth, the difficulties facing women in the later part of their life in our present population, as population dynamics shift from control of growth to managing the consequences of ageing. The statistics are quite revealing: as women can expect to live over 80 years, they will spend an additional 30 years (or 40% of their life) after the menopause. The important consequences are seen in the heart and vascular system, the bone and the brain – with the expected disease burden, not only of cancer, but also heart disease, stroke, osteoporotic fracture and dementia.

The LAW study (longitudinal assessment of ageing in women) was designed to address the question: is it possible to live and grow old healthily? The study was a prospective clinical evaluation of psychosocial and pathophysiological changes in a population-based cohort of women, randomly recruited and aged 40-80 years. In its fifth year of a 5-year programme, the study was able to retain 97% of its cohort of 500, having performed 63,000 tests in 10,000 visits.

Findings

Although the longitudinal data are yet to become available, the clinical implications arising from the following interim results are interesting:

- About 5% have unsuspected valvular abnormalities by echocardiography. Deterioration of diastolic function is progressive and arterial stiffness increases over the four decades of life in the cohort.
- Although there is no change in intellectual ability, gradual cognitive decline occurs with age.
- Postural stability is reduced from age 40 onwards as a result of poor sensory perception, muscular balance and sensorimotor integration.
- Nearly 40% have osteoporosis; reduction in bone density is progressive. Overweight women show higher bone density.
- Markers of bone turnover increase with age; alkaline phosphatase levels correlate with bone density.
- Vitamin D deficiency is uncommon; after age 70, about 40% have marginal deficiency but frank deficiency is rare, even after age 70.
- Lean mass is maintained until a sharp decline from age 70; fat mass increases between age 50-70, with some decrease from age 70. Body contour is related to percentage of fat/lean mass.
- Age-related changes in FSH, oestradiol and DHEA-S are confirmed. Androstenedione, total/free testosterone and thyroid hormones remain unchanged.
- Genital prolapse is strongly associated with mode of delivery (16-fold risk) and age (age >60, 1.8-fold risk); urinary incontinence associated with body mass index and age.

Conclusion

This large database will form the basis for the identification of risks factors from this multidisciplinary evaluation, factors which are strongly associated with adverse health-related changes especially in the cardiovascular, cognitive and bone systems. It is envisaged that a plan to modify these risk factors will be developed and tested in a randomized controlled intervention study. The study outcome will have a significant impact on healthy ageing and sustainable health for individual women and the community.

BIOMEDICAL ETHICS: PRACTICE AND CHALLENGES IN SOUTHEAST ASIA

Darryl M
Regional Unit for Social and Human Sciences in Asia and the Pacific (RUSHSAP), UNESCO Bangkok, 920 Sukhumvit Road, Prakanong, Bangkok, Thailand 10110; Eubios Ethics Institute, Japan, New Zealand, Thailand; United Nations University, Japan

Introduction

This paper looks at current practices and characteristics of bioethics in Southeast Asia and the Pacific, and how medical ethics is evolving. Ethics is a concept balancing benefits and risks of choices and decisions. The underlying heritage of ethics can be seen in all cultures, religions, and in ancient writings from around the world. We in fact cannot trace the origin of bioethics back to their beginning, as the relationships between human beings within their society, with nature and God, are formed at an earlier stage than our history would tell us.

There are at least three ways to view ethics:

1. **Descriptive ethics** is the way people view life, their moral interactions and responsibilities with others in their life. Information we gather is used to describe many things, and there are many ethical issues related to gathering information and storing information.

2. **Prescriptive ethics** is to tell others what is ethically good or bad, or what principles are most important in making such decisions. It may also be to say something or someone has rights, and others have duties to them. It is related to policy making and law.

3. **Interactive ethics** is discussion and debate between people, groups within society, and communities, and clearly information ethics is central to shaping the types and forms of interactions that are possible.

This paper will give examples of trends in different cultures with respect to these approaches to ethics in a range of medical ethics issues. Some trends are regional but most are related to some aspects of globalization, the expansion of respect for human rights, and the shift towards individualism away from communitarian ways of approaching ethics. Modern Western medicine took hold in Asia in the nineteenth century (1). The rapid progress of medical technology has led to challenges in the way that medicine is practised. The existing systems and patterns that are seen in the relationships between patients, families, health professionals, and the society in general changed. At the same time, as technology was transferred, some values were also imported beyond the general acceptance that new technology must be better than old (2). A number of countries in Asia and the Pacific were colonized, and a few communities and Islands exist still as colonies, which has significantly influenced their values and the practice of medicine.

One of the current issues in cross-cultural ethics is whether respect for individual autonomy and informed consent should be universal, and who should be told the truth about medical diagnoses first? The issues are faced in not only Japan or Asia, but in most traditional societies. Compared to a few years before the modern response is to reject 'paternalism' and over-dominant health care professionals who make decisions for patient's treatment without adequate respect for their voices and values. In the past many more health care professionals, and especially physicians, thought it was not in a patient's best interest to be told. Whether past doctors were less or more competent to explain and counsel the patient is unknown - though if we could compare the times for average consultations between patient and physician it would give us some part of the indication.

Some health care professionals may also consider that the family knows the patient better than they, and share the responsibility of consultation with family members, so-called 'familial autonomy'. There are some families in all societies who function as one, and other families which function as relationships between individuals (3). It may be difficult to know which type of family each one is. Cases of 'familial consent' are also declining when compared to 150 years ago.

When the change in public opinion on the desire to be told the truth about their disease actually occurred- and in fact whether there was a change in this desire to know what was happening at all, is unknown. It could

have been merely a recognition of civil rights that acknowledged this desire to know what was happening and there may not be any change in desire to know what is happening from the patient's perspective over 150 years. The patients are more able to express themselves now.

The black episode in Asian medical ethics is the war-time experiments conducted on prisoners in Manchuria China, while China was under the Japanese occupation in World War II. At least 3,000 persons, mainly Chinese but some Korean, were murdered by or after vivisection and other experiments in facilities under Unit 731 at several locations in China. The functions included vivisection practice for newly qualified army surgeons, intentional infection of diseases, trials of non-standardized treatments, and discovering the tolerances of the human body (4). Neither Japanese nor Chinese bioethics has sufficiently analysed these experiments and the ethical issues they raise (4, 5, 6), in contrast to the German preoccupation with their war crimes. Because of the opportunity to have access to the best medical research facilties in Asia, many physicians went to the Unit, and after the war it was only in the mid-1990s that some members of the Unit started to confess and apologise for their actions, as they reached old age. However, the discussion of the issues in medical ethics has only recently begun. Since the best medical students often trained in Unit 731, because it was the best equipped research laboratory in Asia at the time, the preoccupation with technical as opposed to spiritual issues of medicine is consistent with mentality of medical experimentation that lead to such extremes.

When individuals in Asia are asked to give their reasoning for their opinions over bioethical issues such as genetic manipulation of humans or animals, there is as much variety in opinions expressed by members of the general public in Japan as in Australia (7). From the results of the International Bioethics Survey conducted in 1993 in ten countries in the Asia Pacific Region (Australia, Hong Kong, India, Israel, Japan, New Zealand, the Philippines, Russia, Singapore, Thailand), we can see many people perceive simultaneously both benefits and risks from science and technology (7). The diversity of reasoning exposed in the survey on a variety of questions was independent of education or age, and similar diversity of reasoning was found among members of the public, high school biology teachers, and scientists. The overall statistical results are similar to results of surveys in Australasia, Europe, India, Russia, Thailand and the U.S.A. Sadly, we cannot compare to 150 years ago because surveys were not conducted on these issues.

Assisted reproductive technology is being used in Asia, in countries with low birth rates like Japan, and those with high birth rates like India. There have been many children born from the use of in vitro fertilization (IVF) followed by embryo transfer. There are issues of gender selection in Korea and India, as well as some other countries. Comparisons to medical ethics of reproduction over 150 years will be made.

We need in-depth cross-cultural dialogue and study rather than defining one ethics as Asian and one as not. The interesting point for cross-cultural ethics is at what point do you call something distinctly 'Malaysian' or 'Asian' or 'Tongan'. The answer to this may depend upon what literature and practices we are familiar with. Tsai and others have shown that ancient Chinese medical ethics may follow a four principles approach, but with more emphasis on beneficence than autonomy (8).

One of the dramatic changes is the decrease in trust and respect towards physicians over the past 150 years. In the International Bioethics Survey conducted in 1993 in ten countries across Asia and the Pacific, Japan was found to be the least trusting of statements by doctors (7). Arguably, the lack of trust has been a barrier in the implementation of some techniques, such as organ transplants (9). One of the reasons for a lack of trust is the lack of truth-telling and openness (10).

The majority of the world's population live in Asia, the popular international religions of the world originated in Asia, and the world's largest English-speaking country (India) is in Asia. Considering this, we may ask why there have hitherto been so few papers from Asia published in most journals dealing with medical or environmental ethics. While the economic centre of the world has been shifting to Asia, and most people are using products made from Asian-based companies, few papers in bioethics have been written from Asia. This is one of the reasons why I founded and continue to edit the *Eubios Journal of Asian and International Bioethics (EJAIB)* (online http://www.unescobkk.org/eubios/EJAIB.htm). EJAIB publishes about 70-80 papers a year, and is the official journal of the Asian Bioethics Association (11). When we start to explore, there are actually a growing number of publications by authors in or about Asia, and conference proceedings online include around 500 papers, and we could say that the 'Far East of Bioethics' (9) is no longer inaccessible for those who wish access, though there is much more descriptive work required.

There are other key words that emerge from Asia, such as harmony and tolerance, respect and reverence, and

ambiguity (10). There is diversity within every society over the bioethics that each person has, and the relationships that shape the balancing of principles or ideals. While Asia and the Pacific have a rich tradition in views of life, there continues to be a gap between the real world and the ideal. Few of the ideals of respecting life are actually applied to everyday applications, and to deciding how to use medical technology. However, this may not be so different from the real world of the clinic in most societies, and probably there is less gap now than 150 years ago.

Conclusion

The media is clearly a major factor in influencing bioethical decisions in all countries. The discussion of bioethics can transform the whole style of society. The bioethics debate may be the catalyst required to transform countries from paternalistic feudalism through paternalistic democracy into democracies. People of any country may resist the rapid change and globalization of ethics, ideals, and paradigms as ethnic and national identities may be changed, or lost, especially countries with such a long history of culture. How countries approach globalization is a fundamental question, but many individuals in countries with access to common news media have already answered the question by their converging lifestyles and values. To the extent that human rights and the environment are more respected, this trend is to be encouraged.

References

Note that many of these are online at the Eubios Ethics Institute website http://www2.unescobkk.org/eubios/

1. Macer DRJ. Bioethics in Asia in Encyclopedia of the Human Genome: Nature MacMillan, 2003; pgs 277-280.
2. Macer DRJ. End of life care in Japan, in Blank RH, eds., End of Life Care Across the World, MIT Press, 2005.
3. Asai A. Barriers to informed consent in Japan. Eubios J Asian Int Bioeth 1996; 6:91-3.
4. Tsuchiya T. Why Japanese doctors performed human experiments in China 1933-1945, Eubios J Asian Int Bioeth 2000; 6.6: 179-80.
5. Morioka M. Commentary on Tsuchiya, Eubios J Asian Int Bioeth 2000; 6.6: 180-1.
6. Nie JB. Challenges of Japanese doctor's human experimentation in China for East Asian and Chinese bioethics, Eubios J Asian Int Bioeth 2001; 11.1: 3-7.
7. Macer DRJ. Bioethics for the People by the People Christchurch: Eubios Ethics Institute, 1994.
8. Tsai DFC. Ancient Chinese medical ethics and the four principles of biomedical ethics. J Med Ethics 1999; 25(3).
9. Macer DRJ. The 'far east' of biological ethics. Nature 1992; 359: 770.
10. Macer D. Bioethics in and from Asia, J Med Ethics 1999; 25: 293-295.
11. Macer DRJ. Bioethics is love of life. Christchurch, New Zealand: Eubios Ethics Institute 1998.

PROBLEM-BASED LEARNING: DOES IT MATTER WHAT WE CALL IT?

Azila NMA
Department of Molecular Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Introduction

With changing demands in healthcare, the development of qualities and skills of the affective domain becomes a desirable learning outcome. These include development of appropriate attitude and value systems, ethics, professionalism, social responsibility, critical reasoning, problem-solving and communication skills, and may also include managerial, entrepreneurial and life-long learning skills. Therefore, in the last three decades delivery approaches of medical education have shifted from factual didactic teaching towards student-centred contextual learning, with the most prominent approach being problem-based learning (PBL) (1,2). Evidence indicates that active participation in learning is more satisfying than passive transfer of knowledge, and it enhances retention and recall (3). The popularity of this paradigm shift has also been encouraged by studies implying that PBL improves these qualities with few, if any, detectable knowledge deficits (4, 5, 6).

However, as the dominance of PBL began to grow in many regions one could note the presence of those who resist the change, even in the medical schools at which PBL is well established, such as the Universities of Maastricht, McMaster, Southern Illinois, and New Mexico (7). There are commentaries (5) and papers (4) published that critique the effectiveness of PBL. However, a common concern of medical teachers, especially in Asia, is that the PBL approach involves too few structured teaching activities. Although students initially often feel more motivated to acquire the implicit competence of the practising doctor rather than to absorb large volumes of explicit scientific theories their anxiety sets in when they face assessment. To address these concerns, various strategies were utilised by the implementers of PBL or 'PBL-oriented' curriculum, such as one, inserting various formalized educational initiatives reminiscent of traditional medical school courses, two, developing a variety of reusable resources (guide or block books, multimedia or focussed notes) to impart factual knowledge more efficiently, three, developing more integrated cognitive techniques for facilitating the comprehension of complex data, four, providing structured self-learning packages, and five, using various patient case formats. As many schools world-wide experiment with PBL with a variety of modifications, many names have emerged either to improve acceptance by their academic staff members or to reflect the extent of PBL included. This paper attempts to clarify this confusion.

Educational Considerations

1. ***Theoretical and Cognitive Psychological Considerations***

   The main focus of traditional medical teaching-learning outcomes was on the development of **cognitive** and **psychomotor domains**. In the cognitive domain the emphasis has been on content knowledge and factual recall with trends to improve intellectual skill of discriminations, forming concrete and defined concepts, and understanding rules. In recent years educators had stressed the importance of the **affective domain** to complement the cognitive and psychomotor domains. Therefore, a mixture of teaching-learning methods had been utilised. However, it is pertinent to note that method alone is not adequate. What matters is what happens within the method.

   - Research has shown that rating considerations by students for effective teachers were those who are better communicators and have worked out how to help students learn new concepts, principles and problem-solving skills and were able to discuss materials which facilitate better learning (8).
   - Findings indicated that appropriate instructional design is required to achieve intended learning outcomes. Instructional events that provide and promote information gathering and correlations tend to enhance the possibilities of learning (9).

2. ***The essence of Problem-based Learning (PBL)***
In the PBL approach, problems or case scenarios act as stimuli for learning, encourage active processing of information and activation of prior knowledge, provide opportunities for elaboration and organization of knowledge (9,10). Problem-based learning involves a three-way interaction, the **curriculum** with its associated learning resources, the **learners** and their level of prior knowledge and the **teachers** with their facilitation skills. Schmidt (9) cited three educational principles to suggest information processing orientation in PBL (9). First, prior knowledge provides a platform in helping students understand and structure new information, showing that current learning is affected by past learning. Secondly, with contextual learning, the closer the resemblance between a situation in which something is learnt with a situation in which it will be applied in practice, the more likely the transfer of learning will occur. Thirdly, information will be better understood and retained if there is an opportunity for **elaboration of knowledge**, such as discussion, answering questions, teaching peers and giving critique. Davis and Harden (6) mentioned various stages of a continuum that spanned from the traditional teacher-centred content-oriented approach to the problem-based, task-based student-centred approach (Table 1).

Table 1. Problem-based learning continuum (adapted from Davis and Harden (6))

'Genomic clones' of PBL	Learning orientation
1. Theoretical learning (Rul)	Information provided using traditional lecture and standard textbooks.
2. Problem-assisted learning (Rul -> Eg)	Information and principles taught first with the opportunity to apply it to problems/cases.
3. Problem-focused learning (Rul -> Eg -> Rul)	Information provided followed by a problem. Learning of the principles of the subject then follows.
4. Cooperative learning [CL] (Rul -> Eg)	Working as a team with cases used to either trigger or integrate learning.
5. Problem-initiated learning (Eg??) -> Rul	Problems/cases used as a trigger at the beginning of learning but only to initiate interest in the topic.
6. Problem-based mixed approach [Hybrid PBL] (mixed Rul -> Eg and Eg -> Rul)	A combination of problem-based and information-based learning.
7. Embedded PBL (mixed Rul -> Eg and Eg -> Rul)	Isolated PBL course within a traditional programme, e.g., a PBL physiology course in the year 1 of a basically traditional medical programme.
8. Case-driven learning [CDL] (Eg -> Rul)	The problem, which could be the real world tasks or health care cases used as the trigger, is the driving force for the learning of appropriate principles or rules.
9. Prog. for integrated learning [PILs] (Eg -> Rul)	(Eg -> Rul)
10. Problem-/Task-based learning (PBL/TBL) (Eg -> Rul)	

Eg - Concepts and principles built/learnt out of working on examples, patients and/or tasks
Rul - Emphasis on theoretical concepts and principles

Although this list of continuum may add confusion to the new PBL novices, it, however, provides one a view that there is a range of options available in trying to implement PBL, two curriculum developers and teachers implementing a medical programme with a discussion reference on the stance to be taken with regard to PBL, three a useful way to describe and evaluate where their curriculum stands on the PBL continuum.

In contrast we are also constantly reminded, by the PBL purist (2), of the risk of compromising the benefits of PBL when it is blended, hybridized, or placed in competition with more traditional approaches to education. It is said that in curricula that combine PBL with traditional methods, students may view PBL as secondary to a more traditional aspects of the curriculum, especially if assessment strategies do not reflect the objective of the curriculum in a significant way. This opinion seems to concur with our local setting where the traditional curriculum delivery is still dominant. In addition, close association between lecture and tutorial materials may attenuate students' self-directed evaluation of new information and provide a false sense of a deeper understanding.

3. ***Influence of teachers stance on student learning even in a PBL oriented curriculum.*** Regardless of which stage of the PBL continuum used to deliver the curriculum, an important factor that affects the way students learn is the learning environment. Given that all facilities are equally available to students in an institution, the teaching conceptions of the teacher is a powerful force affecting the way students learn (7). Thus within the same curriculum, it is proposed (12) that various number of models could be in operation within the classroom/group, related to the teacher/facilitator on duty. Table 2 shows five models classified according to the teachers' stance on knowledge. In Model I, the teacher sees himself as a guide to knowledge acquisition and problem solution inducing passive learning while in Model II he views his role as a demonstrator of excellence in practice inducing learning for professional action. In ModelV the teacher views PBL as a way to learn critical contestability thus encouraging students to not only manage their own learning but to develop their own critical perspectives.

Conclusion

PBL is definitely 'spreading' in medical schools. However, its implementation from its initial conceptions will change because of both demands and opportunities placed on schools, and because of 'poor' or half-hearted implementation. Some will make more use of the 'pure' model; other will make various modifications which hybridize with traditional methods. The approach eventually implemented by each institution will reflect the willingness of their faculty to shift from the role of 'instructor' of knowledge to 'facilitator' of learning and to accept central rather than departmental control of the curriculum. It will also be influenced by the desired outcomes of the course, the 'readiness' of staff and students and the availability of resources.

Whichever the delivery approach is used or called, a point to emphasise is that we should strive to achieve an optimal balance between factual content-based 'teaching-learning' activities and practical performance-based 'training' components of the undergraduate medical programme, including behaviour and attitude. For planners/teachers, the key is not to decide whether to implement PBL or not but to consider the extent to which they should introduce PBL into their own teaching/curriculum. Therefore, there is continuing necessity for training teachers so that they understand the PBL philosophy and to be able to facilitate small-group PBL sessions effectively. Finally, assessment methods for students in PBL programmes need to be consistent with how students learn.

Table 2. Models for problem-based learning (adapted from Sanin-Baden)

Purpose for using PBL	**Model I** Epistemological competence	**Model II** Professional action	**Model III** Interdisciplinary understanding	**Model IV** Trans-disciplinary learning	**Model V** Critical contestability
Teachers's stance on knowledge	Propositional	Practical & performative	Propositional, Practical & performative	Examine & testing out of given knowledge & framework	Contingent, contextual and constructed
Facilitator	A guide to obtain solution & to understand the correct propositional knowledge	Demonstrator of skills & a guide to 'best practices'	A coordinator of knowledge & skill acquisition acros boundaries of both	An orchestrator of opportunities for learning (in its widest sense)	A commentator, a challenger and decoder of cultures, disciplines and traditions
Problem scenario	Solution known & designed to promote cognitive understanding	Focused on real life situation that requires an effective solution	Need to acquire knowledge to do problem (knowledge with action).	Characterised by resolving & managing dilemmas	Multidimensional, offer options for alternative ways of knowing and being
Student and Student Learning	Receivers of knowledge & apply knowledge to solve/manage a problem	Outcome focus acquisition of knowledge & skill for work	Synthesize knowledge with skills across discipline boundaries.	Critical thought and moving away from discipline to understand them	Explorers of underlying structures & belief systems
Assessment	Testing of knowledge to ensure students have developed epistemological competence	Testing of skills and competencies for the work place supported by a body of knowledge	Examine skills & knowledge in a context that may have been learned in context	Demonstrate an integrated understanding of knowledge across disciplines	Open-ended and flexible

Reference

1. Albanese MA, Mitchell S. Problem-based learning: A review of literature on outcomes and implementation issues. Acad Med 1993; 68, 52-80.
2. Camp G. Problem-based learning: A paradigm shift or a passing fad? Med Educ. 1996; 1:2.
3. Bransford JD, Brown AL, Cocking RR, eds, How people learn: brain, mind, experience, and school. National Academy of Science, Washington DC; National Academic Press, 2000.
4. Norman GR, Schmidt HG. Effectiveness of problem-based learning curricula: theory practice and paper darts. Med Educ 2000; 69(9): 557-565.
5. Arrow R, Norman G. The effectiveness of problem-based learning: the debate continues. Is meta-analysis helpful? Med. Educ. 2003; 37: 1131-32
6. Davis MH, Harden RM. Problem-based learning: a practical guide. AMEE Education Guide. Centre for Medical Education, Dundee, Scotland, 1999.
7. Personal Communications.
8. Brown G. Effective Teaching. In Quality Assurance for University Teaching. Society for Research into Higher Education and the Open University Press 1993; pgs 211-232.
9. Okey JR. Procedures of lesson design. In : LJ Briggs, et al, eds. Instructional Design: Principles and Application. 2nd Edition. Education Technology Publications 1991; 192-208.
10. Schmidt HG. Problem-based learning: rationale and description. Med Educ 1983; 17:11-16.
11. Barrows HS. Practice-based learning applied to medical education. Springfield Illinois: Southern Illinois University School of Medicine, 1994.
12. Sanin-Baden M. Critical perspectives on PBL. In: Problem-based learning in higher education: untold stories. London: University Press, 2000; 123-134.

EMERGING VIRAL INFECTIONS: A FRIGHTENING APOCALYPTIC FUTURE

Lam SK
Faculty of Medicine, University of Malaya and Asia Pacific Society for Medical Virology, Kuala Lumpur, Malaysia

Introduction

In the early 1990s, the World Health Organization initiated a new programme on Emerging and Re-emerging Infections for member countries because of increasing incidence of global outbreaks. Since then, the world has witnessed over 30 outbreaks that fall into this category. Old diseases like dengue and tuberculosis have re-emerged and posed significant public health problems. Antibiotic resistant bacteria like methicillin-resistant *Staphylococcus aureus* are creating challenges in global health care.

Many of the emerging infectious diseases that have the potential for global spread are found to be due to viruses and have their origin in Southeast Asia. Malaysia has been responsible for a number of these outbreaks in the last decade. In 1997, an outbreak of the fatal hand, foot and mouth disease caused by enterovirus 71 resulted in the death of 40 children due to viral encephalitis (1). The outbreak of polyarthritis in 1999 was found to be caused by chikungunya virus and believed to be brought in by migrant workers from a neighbouring country (2). This disease has now become endemic in the country.

The most dramatic emerging disease ever experienced in Malaysia was the severe outbreak of viral encephalitis among pig farmers and the causative agent was identified to be a novel deadly virus, subsequently named Nipah virus (3). Since then, there has been no evidence that Nipah virus has been active in the country despite the fact that Pteropus fruit bats are a known reservoir (4). However, there is serological evidence that the virus is present in bats in several countries, including Cambodia, Thailand and India. Since 2001, there have been at least four outbreaks of Nipah infection in Bangladesh (5). Several unusual characteristics make the Bangladesh outbreaks somewhat different from that seen in Malaysia. There were cases among young children whereas mainly adults were infected in Malaysia. Pigs were not involved in Bangladesh and it was speculated that infection was the result of children consuming fruits partially eaten by fruit bats. The mortality rate was between 60 to 70%, which was higher than that seen in Malaysia (40%). Another unusual feature of the Bangladesh outbreaks was evidence of familial clustering of cases, suggesting human-to-human spread, a phenomenon not seen in Malaysia. Since these bats are migratory by nature, it will not be surprising that the virus will further spread in the future.

In the Southeast Asian region, two major viral outbreaks, severe acute respiratory syndrome (6) and avian influenza A (7), have occurred in Hong Kong and believed to have originated from China. Both these fatal respiratory diseases are zoonotic in nature. The fear of a pandemic avian influenza is highlighted by the genetic changes seen in the H5N1 virus that allow the virus to freely cross species barriers. From aquatic birds, the virus has now become endemic in domestic poultry such as chicken, ducks, geese and quails. Up to 80% of free-range domestic ducks are believed to be infected with H5 virus, displaying no or mild symptoms, leaving them free to disseminate the virus widely. In addition, tigers, leopards and even cats have been fatally infected by this virus and it will not be surprising if these felines may prove to be a more efficient source of human infection in the future. In over-crowded mixed farms as well as backyard farms, the interchange of genetic materials among different animals, including pigs, may lead to a H5 strain that will spread rapidly among humans, much like the H3 and H1 influenza A viruses. If this H5 reassortant strain maintains its high virulence of at least 50% mortality, we are indeed facing a bleak future.

The convergence of many risk factors provides an ideal setting for the emergence and re-emergence for infectious diseases (8). This is especially so in developing countries in Southeast Asia with poor access to basic amenities such as clean water and good sanitation. Dependency on natural resources and the opening of pristine forests for agriculture, logging and dam building will result in ecological changes and alter the transmission patterns. Increased human contacts with exotic microorganisms in animal reservoirs and the environment as a result of changing land use patterns can lead to the emergence a new infectious diseases. Increasing population in developing countries and demographic changes due to rural-urban migration will further erode existing health and social infrastructures.

Climatic changes such as *El Nino* have an impact on disease burden transmitted by mosquitoes. Dengue has re-emerged as an important cause of epidemics in many countries and Southeast Asia and the Western Pacific have reported increasing incidence. The persistence of *Aedes aegypti* mosquito density has already rendered the introduction of chikungunya virus into the country through migrant workers and it is feared that yellow fever virus which shares the same vector may one day finds its way into the country. This possibility becomes real because of increasing tourism and trade with yellow fever endemic countries.

In the Southeast Asia region, more developed countries like Singapore and Malaysia have become dependent on migrant workers from less developed countries such as Indonesia, Bangladesh, Pakistan, India, Thailand and Myanmar. In Malaysia, over a million workers are currently employed to service the various industrial sectors. Many of these workers enter the country to work illegally and are not subjected to medical screening which is mandatory prior to entering the country. A pilot study among migrant workers in Malaysia showed that these workers had a high carriage rate for viral hepatitis B, C and E as well as HIV, and suffered from sexually transmitted diseases due to resistant bacteria pathogens (9). The spread of HIV in the region can also be attributed to substance abuse such as intravenous drug use and to sexual promiscuousity. Due to cultural and religious sensitivities, control programmes involving needle exchange, sex education and condom usage are not actively promoted.

Good farming practices are the exception rather than the norm in many countries in Asia, creating the potential for virus spread. Intense open mixed farming has contributed to inter-species spread and genetic exchanges. Backyard farms and free-range domestic animals such as ducks, chickens and pigs abound and the keeping of fighting cocks is proving to be unusual control problems in the fight against avian influenza. The traditional preference for freshly slaughtered poultry in market places has also posed serious problems in control measures. In addition, exotic meat is a gastronomic delight for Asians, especially among the Chinese, and this has led to the proliferation of wildlife markets and the transmission of virus such as SARS coronavirus to humans.

WHO has urged each member country to have a plan of preparedness for emerging diseases and global pandemics in the light of the emergence of H5. One of the recommendations in the face of an influenza pandemic is the stockpiling of antivirals and vaccines. Due to economic reasons, such stockpiles are less than adequate and the scarcity of expensive antivirals such as oseltamivir will definitely deprive access to developing countries. A pandemic vaccine for avian influenza requires high technology such as reverse genetics and this is not widely available in the region.

Besides avian influenza, other viral outbreaks such as West Nile encephalitis, Nipah encephalitis, African haemorrhagic fevers like Ebola and Marburg will continue to pose global treats. Surveillance of emerging and re-emerging diseases in Southeast Asia is of paramount importance given the fact that the region is a hotspot of emerging diseases.

Conclusion

The question is not if there will be a global pandemic of a disease such as avian influenza, but when. The writing is on the wall but despite this early warning, we still face a frightening apocalyptic future due to our inadequacies and the ability of this virus to outsmart us.

References

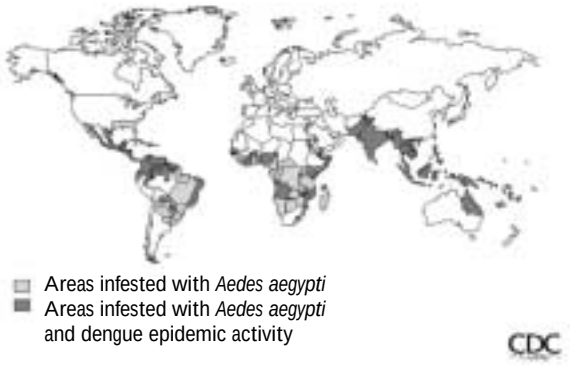
1. Lucy Lum CS, Wong KT, Lam SK, et al. Neurogenic pulmonary oedema and enterovirus 71 encephalomyelitis. Lancet 1998; 352, 1391.
2. Lam SK, Chua KB, Hooi PS, et al. Chikungunya infection - An emerging disease in Malaysia. Southeast Asian. J Trop Med Public Health 2001; 32: 447-451.
3. Chua KB, Goh MJ, Wong KT, et al. Fatal encephalitis due to Nipah virus among pig farmers in Malaysia. Lancet 1999; 354:1257-59.
4. Chua KB, Koh CL, Hooi PS, et al. Isolation of Nipah virus from Malaysian Island flying foxes. Microbes and Infection 2002; 4: 145-151.
5. Vincent P. Hsu, Mohammed Jahangir Hossain, Umesh D. Parashar et al. Nipah virus encephalitis reemergence, Bangladesh. Emerg. Infect. Dis. 2004; 10 : 2082-2087.
6. Yuen KY, Chan PKS, Peiris M, et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. Lancet 1998; 351:467-471.
7. Nelson Lee, David Hui, Alan Wu, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003; 348:1986-1994.
8. I.O.M. Microbial Threats to Health: Emergence, Detection and Response. In: Smolinski MS, Hamburg MA, Lederberg J, eds., The National Academic Press, 2003.
9. Ngeow YF, Ng KP, Savithri DP, et al. Health problems of foreign workers - Microbiological investigations. JUMMEC 2002; 1:67-69.

DENGUE AND DENGUE HAEMORRHAGIC FEVER IN MALAYSIA

Shamala DS
WHO Collaborating Centre for Arbovirus Reference and Research (DF/DHF), Department of Medical Microbiology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.

Introduction

Dengue and dengue haemorrhagic fever (DHF) are caused by one of four closely related, but antigenically distinct, virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4) of the genus Flavivirus (1). Infection with one of these serotypes does not cross-protect, so persons living in a dengue-endemic area can have up to four dengue infections during their lifetimes. Dengue is an urban disease of the tropics, and the viruses that cause it are maintained in a cycle that involves humans and the *Aedes aegypti*, a domestic, day-biting mosquito that prefers to feed on humans. In some regions other Aedes species, such as *Ae. albopictus* and *Ae. polynesiensis* are also involved. Infection with a dengue virus serotype can produce a spectrum of clinical illness, ranging from a non-specific viral syndrome to severe and fatal hemorrhagic disease. Important risk factors for DHF include the strain and serotype of the virus involved, as well as the age, immune status, and genetic predisposition of the patient.



World Distribution of Dengue – 2000

Annually, there are an estimated 100 million cases of DF and 250,000-500,000 cases of DHF in the world with the average case fatality rate being 5%. Half of the world's population live in areas at risk of infection and these are popular destinations, too. The population of the world is projected to be 8.3 billion by the year 2025 with the increase occurring in urban settings, which has resulted in uncontrolled and unplanned urbanization of developing countries especially in the tropics. With modernisation, especially increased mobility of people, there has been a global resurgence of epidemic dengue fever and the emergence of DHF is related to these changes. The first reported epidemics of dengue fever occurred in 1779-1780 in Asia, Africa, and North America, indicating that these viruses and their mosquito vector have had a worldwide distribution in the tropics for more than 200 years. A global pandemic of dengue began in Southeast Asia after World War II and has intensified during the last 15 years. In Southeast Asia, epidemic DHF first appeared in the 1950s, but by 1975 it had become a leading cause of hospitalization and death among children in many countries. In the 1980s, DHF began a second expansion into Asia when Sri Lanka, India, and the Maldives Islands had their first major DHF epidemics; Pakistan first reported an epidemic of dengue fever in 1994. In Taiwan and the People's Republic of China, epidemic dengue fever recurred – occurred after a 35-year absence in 1980. Singapore also had a resurgence of dengue/DHF from 1990 to 1994 after a successful control program had prevented significant transmission for over 20 years (5). In other countries of Asia where DHF is endemic, the epidemics have become progressively larger in the last 15 years.

Despite poor surveillance for dengue in Africa, we know that epidemic dengue fever caused by all four serotypes has increased dramatically since 1980 with most activity occurring in East Africa. Epidemic dengue fever re-emerged as a public health problem in the Americas in the late 1970s after a 40-year quiescence, which was due to an *Ae. aegypti* eradication programme in 1946 to prevent urban epidemics of yellow fever. In the 1970s, surveillance and control programmes waned or merged with other control programmes and hence by the 1980s *Ae aegypti* had reinfested these areas. Hence from a state of non-endemicity (no viruses) or hypoendemicity (only a single serotype) a state of hyperendemicity was reached with all four serotypes circulating. This resulted in increased frequency of epidemic activity and the emergence of DHF as a major public health problem. The sequence of events associated with the changing epidemiology of dengue in the Americas was nearly identical to that which occurred in Southeast Asia in the 1950s-70s.

The reasons for this dramatic global emergence of dengue/DHF as a major public health problem are complex and not well understood (10). However, several important factors can be identified. Firstly, effective mosquito control is virtually nonexistent in most dengue-endemic countries. Ultra-low-volume insecticide space sprays for adult mosquito control has been shown to be a relatively ineffective approach for controlling *Ae. aegypti*. Secondly, major global demographic changes such as uncontrolled urbanization and concurrent population growth especially in the tropics have resulted in substandard housing and inadequate water, sewer, and waste management systems, all of which increase *Ae. aegypti* population densities and facilitate transmission of *Ae. aegypti*-borne disease. Consumer goods packaged in non-biodegradable plastic and automobile tyres, discarded into the environment provide ideal larval habitats. This has led to increased population densities of the principle mosquito vector, *Ae. aegypti*. Thirdly, increased travel by airplane has helped transport dengue viruses between population centres of the tropics, resulting in a constant exchange of dengue viruses and other pathogens. Lastly, in most countries the public health infrastructure has deteriorated.

The earliest record of dengue in Malaysia was published by Skae in 1902 of an outbreak in Penang. Subsequently in 1904, 1932 qnd 1933 more reports were made of dengue outbreaks in various parts of Peninsular Malaysia largely in ports and large cities. Dengue virus was first isolated in 1950 by Smithburn and the first laboratory confirmation was carried out by the Institute of Medical Research in 1953. Since then, pockets of epidemics began to occur in urban areas of Peninsular Malaysia. In Malaysia, dengue was made a notifiable disease in April 1971. From then on increased numbers were noted and DF/DHF/DSS became a major public health problem. Between 1973-1987 the mean incidence of DF was noted to be 2-11 per 100,000 while that of DHF was 0.5-8 per 100,000. The major ethnic group affected were the Chinese and the major age group being 10-19 years. A seasonal pattern was noted with cases increasing following the rainy seasons. Most cases were in urban areas. Reasons that were cited for the various outbreaks as well the increase in cases were exodus of susceptibles from non-endemic to endemic areas, rapid urbanization, a disturbance in human ecology, creation of slums and squatters and living conditions that perpetuated vector breeding.

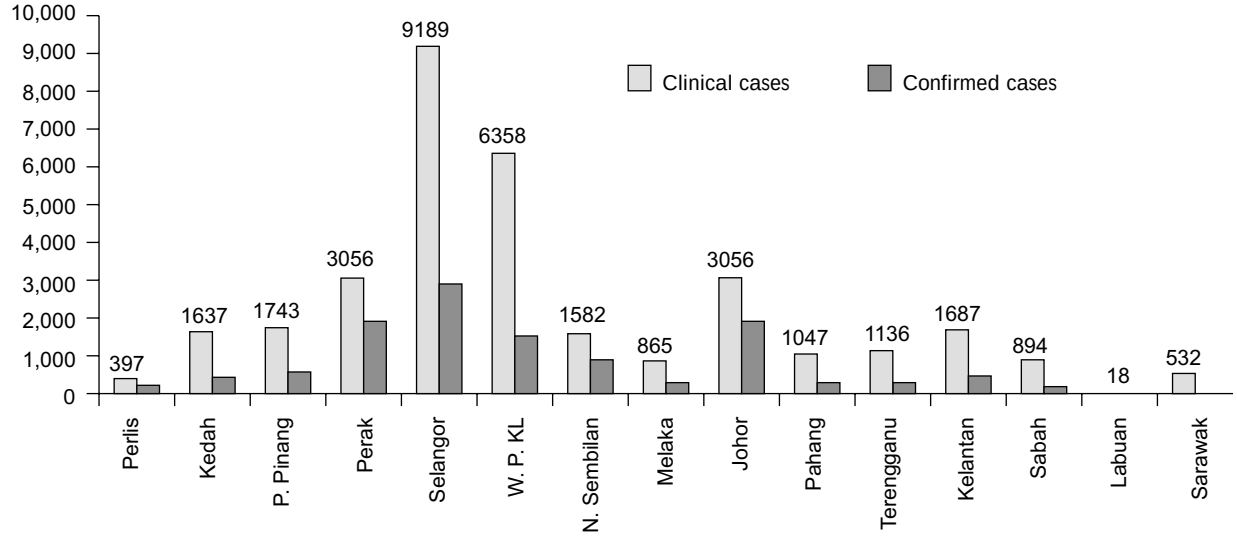
Table 1, 2 and 3 depict the data for the year 2004. A total of serologically confirmed cases were 11,697 noted in the country. This is a significant dip from the previous year (15493). Selangor, Federal Territory, Perak and Johor reported the most number of serologically confirmed cases. Looking at the number of cases versus the number confirmed it is noted that up to May 2004 40-45% were consistently confirmed. The number of clinical cases is between 32,000 and 33,000 per year from 2002-2004. Racial, age, sex and area distribution show that the most infections were noted among the Malays, with the major age group being 21-45 years. There were more males than females with more cases predominating in urban areas. Table 2 shows that the major years of activity were 1998 and also in 2002. As can be seen in Table 3, the major circulating virus changed every 3-4 years with dengue 1 being the current predominant virus.

Dengue fever (DF) may be asymptomatic or lead to a range of clinical presentations even death. Clinically it can be confused with influenza, rubella, malaria, chikungunya, leptospirosis and typhoid. The incubation period is 4-7 days (range of 3-14). Typical symptoms include a sudden onset of fever, frontal headache, retro orbital pain, muscle and joint pain, weakness, depression, nausea, vomiting and an itchy rash. The febrile painful period of DF lasts 5-7 days, and may leave the patient feeling tired for several more days. The vast majority of infections are asymptomatic or minimally symptomatic. Population based studies have shown increasing severity in the clinical features of DF with increasing age and with repeated infections. Leukopenia and mild thrombocytopenia are frequently seen as well as haemorrhagic manifestations such as petechial rash, epistaxis, gum bleeding, gastrointestinal bleeding, microscopic haematuria and hypermenorrhoea, though less frequently but not rare. Clinical laboratory findings include a neutropenia followed by lymphocytosis, often marked by atypical lymphocytes. Liver enzyme levels such as alanine aminotransferase and aspartate aminotransferase, may be elevated. Thrombocytopenia is also common in dengue fever. Generally, DF is self-limiting and rarely fatal, but the convalescent phase may be prolonged for weeks and may be associated with weakness and depression. No permanent sequelae are known to be associated with this infection.

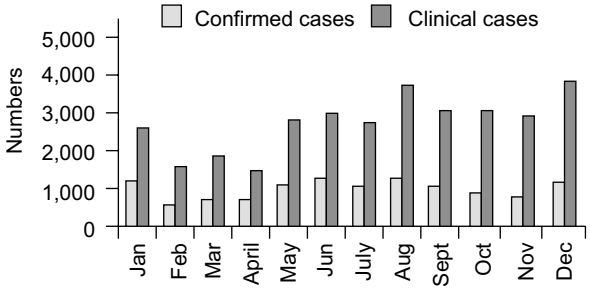
The more severe manisfestation, Dengue Haemorrhagic Fever (DHF), once primarily a children's disease is now seen in all age groups. Most cases occur in individuals with prior dengue exposure. DHF has been classified into four grades according to severity of shock and bleeding. It is defined as a acute febrile illness, with minor or major bleeding, thrombocytopenia, plasma leakage, pleural or other effusions or hypoalbuminemia/ proteinaemia. Pathophysiologically, plasma leakage differentiates DF and DHF. A positive tourniquet, collection of exudates at pleural and abdominal cavities, a progressively decreasing platelet count and a rising haematocrit (signifying abnormal capillary permeability)

Table 1. Epidemiology of dengue in Malaysia in 2004

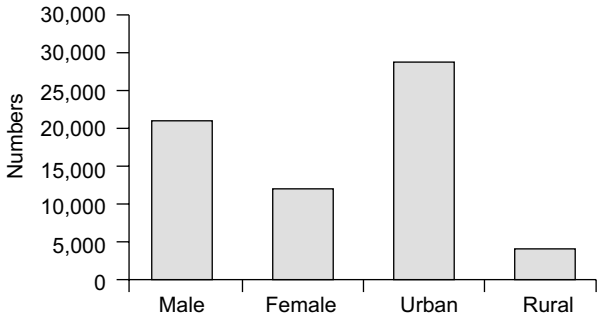
Clinical and serologically confirmed cases – Distribution by State



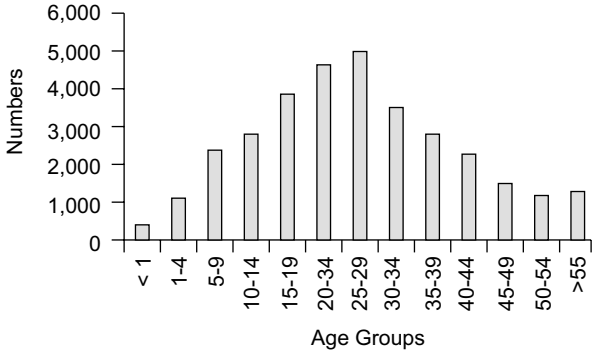
Monthly distribution of dengue in Malaysia in 2004



Sex & area distribution of dengue cases in Malaysia in 2004



Age distribution of dengue cases in Malaysia



Race & area distribution of dengue cases in Malaysia in 2004

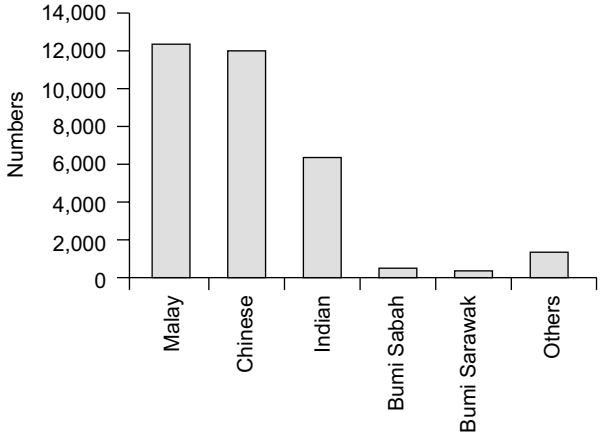


Table 2. Serologically confirmed cases in Malaysia in 1990 - 2004

Year	Number
1991	3070
1992	2777
1993	3514
1994	2746
1995	5212
1996	6058
1997	7938
1998	13742
1999	4718
2000	3723
2001	8669
2002	**15473**
2003	**14170**
2004	**11697**

Table 3. Circulating Viruses in Malaysia 1985-2004

Year					Total
1985	DEN 3*	DEN 4	DEN 2		
1986	DEN 3	DEN 1	DEN 4	DEN 2	
1987	DEN 1	DEN 3	DEN 2	DEN 4	
1988	DEN 1	DEN 2	DEN 4	DEN 3	
1989	DEN 2	DEN 1	DEN 3	DEN 4	
1990	DEN 2	DEN 1	DEN 3	DEN 4	
1991	DEN 2	DEN 3	DEN 1	DEN 4	
1992	DEN 3	DEN 2	DEN 4	DEN 1	
1993	DEN 3	DEN 2	DEN 4		
1994	DEN 3	DEN 2	DEN 1	DEN 4	
1995	DEN 3 (89)	DEN 2 (48)	DEN 1(24)	DEN 4 (2)	163
1996	DEN 1(37)	DEN 2 (37)	DEN 3 (2)		76
1997	DEN 1(64)	DEN 2(33)	DEN 3(3)		100
1998	DEN 2 (42)	DEN 1(36)	DEN 3(3)		81
1999	DEN 2(46)	DEN 1(16)	DEN 3(2)		64
2000	DEN 2(28)	DEN 3(16)	DEN 1(5)		49
2001	DEN 2 (45)	DEN 3(12)	DEN 4(8)	DEN 1(6)	71
2002	**DEN3(70)**	**DEN 1(63)**	**DEN 2(21)**	**DEN 4(13)**	**167**
2003	**DEN 1(105)**	**DEN 3(29)**	**DEN2(16)**	**DEN 4(5)**	**155**
2004	**DEN 1 (183)**	**DEN 3 (26)**	**DEN 2 (15)**	**DEN 4 (6)**	**230**

(numbers in **bold** – actual number of isolates)

indicate increased probability of impending shock. Although intravenous fluids maybe all that is required for treatment, good nursing care and observation is essential as the above changes may happen very quickly or the patient may present in a critical condition. Dengue Shock Syndrome (DSS) is the most severe form and is defined as DHF with signs of circulatory failure, narrowing pulse pressure, hypotension and frank shock. The development of such signs or any suggestion of hypotension are indications for hospital admission and management. Prognosis depends on prevention or early recognition and treatment of shock. In hospitals with experience the case fatality rate can be as low as 0.2%. Once shock has set in the fatality rate may be as high as 12-44%. There has been some unusual but well-described manifestations of dengue infection such as DF with severe haemorrhage, liver damage, cardiomyopathy, and encephalopathy where the risk of death is high. Neurological manifestations such as altered consciousness; convulsions and coma have also been described. A recent documented possibility is the invasion of the central nervous system.

Dengue viruses belong to the family Flaviviridae, a family containing more than 70 viruses that cross-react in serological tests as they share group antigens, thus complicating diagnosis. Laboratory diagnosis depends on virus isolation and serologic tests. Circulating virus remains detectable in the blood during the febrile period after which they are rapidly cleared with the appearance of specific antibody.Virus isolation is carried out using a mosquito cell line. After a few days of incubation, the virus is detected using a indirect fluorescent antibody test. Serological diagnosis depends on the presence of IgM antibody or a rise in IgG antibody titre in paired acute and convalescent phase sera. More than 90% of patients are IgM positive by the sixth day of illness but the IgM antibody may be due to infection up to three months earlier. Commercial kits for the measurement of antibodies include the ELISA kits, a dipstick and rapid immunochromatographic dot-blots. The ELISA kits sensitivities range from 87 -90% while the specificities are close to 100%. For the rapid tests sensitivities are in the range of 75-80%. For a diagnosis of 'confirmed' dengue, dengue virus should be identified by isolation or there should be a four-fold rise in antibody titre.The use of polymearse chain reaction (PCR) may shorten the time of detection but this test is still experimental and no commercial products are available. Recently the WHO Collaborating Centre at the University of Malaya Medical Centre developed a multiplex PCR that is able to detect and serotype virus in clinical samples in 3-4 hours.A Real Time Multiplex assay that is able to detect, serotype and quantitate viral RNA was also developed and can be completed within two and half hours. Both assays have a sensitivity of 99% and a specificity of 100%. However, in the presence of IgM the sensitivity drops to 75% for the Multiplex PCR and 89% for the Real Time assay. Both assays can be utilised to amplify the virus RNA from the onset of illness.

The risk of DHF is higher where two or more viruses are circulating simultaneously. Also the presence of dengue antibodies acquired either actively by prior infection or passive via maternal antibodies in milk or in utero are some of the contributory factors. Thus antibody actually enhances viral infectivity at non-neutralising concentrations. This hypothesis known as Antibody-dependant enhancement (ADE) is a process in which the virus is complexed with specific antibody thus enhancing its uptake by mononuclear cells (the primary site for virus replication). Virus replication in these cells results in the release of vasoactive mediators which increase vascular permeability and the haemorrhagic manifestations that we see in DHF. But this hypothesis is not unanimous as there is a small but consistent percentage of DHF/DSS cases that are due to primary infections, that is, no pre-existing antibody in these individuals. Epidemiological and laboratory studies suggest also that virus strain, individual susceptibility and good nutritional status may also be important as risk factors for DHF.Therefore, to ensure that a vaccine gives immunity and does not enhance immunopathology, it must give protection to all the four serotypes, give high levels of immunity and give life-long immunity. Many approaches are being taken in vaccine development such as recombinant subunit vaccine, live recombinant vaccines and live attenuated vaccines.The lack of understanding of the immunology and immunopathology of the disease and of a suitable animal model as well as the inherent dangers of using live vaccines, means vaccine development has been slow. Currently, candidate attenuated vaccines are on trial in Thailand.

Prevention and control currently depends on controlling the mosquito vector, *Ae. aegypti*, in and around the home where most transmission occurs. Space sprays with insecticides to kill adult mosquitoes are not usually effective as ULV-aerosols have little impact on the adult female *Ae. aegypti* and no impact on the immature stages. The most effective way is larval source reduction, i.e., eliminating or cleaning water-holding containers that serve as the larval habitats in the domestic environment. The task might seem a simple matter of treatment and elimination of infested containers but they are hard to sustain as they are labour intensive requiring discipline and diligence and are intrusive. In recent years, there has been an increased focus in the role of the community in mosquito control. The rationale is that sustainable

Ae. aegypti control can only be accomplished by the people who live in areas where transmission occurs and who by their lifestyles help create mosquito larval habitats. Community participation requires extensive social marketing of dengue prevention, with health education and community outreach. This process, however, is a slow one and may take years for effective disease control to be achieved by community participation alone. Hence, government participation in the form of elimination of mosquito production sites on a larger scale and some though limited use of larvicides and adulticides.Vector control should be dealt with in the same way as garbage disposal, that is, a life-long job. In addition, active laboratory based surveillance that can provide early warning for epidemic activity is essential. Health officials should know at any point in time where dengue transmission is occurring, what serotypes are circulating and severity of illness associated with dengue infection. This will then be followed by a rapid contingency mosquito control plan to prevent an epidemic when the surveillance system predicts increased transmission. Therefore, an active community participation working in partnership with the government is needed to achieve effective disease prevention. Another equally important component of a sustainable prevention programme is the education of the medical community on clinical diagnosis and management of DHF cases so as to help understand the pathophysiological changes that occur in DHF and hence keep fatalities low.Apart from this, research efforts are needed in the development of good antivirals that can be targeted at all four serotypes. However, being an RNA virus the possibility of resistance developing exists. Also research into more effective disease prevention strategies, the changing epidemiology, disease pathogenesis and safe and effective dengue vaccines are essential.

Conclusion

Community-integrated programmes would certainly be useful not only for keeping dengue epidemics at bay but also all other infectious diseases transmitted similarly and with an endemic nature.

References

1. Halstead SB. Antibody, macrophages, dengue virus infection, shock and haemorrhage: a pathogenic cascade. Ref Inf Dis 1989; 11: S830-39.

2. Lam SK, Devi S and Pang T. Detection of specific IgM in dengue infection. Southeast Asian J Trop Med Public Health 1987; 18: 532-8.

3. Gubler DJ and Clark GG: Dengue/dengue haemorrhagic fever : the emergence of a global health problem. Emerging Infect Dis 1995; 1(2): 55-57.

4. Brown JL, Wilkinson R, Davidson RN. Rapid diagnosis and determination of duration of viremia in dengue fever using polymerase chain reaction. Trans R Soc Trop Med Hyg 1996; 90:140-43.

5. Rigau-Pérez JG, Gubler DJ, Clark GG, et al. Dengue and dengue haemorrhagic fever surveillance. Lancet 1998; 352: 971-977.

6. Gubler DJ. The global pandemic of dengue/dengue haemorrhagic fever : current status and prospects for the Future. Ann. Acad Med Singapore 1998; 27: 227-34.

7. Halstead SB. Antibody, macrophages, dengue virus infection, shock and haemorrhage: a pathogenic cascade 1989. Rev Inf Dis 1989; 11: S830-39.

8. Lam SK, Devi S, Pang T. Detection of specific IgM in dengue infection. Southeast Asian J Trop Med Public Health 1987; 18: 532-8. 11 (3) : 480-496.

9. Shu PY, Huang JH. Current advances in dengue diagnosis. Clin Diagn Lab Immunol 2004; 11 (4) : 642-650.

10. Kao CL, King CC, Chao DY, Wu HL, et al. Laboratory diagnosis of dengue virus infection: current and future perspectives in clinical diagnosis and public health. J Microbiol Infect, 2005; 38: 5-16.

UNESCO AND GLOBAL BIOETHICS: MEDICAL EDUCATION, ETHICS COMMITTEES AND CULTURE

Darryl M
Regional Unit for Social and Human Sciences in Asia and the Pacific (RUSHSAP), UNESCO Bangkok, 920 Sukhumvit Road, Bangkok, Thailand 10110; Eubios Ethics Institute, Japan, New Zealand, Thailand; United Nations University, Japan

Introduction

This paper will introduce some of the challenges of the work of the Ethics of Science and Technology Division of UNESCO, and of the Asia-Pacific regional office in Bangkok, in relation to bioethics. The programs respond to the global calls for bioethics debate and discussion, including establishment of programs in bioethics education and of ethics committees. The implementation of international standards in ethics of science and technology and bioethics is important, and there are currently two International Declarations on Bioethics that were both unanimously accepted by UNESCO General Conference (Universal Declaration on the Human Genome and Human Rights, 1997; International Declaration on Human Genetic Data, 2001), and one Declaration on Bioethics that is now being debated by government experts that may be accepted at the end of 2005. Regional and National workshops and seminars to increase knowledge and awareness of these Declarations for Policy Makers, Parliamentarians, health care professionals, academics and civil society groups, are being conducted.

UNESCO is attempting to generate sustainable ethics teaching and promotion programmes, supported by coordinated (between HQ and RUSHSAP) comprehensive databases of experts, existing professional networks, international legal instruments, national legislation, codes of ethics, institutions, and current teaching curriculum and research activities in bioethics. Networking partners in the development of ethics teaching in the region is ongoing. The assembly and maintenance of on-line free access teaching resources, and links to all regional laws and guidelines related to professional ethics, including environmental ethics, ethics of sustainable development, bioethics, science ethics and cyber ethics will be made. This will also be fed into the Global Ethics Observatory (GEO) database project. Establishment of documentation centres in the region is also planned.

The discussion of bioethics can transform the whole style of society. The bioethics debate may be the catalyst required to transform countries from paternalistic feudalism through paternalistic democracy into democracies. People of any country may resist the rapid change and globalization of ethics, ideals, and paradigms as ethnic and national identities may be changed, or lost, especially countries with such a long history of culture. How countries approach globalization is a fundamental question, but many individuals in countries with access to common news media have already answered the question by their converging lifestyles and values. To the extent that human rights and the environment are more respected, this trend is to be encouraged.

There is substantially more research into medical ethics now than 150 years ago, and there are many research priorities. One approach for future study is exploring the question of how traditional views that 'Bioethics is love of life' (1) can be applied to modern dilemmas. From the past years of research across many countries I think 'love' can be a fruitful language for debate in bioethics, despite its ambiguity. We can consider the four principles of love bioethics, as self-love (autonomy), love of others (justice), loving life (non-maleficence) and loving good (beneficence). It has been argued that love is not only a universally recognized goal of ethical action, but is also the foundation of normative principles of ethics. These fundamental principles of ethics may not have changed over time, but the emphasis placed on them has shifted. There was more beneficence a century ago but now there has been more precedence given to autonomy. As for the importance of justice and non-maleficence the trends in different localities are more difficult to determine.

There is an existing mandate for the education and establishment of ethics committees as can been seen in the excerpts below from the 'Universal Declaration on the Human Genome and Human Rights' unanimously approved in mid-November, 1997 at the General Conference of UNESCO, after numerous drafts from the International Bioethics Committee from 1993-1997.

Firstly, on education in bioethics and scientific research we can see the following articles:

'12.a) Benefits from advances in biology, genetics and medicine, concerning the human genome, shall be made available to all, with due regard for the dignity and human rights of each individual.

b) Freedom of research, which is necessary for the progress of knowledge, is part of freedom of thought. The applications of research, including applications in biology, genetics and medicine, concerning the human genome, shall seek to offer relief from suffering and improve the health of individuals and humankind as a whole.

14. States should take appropriate measures to foster the intellectual and material conditions favourable to freedom in the conduct of research on the human genome and to consider the ethical, legal, social and economic implications of such research, on the basis of the principles set out in this Declaration.

15. States should take appropriate steps to provide the framework for the free exercise of research on the human genome with due regard for the principles set out in this Declaration, in order to safeguard respect for human rights, fundamental freedoms and human dignity and to protect public health. They should seek to ensure that research results are not used for non-peaceful purposes.

20. States should take appropriate measures to promote the principles set out in the Declaration, through education and relevant means, inter alia through the conduct of research and training in interdisciplinary fields and through the promotion of education in bioethics, at all levels, in particular for those responsible for science policies.

21. States should take appropriate measures to encourage other forms of research, training and information dissemination conducive to raising the awareness of society and all of its members of their responsibilities regarding the fundamental issues relating to the defense of human dignity which may be raised by research in biology, in genetics and in medicine, and its applications. They should also undertake to facilitate on this subject an open international discussion, ensuring the free expression of various socio-cultural, religious and philosophical opinions.'

There is also a strong basis for establishing ethics committees:

16. States should recognize the value of promoting, at various levels as appropriate, the establishment of independent, multidisciplinary and pluralist ethics committees to assess the ethical, legal and social issues raised by research on the human genome and its applications.

23. States should take appropriate measures to promote, through education, training and information dissemination, respect for the abovementioned principles and to foster their recognition and effective application. States should also encourage exchanges and networks among independent ethics committees, as they are established, to foster full collaboration.'

Thus there are clear mandates in all member countries for establishment of ethics committees, and there was also universal support for some common principles of bioethics as seen in the articles that apply them to issues raised by genomics, namely:

5. a) Research, treatment or diagnosis affecting an individual's genome shall be undertaken only after rigorous and prior assessment of the potential risks and benefits pertaining thereto and in accordance with any other requirement of national law.

b) In all cases , the prior, free and informed consent of the person concerned shall be obtained. If the latter is not in a position to consent, consent or authorization shall be obtained in the manner prescribed by law, guided by the person's best interest.

c) The right of each individual to decide whether or not to be informed of the results of genetic examination and the resulting consequences should be respected.

d) In the case of research, protocols shall, in addition, be submitted for prior review in accordance with relevant national and international research standards or guidelines.

e) If according to the law a person does not have the capacity to consent, research affecting his or her genome may only be carried out for his or her direct health benefit, subject to the authorization and the protective conditions prescribed by law. Research which does not have an expected direct health benefit may only be undertaken by way of exception, with the utmost restraint, exposing the person only to a minimal risk and minimal burden and if the research is intended to contribute to the health benefit of other persons in the same age category or with the same genetic condition, subject to the conditions prescribed by law, and provided such research is compatible with the protection of the individual's human rights.

6. No one shall be subjected to discrimination based on genetic characteristics that is intended to infringe or has the effect of infringing human rights, fundamental freedoms and human dignity.

7. Genetic data associated with an identifiable person and stored or processed for the purposes of research or any other purpose must be held confidential in the conditions set by law.

8. Every individual shall have the right, according to international and national law, to just reparation for any damage sustained as a direct and determining result of an intervention affecting his or her genome.

9. In order to protect human rights and fundamental freedoms, limitations to the principles of consent and confidentiality may only be prescribed by law, for compelling reasons within the bounds of public international law and the international law of human rights.

10. No research or research applications concerning the human genome, in particular in the fields of biology, genetics and medicine, should prevail over respect for the human rights, fundamental freedoms and human dignity of individuals or, where applicable, of groups of people.'

Conclusion

In conclusion, there is an existing basis for developing bioethics in all regions of the world, and UNESCO will work with those in every culture to help elaborate bioethics for the people by the people.

References

1. Macer DRJ. Bioethics is Love of Life. Christchurch: Eubios Ethics Institute, 1978.

RELEVANCE OF THE MEDICAL ACT 1971 IN BIOMEDICAL RESEARCH

Yeoh PH
Malaysian Medical Council, Kuala Lumpur, Malaysia

Introduction

This is a time of impending changes both in the Law governing the registration of medical practitioners as well as the regulations that regulates the conduct of doctors.

At Independence in 1957, we inherited the Medical Registration Ordinance 1952 of the States of Malaya as the legislation to register doctors. With the formation of Malaysia in 1965, a new Medical Act was enacted and passed on 1st October 1971. With this new Act, the following Ordinances were repealed:

1. The Emergency (Essential Powers) Ordinance No. 65, 1971,
2. Medical Registration Ordinance 1952 of the States of Malaya,
3. Medical Registration Ordinance of Sabah and
4. the Medical Registration Ordinance of Sarawak.

Many amendments to the body of the Act as well as the enabling Regulations have been made over the years on ad hoc basis. Many of the provisions suitable for the country and for the practice of medicine at that time are no longer applicable or have been superceded by rapid advancement in medical research as well as the economic status of the country.

The Medical Act 1971 sets out the functions and powers of the Minister of Health and the Malaysian Medical Council (MMC) which is the statutory body that enforces the provisions of the Act. It provides for Minister to make Regulations with respect to how the MMC operates to enforce the provisions of the Law.

The principle function of the MMC is the registration of medical practitioners to practise western scientific allopathic medicine in this country. As a corollary to this, it also determines the qualifications that can be accepted, the standards of practice of doctors and also exercises disciplinary powers over all registered medical practitioners.

In the 1970s, the newly registered doctor was given a four-page leaflet entitled 'MMC Medical Ethics'. This contained what was expected of the doctor with respect to ethical standards of practice. This was replaced in December 1986 with a more detailed Code of Professional Conduct (CPC) detailing the expected standards of practice of Registered Medical Practitioners and grounds for disciplinary action.

The Code was mainly descriptive in its expectations. In January 2001, in line with a GMC publication of a similar name, a new set of guidelines entitled 'Good Medical Practice' (GMP) was adopted by the MMC to serve as a guide to medical practitioners. It contains the moral and professional obligations expected of the medical practitioners in this country. At same time Practice Guidelines on Confidentiality was also adopted and incorporated as part of the GMP document.

In the preamble to the CPC, it is stated as a warning that:
'The practice of Medicine is an ancient profession and the community has great expectations of its practitioners and places great trust in them. Without this trust it would be impossible to practice medicine and the profession as such expects a high standard of professional and personal conduct from its members. These are embodied in various Codes of Ethics which vary in detail from country to country but all place first and foremost the health and welfare of the individual and the family under the care of a practitioner'.

and that

'Underpinning the Code of Ethics are statutes which make it an offence punishable under the law of the country to transgress certain outer limits of the expected norms of professional conduct. These minimum standards of conduct are assessed by their peers in the profession, assembled as the Malaysian Medical council established under the Medical Act 1971. Breaches of these minimum standards are referred to as '*infamous conduct in a professional respect' or 'serious professional misconduct*'.

We are informed that our actions, if contrary to the CPC or the GMP as sanctioned by the MMC can be an offence punishable under the Law of the Country; and breaches of the Code translates as 'acts of infamous conduct' and subject us to disciplinary action.

Disciplinary jurisdiction over registered medical practitioners is conferred upon the Malaysian Medical Council by Section 29 of the Medical Act, 1971 which reads as follows:

1. The Council shall have disciplinary jurisdiction over all persons registered under this Act.
2. The Council may exercise disciplinary jurisdiction over any registered person who:-
   (a) has been convicted in Malaysia or elsewhere of any offence punishable with imprisonment (whether in itself only or in addition to or in lieu of a fine);
   (b) has been guilty of infamous conduct in any professional respect;
   (c) has obtained registration by fraud or misrepresentation;
   (d) was not at the time of his registration entitled to be registered; or has since been removed from the register of medical practitioners maintained in any place outside Malaysia.

Forms of Infamous Conduct are categorized under four main headings.

1. Neglect or disregard of professional responsibilities.
2. Abuse of professional privileges and skills.
3. Conduct derogatory to the reputation of the medical profession.
4. Advertising, canvassing and related professional offences.

These are grounds on which a doctor can be charged under the Law (a 'criminal' offence).

With the development of 'evidence based medicine' over the last two decades, there has been the adoption of many Consensus Documents and Clinical Practice Guidelines which now governs our every day practice. What has been much debated is whether Guidelines imply mandatory compliance. In a court of Law, will deviation from guidelines lead to a failure of defence, and hence a conviction?

The MMC has itself approved and will be adopting several guidelines which are quite prescriptive. One of the guideline is on 'Clinical Trials and Biomedical Research' (*Appendix 1*).This Guideline complements, and should be read in conjunction with the Code of Professional Conduct of the Malaysian Medical Council.

Should these guidelines be adopted by the MMC, any violation of them may constitute grounds for disciplinary action. And when a doctor is charged by the MMC, he is in essence being charged for a violation of the Medical Act 1971.

Should Biomedical Research be subjected to legal oversight? The revelation of genocidal human experimentations carried out during World War II resulted in a great outcry for the establishment of strict guidelines on biomedical research. The resultant Nuremberg Code was widely endorsed by the medical profession.

Certainly there are those who feel that guidelines, even those adopted by the World Health Organization, are nothing but suggestions which have not mandatory compliance. Because of possible conflict of interest situations, institutional safeguards in the form of Institutional Review Boards are not entirely foolproof and penalties for violations often may be inadequate.

If we agree that Guidelines for Biomedical Research should be elevated to 'legal' provisions, should they then be descriptive or prescriptive? The existing CPC of the MMC in addressing Biomedical Research makes general statements as follows:

1.5. Medical Research

In the scientific application of medical research carried out on a human being, it is the duty of the practitioner to remain the protector of the life and health of that person on whom biomedical research is being carried out.

1.5.1. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation at any time. The practitioner should then obtain the subject's freely-given informed consent, preferably in writing.

1.5.2. The practitioner can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

1.5.3. A medical practitioner shall use great caution in divulging discoveries or new techniques or treatment through non-professional channels.

1.5.4. The results of any research on human subjects should not be suppressed whether adverse or favourable.

Conclusion

The proposed MMC Guideline on Good Practice: Clinical and Biomedical Research (CBR) adopts the basic principles outlined by the International Committee on Harmonisation of Good Clinical Practice (ICH-GCP). It prescribes all the basic issues including relevance of the proposed study, getting approval, insurance and liability, informed consent, as well as proper collection, analysis and compilation of data, and subsequently to disposal of the reports.

The academic institutions must act to influence the direction to be taken by the MMC by giving its input. A new Medical Act has already been drafted to replace the existing Act, giving the MMC wider as well as more discretionary powers on the categories of disciplinary punishment it can inflict on a doctor found guilty of infamous conduct.

References

1. Medical Act 1971.
2. Code of Professional Conduct Malaysian Medical Council December 1986
3. Good Medical Practice. Adopted by Malaysian Medical Council January 2001.

ADVANCES IN IMAGING OF SPORTS INJURIES

George J[1], Ramlan AA[2]
[1] Department of Radiology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia
[2] Institute of Sports, Malaysia

Introduction

Sports injuries is getting a higher profile these days because matches are being televised across the globe. When an elite athlete is injured, he nows tends to get immediate attention from a Sports physician or an Orthopaedic Surgeon. The majority of injuries are soft tissue injuries but it is important for these athletes and their team managers to know the extent of the injury early so that the correct management can be instituted early.

As most injuries involve the soft tissues in and around joints two imaging modalities are especially useful, ultrasound and MRI. Plain x-rays are done if there is concern that there may be a fracture and this should be done in two or more views depending on the degree of clinical suspicion. The bone scan is performed often when plain films are normal but there is suspicion of a stress fracture and in footballers, this is usually in the lower tibial region. Ultrasound can be used to detect the periosteal elevation associated with the stress fracture from our experience even when the plain film is normal. I shall now highlight some of the recent research done in the University of Malaya which is original and changing our perspective on many areas in imaging of sports injuries.

Anterior Cruciate Ligament

Our own experience(Table 1)(1) (Case Number 3) shows using a sequence called Constructive Interface in Steady State (CISS) which was originally used to examine the cranial nerves was able to show the partial tears more clearly than T1 and T2 images with statistical significance. Since slice thickness is only 1.5 mm in CISS compared to standard 4mm thickness in T1 and T2 imaging, there is better resolution and more images through the ACL. Some of these tears may not be seen by the arthroscopist as they are intrasubstance and therefore cannot be proven but comparison with a normal CISS image of the ACL will show shows a clearly bright fluid present within the ACL in the partial tear group.

Table 1. Comparison of CISS with other sequences in detecting and grading of the ACL abnormality (Grading by Musculoskeletal Radiologist)

Grade ACL N=33	T1 No. of cases	T2 No. of cases	FLASH No. of cases	CISS No. of cases
0 Normal	21 (64%)	22 (67%)	20 (61%)	19 (58%)
1 Indeterminate	1 (3%)	0	0	1 (3%)
2 Partial tear	1 (3%)	1(3%)	4 (12%)	5 (15%)

Clinically, these patients with partial tears may have some laxity but with an end point still present. There are some patients with no anterior draw sign and yet full tear of the ACL on MRI. As I shall describe later, we have replaced the Flash axial image with the CISS axial image due to the above reason for better detection of partial tears of the ACL and also better cartilage grading. So imaging with the CISS sequence is a definite advance in our experience in imaging of the knee for ACL injury even compared to 3D SPGR images. In addition, where there is suspicion of ACL tear, we shall perform both a sagittal and axial CISS image.

ACL tear: Secondary signs

It is well-known that there are several secondary signs of ACL tear described in the literature. One of these signs is the anterior tibial translation. In the literature, the number 5 mm and 7 mm of translation is bandied as being a cut off point for anterior tibial translation. In our original study done as a medical student elective project, we found that MRI measured normal laxity maximum was up to 9 mm, partial tear laxity maximum was up to 12 mm and thereafter there was always a full thickness tear (2). (Table 2).

Table 2. ACL tears and femorotibial displacement.

		Lateral displacement (mm)
Complete ACL tear	N Valid	32
	Missing	0
	Minimum	3
	Maximum	**21**
Partial ACL tear	N Valid	5
	Missing	0
	Minimum	0
	Maximum	12
Normal ACL	N Valid	35
	Missing	0
	Minimum	–8
	Maximum	9

These measurements are taken from the lateral 2nd and 3rd sagittal slices of the MRI where the displacement was found to be maximum. This has great bearing on the reporting of our MRI now as when there is difficulty with judging whether there is a partial tear or not we now see if the measurement is more than 9 mm and report partial tear. This study also suggests that inherent laxity in the Malaysian population has a whole is probably more lax than the Western population and should be taken into bearing when clinical examinations are performed on Asians and MRI is mandatory when there is more than 5 mm of anterior tibial displacement clinically with an apparent end point or when one feels the clinical examination is not adequate from experience. It is also interesting to note the degree of negative tibial translation in the normal population which may account for why some patients have minimal anterior drawer sign but have an ACL tear as they have up to 8 mm of anterior translation before the tibial displacement starts being considered.

Meniscal tears

Meniscal tears are not reliably diagnosed by clinical examination and MRI has an important role in this context to prevent the need for arthroscopy when the only question of injury is a meniscal tear.

In our institution, we have done some original work (3) to grade the types of meniscal tears that are not frequently diagnosed by radiologists particularly, on the antero - lateral aspect of the knee.

Orthopaedic examination of the knee does not reveal whether the injury involves the instrasubstance portion of the meniscus or the meniscocapsular portion of the meniscus.

This has an important bearing as we have confirmed cases where there are peripheral tears of the outer third of the meniscus or meniscocapsular tears of minimal separation (Grade 1 and 2), self-reparative healing without the need for surgery is possible in about 3-4 weeks after the acute injury.

About 15% of suspected meniscocapsular tears are thought to be due to these meniscocapsular injuries. At the University Hospital, we have published normal and abnormal appearances of the meniscofemoral and meniscotibial ligaments anterolaterally (3). The classification for these tears are based on the degree of tear of the meniscocapsular complex i.e., Types 1 to Type III with Type 1-torn meniscofemoral or meniscotibial attachment, type 2-torn meniscofemoral and meniscotibial attachment with separation of 3 mm or less, and Type 3-torn meniscofemoral and meniscotibial attachments with separation of the meniscus and capsule by more than 3 mm. Thus far, it has been shown that early grades of tear can be left to conservative treatment with full symptomatic relief in the majority of cases and when the symptoms persist for more than six weeks, then surgery may be required.

The other meniscal tear that is often missed with accuracy of around 75% by general radiologists is that of the bucket handle tear. This is because the foreshortening of the meniscus is not picked up by the

radiologist. With the help of a Masters thesis student and then followed by a medical student we determined the normal morphometric ratios in the Malaysian population of the anterior to posterior horn on the first four lateral and medial sagittal slices from the T2 sagittal images of the knee. We were then able to get the range of ratios for these four levels and develop a software programme into which one only needed to put in the easily obtainable measurements from the sagittal images to predict if there was a high chance of a tear being present. The ratios obtained for the Malaysian population are tabulated in the paper by the author taken from Master's student's thesis (3).

The software is now developed after testing and a medical student who had no prior MRI experience was able to get a 90% sensitivity in picking up a meniscal tear using the calculator.

Bowtie sign in the Malaysian population

This sign is widely reported in the literature not so much for its presence but its absence as an indicator of a bucket handle tear of the meniscus. It is reported that the absence of two bowties on the medial and lateral side respectively is indicative of a bucket handle tear. In my experience, however, there were several patients who had only one medial bowtie and yet all other planes and in some cases arthroscopy was normal. A medical student elective project was done to look at the bowtie sign in relation to the maximum width of the tibial plateau to see if there was a correlation. In this study, it was noted that indeed the number of bowties did increase with an increased of the tibial plateau but the presence of one medial bowtie was indeed a normal finding in many patients. (Figure 1).

In fact, what we found as significant was that a difference of two bowties between both sides was more significant in predicting a bucket handle tear than just the absence of a bow tie.

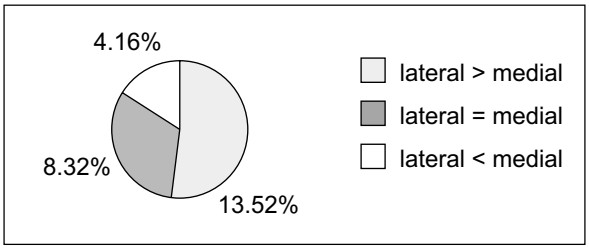


Figure 1. Comparison between number of bowties seen medially and laterally

Cartilage imaging

There is no doubt that this is an area of major interest to all those who manage patients with knee injuries. Disler reported overall sensitivity of 93% and specificity of 94% using a fat surpressed 3D spoiled gradient echo sequence. There are two main disadvantages to this approach: lack of reliable contrast between cartilage and fluid that outline surfaces defects and long imaging times.

To overcome this difficulty, we experimented with the use of 3D CISS as described earlier. We stumbled on using this sequence based on the experimentation to look at the ACL. The advantage of the axial CISS image is that it shows excellent differentiation between the cartilage and fluid, shows the cartilage more sections into the intercondylar region, shows very thin plica clearly (1). Currently, we are undertaking a study to validate the use of CISS comparing actual macroscopic samples of cartilage taken from knee replacement operations with MRI. Thus far, there appears to be excellent correlation between the samples and even Grade 1 grading of cartilage erosion (i.e., less than 50% erosion).

Conclusion

At the University of Malaya, we are at the forefront of latest research and protocols with regards to imaging of sports injuries. We hope to report further on the progress of our research in the near future.

References

1. Zainab W, George J. Comparison of 3D CISS and 2 D Flash Imaging for detection of cartilage injury and ACL tears. Master's of Radiology thesis 2002.

2. Phase 1 – Medical Students elective – Faculty of Medicine 2004. University of Malaya. Comparison of anterior tibial translation according to age, sex and ethnic groups where the anterior cruciate ligament may be intact, partially torn or completely torn.

3. George J, Ramlan AA , Saw KY, et al. Radiological Classification of menisco-capsular tears of the antero-lateral portion of the lateral meniscus of the knee. Austral Radiol 2000; 44: 19-22.

NATIONAL CANCER REGISTRY OF MALAYSIA: WHERE DO WE GO FROM HERE?

Gerard Lim CC, Sanjay R, Haniff J, Halimah Y, Lim TO, Ng KH, Ibrahim H, Purushothaman V.
Department of Radiotherapy and Oncology, Hospital Kuala Lumpur, Jalan Pahang, 50586 Kuala Lumpur, Malaysia

Introduction

The National Cancer Registry provides one of the strongest evidences that cancer is a serious national health problem in Malaysia. The first two reports of the National Cancer Registry (1, 2) have received commendations locally and from overseas for the quality of content and transparency in analysis. Few cancer registries in the world cover a population as large as 20 million. It is encouraging to note that cancer notifications to the National Cancer Registry have progressively increased through the years as shown below:-

2002	36,619
2003	42,985
2004	47,780

The Advisory Committee of the National Cancer Registry plays a vital role in the governance of the National Cancer Registry, and is responsible for setting objectives, policies, direction and progress of the registry. The membership of this committee is widely represented by members from sponsors, source data producers, Cancer Registry Unit and the Users (public health practitioners, health providers, decision-makers, researchers). Active participation from all relevant agencies is encouraged in planning, development and direction of the National Cancer Registry.

Taking into account the general diversity of cancers that occur, the National Cancer Registry has established sub-committees for each major cancer site. These committees are composed of members from the medical profession and allied health, who possess subject matter expertise in their respective areas. Together, all these members form the National Cancer Registry Expert Panel. The expert panels are responsible for undertaking quality control of the reported data and to classify the reported tumours according to ICD-O classification. Following the analysis of the data, the expert panels are also tasked with the responsibility of undertaking a literature review, interpreting and writing the section of the report relevant to the panels' expertise. The pivotal role played by the expert panel is one of the reasons the registry is able to cater to a large population. Active participation by the members of the medical profession and allied health is vital to the quality of the data that is published. The participation by experts from the Ministry of Health, Universities, and private sector in previous years has been very encouraging.

The National Cancer Registry collects cancer notifications from all registered source data providers (SDPs) on a monthly basis. To ensure sustainable compliance of SDPs, a simplified format was used to collect the essential data needed. SDPs who are late on their notification are duly reminded by computer-generated reminders and frequent calls from the Cancer Registry Unit. The SDPs form an integral component of the National Cancer Registry; hence the importance in maintaining a personal link with them. Their continued participation is acknowledged in various ways.

In 2002, the database used a back-end supported by Microsoft Access. The high number of notifications had led the National Cancer Registry to upgrade the database to Microsoft SQL in 2004. The upgraded database also strengthened the security of data and increased the efficiency in handling huge data loads. The database system is complemented by the 'QualityStage' software from 'Ascential' which has simplified the process of standardizing the data, automatically coding the records and de-duplicating the patients' records. This system will enable the determination of patients' outcome by matching against National Registration Department data in the future.

With the high notifications of the SDP being managed by the computer system, the National Cancer Registry has now collected a lot of data. Data needs to be transformed into information which is readily understood and interpreted. This is where data management, expert panel review, statistical analysis and report writing activities become vital.

The National Cancer Registry has built a keyword dictionary that is used by the computer system to automatically code the records according to ICD-O topography classification. These preliminary coded records are then verified by the expert panel members. This process of individually reviewing the record and classifying them gives us confidence in the classification of the cancers.

In line with the National Cancer Registry's objective to support and stimulate cancer research, registry-based studies have been commenced. In mid-2004, the National Cancer Registry embarked on the International Gastric Survey (REGATE) in collaboration with a pharmaceutical company. While this is an industry-initiated study, the National Cancer Registry has also organized an investigator-initiated trial, the Malaysian Cancer Cohort for Gastric Cancer (MCCS/Gastric Cancer). This is a multi-centre, observational study designed to describe the pattern of gastric cancer, its subsequent treatment and outcomes in the Malaysian population. Other registry-based studies that will be initiated in the foreseeable future to study cancers in depth will be studies on breast cancer and lymphoma.

It is hoped that there will be enthusiastic recruitment by clinicians in such studies as this is in line with one of the objectives of the National Cancer Registry in stimulating and facilitating epidemiological research on cancer.

One of the latest developments in the registry is a prototype called 'eCancer'. This encompasses the state of the art technology for remote data capturing and accessing via the web. SDPs can now report and access their data in real time ANYWHERE ANYTIME. Not only do they have access to their data, they can also have ready-made centre reports at the click of a button. This function is equipped with a high level of security.

Conclusion

The information generated from the National Cancer Registry would be very useful to health planners, e.g., in the Ninth Malaysia Plan. All doctors, non-governmental organizations, professional bodies and industry are strongly encouraged to participate and contribute towards the success of the National Cancer Registry and thus help obtain the information so crucial to cancer prevention and control in Malaysia.The National Cancer Registry is for everybody. Active participation by all is encouraged. The National Cancer Registry is contactable at the website mentioned in the References section below.

References

1. Lim GCC, Halimah Y, Lim TO, eds. The First Report of the National Cancer Registry. Cancer Incidence in Malaysia 2002. National Cancer Registry. Kuala Lumpur 2003 (also available at: http://www.acrm.org.my/ncr).

2. Lim GCC, Halimah Y, eds. Second Report of the National Cancer Registry. Cancer Incidence in Malaysia 2003. National Cancer Registry. Kuala Lumpur 2004 (also available at: http://www.acrm.org.my/ncr).

UPDATE ON NIPAH VIRUS INFECTION

Tan CT
Department of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Pathogenesis of fatal Nipah encephalitis

The overall mortality of acute Nipah encephalitis was 40%. The pathogenesis of the fatal acute Nipah encephalitis was earlier thought to be widespread vasculitis-induced thrombosis and micro-infarct. However, the lack of correlation in the MRI lesions which corresponds to microinfarction and depth of coma; the distinctive neurological signs such as segmental myoclonus suggests a predilection of certain groups of neurons; the demonstration of viral antigen in the neurons with immunohistochemical staining; and the association of high mortality with presence of virus in CSF all support direct neuronal invasion with viral replication as important in the pathogenesis of severe and fatal disease. Analysis of 194 patients from Seremban and the University of Malaysia Medical Center showed that diabetic patients had increased mortality by 123%, presumably due to immunoparesis (1). On the other hand, there was no significant difference in the clinical features and outcome between those patients with and without positive IgM serology for Japanese encephalitis, and none of the 33 fatal cases who had post mortems showed positive immunohistochemical staining for Japanese encephalitis, with no evidence that a subclinical Japanese encephalitis infection aggravated a patient with Nipah encephalitis (2).

Relapsed Nipah encephalitis is seen in 9% of acute encephalitis survivors, and late-onset encephalitis in 5% of those with previous non-encephalitic or asymptomatic Nipah infection at 48 months after the outbreak. The mean duration from the initial infection was 13 months, the longest being 4 1/2 years. The clinical, MRI and pathological features of the relapsed and late-set Nipah encephalitis was that of focal encephalitis. The presentation was usually acute with a mortality rate of 18%. A husband and wife who were pig farmers from Sungei Nipah, Negri Seremban had acute Nipah encephalitis and non-encephalitic Nipah infection in 1999. They both recovered well and did not go back to pig farming. However, in September 2003, 53 months after the initial infection in 1999, both patients developed relapsed encephalitis/late-onset encephalitis within a few days of each other. Environmental factors could be important in precipitating relapsed encephalitis, perhaps by transiently suppressing the immune system (3).

The reservoir of Nipah virus in Malaysia based on serology study is the pteropus bats, *Pteropus hypomelanus* and *Pteropus vampyrus*. Three virus isolates from the urine and partially eaten fruit swabs of a *Pteropus hypomelanus* colony was also successfully obtained. The molecular sequencing confirmed the isolate to be Nipah virus with a sequence deviation of 5-6 nucleotides from Nipah virus isolates from human. A study of 58 residents in Air Batang, Tioman Island, a village with roosting colony of *Pteropus hypomelanus*, showed negative Nipah serology in all the residents. This indicates that the risk of Nipah virus infection directly from the bats is low (4).

Five outbreaks of *Nipah encephalitis* have been reported in Bangladesh since 2001, the latest was in the Tangail district in early 2005. Another Nipah encephalitis outbreak was seen in the Siliguri district, India in 2001. The Siliguri district is neighbouring North Bangladesh. Like in Malaysia, Nipah virus appears to cause a fatal encephalitis illness in human in Bangladesh. However, during the outbreak in Faridpur district, Bangladesh in 2004, there was prominent human-to-human spread of infection, with some patients showing florid pulmonary involvement. Three patients with brain MRI in the 2004 outbreak also showed confluent high signal lesions involving both grey and white matter, which is different from the acute Nipah encephalitis in the Malaysian outbreak, suggesting a difference in the pathology from the Malaysian patients (5). The RNA of Nipah virus in Bangladesh has 95% homology with that causing the outbreak in Malaysia. *Pteropus giganteus* has been found to be the reservoir for Nipah virus in Bangladesh.

Antibodies to Nipah-like virus have been found in 12% of *Pteropus lylei* in Cambodia. *Pteropus lylei* is also seen in Thailand, indicating potential human Nipah virus infection elsewhere in Southeast Asia.

References

1. Chong HT, Tan CT, Goh KJ, Tan KS, et al, Occupational exposure, age, diabetes mellitus and outcome of acute Nipah encephalitis. Neurol J Southeast Asia 2001; 6: 7-11.

2. Chong HT, Tan CT, Karim N, et al, Outbreak of Nipah encephalitis among pig-farm workers in Malaysia in 1998/1999: Was there any role for Japanese encephalitis? Neurol J Southeast Asia 2001; 6: 129-34.

3. Chong HT and Tan CT. Relapsed and late-onset Nipah encephalitis, a report of three cases. Neurol J Southeast Asia 2003; 8: 109-112.

4. Chong HT, Tan CT, Goh KJ, et al. The risk of human Nipah virus infection directly from bats (*Pteropus hypomelanus*) is low. Neurol J Southeast Asia 2003; 8: 31-4.

5. Quddus R, Alam S, Majumdar MA, et al. A report of 4 patients with Nipah encephalitis from Rajbari district, Bangladesh in the January 2004 outbreak. Neurol Asia 2004; 9: 33-7.

MEN'S HEALTH IN THE ASIA PACIFIC REGION

Tan HM
Subang Jaya Medical Centre, Subang, Selangor, Malaysia

Asian countries experienced the same baby boom period, albeit about five years later, as those in the Western World. The peak period of population growth in Asia occurred between 1950s to 1970s (1). Furthermore, life expectancy in the Asia Pacific region has increased tremendously over the last 50 years. A baby boy born today in many developed Asia Pacific countries is expected to live beyond 80 years of age. By 2020, four Asian countries will be amongst the world's top ten countries with the largest elderly population (> 65 years). These include China 230 million, India 142 million, Japan 35 million and Indonesia 29 million (2).

Asian men are definitely living longer but not necessarily better. Demographic data have revealed the average disability period in the ageing male in many Asian countries ranges from 40 to 100% of his aging life (i.e., above 65 years old) (1). In other words, Asian men, generally will be nursing a significant disability or treatment of a major disease in most, if not all, of their life after 65 years old.

The health of an ageing male is the net effect of both current health-related factors and factors that prevailed during earlier periods in the life course (3). The health status or the disease burden of the elderly population has tremendous far reaching consequences to the family, society and their respective countries. All Asian countries, especially those with developing economies, desperately need their male population to be healthier and more productive. A healthy elderly population will continue to be productive, reduce health care cost and reduce financial burden to their family, community and country.

Generally, health care providers give men's health issues short shrift in standard clinical interactions. Rightfully, they tend to focus on common conditions such as hypertension, heart disease and diabetes mellitus. Unfortunately, the majority of the men even with these conditions which warrants close follow up treatments, are not forth coming to see their respective medical practitioners. Commonly, these men with chronic potentially debilitating diseases are seen at a late stage, after suffering end organ damage.

Men's health issue needs a revamp in our approach. A multidisciplinary, well concerted effort to refocus and reorientate our thoughts to provide a holistic care for men's health problems is desperately needed (4). Physicians should not just focus on men with cardiovascular diseases, diabetes and prostate cancer. They must take a wider perspective on men's health issues and put equal emphasis on other conditions that have a substantial and significant impact on men's overall health and quality of life. Medical conditions and diseases like prostatitis, lower urinary tract symptoms (LUTS), sexual dysfunction and Androgen Decline in Ageing Male (ADAM) must be bought into centre stage like other life threatening diseases (5).

In the promotion of Men's Health, qualitative research involving focus groups of the lay public will be needed to understand the attitude, behaviour, concerns and what motivate men to seek preventive health care. Research involving 'social marketing' methodologies will also help health campaigners to determine the best means to communicate with men. Educationists in public men's health forum may also reach out to the men by understanding the local culture and perception of men's general well-being and sexual health. Low back pain, concerns of 'kidney' diseases, urinary problems and sexual dysfunction commonly bring men to consult a physician or therapist because of the fear of harbouring serious 'internal' diseases. This deep-rooted belief of the central and vital function of the 'kidneys' as the most important organ in a man's internal system could be capitalised in the promotion of men's sexual health and general health (6).

An integrated approach by health care provider addressing all the health concerns of men will be more appealing and encourage men to come forth for medical consultations. A truly holistic management to tackle all men's health problem, both life threatening and those with high impact to quality of life, will have the best chance to change the health seeking behaviour of men in the most vulnerable age groups (7).

Physicians need to reorientate their attitudes, thoughts and clinical practice to be receptive and open to men's

health issues and concern (4). New knowledge, skills and training on men's health, diseases and ageing will need to be incorporated into the training of health professionals, and continuing medical education extended to practising physicians.

Convenient and consciously 'male friendly' clinics should be visibly made available. Physicians should be encouraged to go the extra mile to capitalize on the opportunity on preventive health in all male consultations. Changes in attitude and principle to transform from a sickness service to incorporate a health service will yield long-term goodwill and benefits to the primary care physicians. Specialized multi-disciplinary men's health consultations, mimicking the pioneering concept of Mayo's Men's Health Centre which started off as prostate and sexual dysfunction clinics, will be needed to complement the services of the primary care physicians. The overall health of men can be best served through networks of physicians with a focused interest in diverse aspects of men's health (8). It is in this context, the urologists are privileged to play a key role in improving the health and quality of life of the ageing male population.

There is a rapidly increasing growing need for health professionals to address the medical concerns of men in integrated, comprehensive and preventative manners. We need to reverse the prevalent trend towards men suffering suboptimal quality of life and dying early and often unnecessarily from largely preventable causes (4). New models for providing men with health care must be incorporated into main stream medicine. Understanding of masculinity and male risk taking behaviour, creation of supportive male friendly environment and development of men's personal skill and attitude towards their health care are crucial in the promotion and elevation of men's health status (9).

References

1. Tan HM. An ageing world: Challenges ahead. First Asian ISSAM Meeting, Kuala Lumpur, 1-4 March 2001.

2. Lunenfeld B, The aging male, 2001;4(1) : 3-6.

3. Cherry D, Men's health and the ageing male; 2004;1(1): 4-8.

4. Tan HM, Men's health and the ageing male, 2004; 1(1): 2-3.

5. Tan HM. Men's Health: A promising subspecialty. 9th Asia Pacific Society for Sexual and Impotence Research Meeting, Cebu, October 2003.

6. Yin Huihe, Fundamentals of traditional chinese medicine. Foreign Languages Press Beijing, 1995.

7. Tan HM. Men's Health in Asia - The urologist's perspective. 7th Asian Congress Urology, Hong Kong, October 2004.

8. Duncan AK, Hays JT, J Men's health gender 2005; 2; 1, 17-19.

9. Banks I, New models for providing men with health care. J Men's Health Gender 2004; 1: 155-158.

HIGH THROUGHPUT SCREENING

Chung LY
Department of Pharmacy, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Introduction

Plants, micro-organisms and sea organisms are known to provide many leads in drug discovery, particularly, infectious diseases and cancer, as they are complex chemical storehouses, which contain thousands of natural chemical compounds with wide chemical diversity and pharmacophoric diversity. Of the 250,000 higher plant species in the world, 15,000 or 6% are found in Malaysia, and they may provide new chemical entities or chemotypes for drug development.

Currently, major pharmaceutical companies are involved in the screening of potential biopharmaceuticals and the leads derived from the drug discovery programmes have been quite successful. These companies are increasingly interested in medicinal plants, micro-organisms and sea organisms found in developing countries as a source of new biopharmaceutical materials for novel drug entities. Based on a study in USA, it was found that drugs approved by FDA between 1983 and 1999, 70% are of synthetic origin, whilst 30% are of natural product chemotypes. In 1999, of the top 25 selling drugs in US, natural product chemotypes contributed 35% in financial value, USD 18.5B, whilst the other 65% was from synthetic drugs. This clearly shows natural products are important in providing humankind with therapeutic agents.

Traditionally, isolated fractions or pure chemical entities are evaluated using pharmacological models based on the use of animals as the primary screen. However, the costs of animal models are high and the process is slow, and creates a bottleneck. The ever-expanding palette of compounds has made the situation even more acute. Consequently, this demands the use of a more efficient and integrated high throughput screening assays, particularly, with the advent of separation technology and chemistry.

The screening systems adopted are currently receptor-based, cell-based or biochemical (enzymic)-based assays to determine the receptor binding efficiency and in vitro functional activities. These assays have now replaced pharmacological models as the primary screens as they are more cost effective and efficient. An effective primary screening system demands seamless integrations of receptor-based, cell-based or biochemical (enzymic)-based assays.

Screening

Natural products based drug discovery programs have mostly relied on a traditional approach of random screening and bioassay-guided fractionation. The recent scientific and technological advances such as the rapid identification of diverse new targets through genomics, proteomics, cellomics and bioinformatics have increased the number of validated chemotherapeutic targets such as G-protein coupled receptors (GPCR) and ion channels. This has clearly contributed to a paradigm shift in drug discovery approach.

The multidirectional, molecular target-based approach involves screening of natural product libraries through a battery of validated receptor, enzymic or cellular screening assays. To enhance the value of the data obtained for screening hits, appropriate discriminatory tests such as cytotoxicity are included. In addition, the data generated from test samples are compared so that hits can be identified at an early stage. This combination of specific screens, data comparisons and discriminatory assays improve the selection of the hits for further work.

The screens designed must be sensitive, selective and able to screen large numbers of samples. The selection of appropriate screening technique to detect 10-200 nM is important. This is because the concentration of secondary metabolites in the sample is usually low; therefore it is pertinent to be able to detect biologically active compounds which may present at 1-10 mcg/ml in the crude extract.

Before high throughput screening (HTS) implementation, the screening assay must be optimised and validated. For example, 5-HT1a GPCR assay requires the establishment protein linearity, optimisation of temperature, pH, concentration of radioligand and incubation time. In addition, the assay must be validated in terms of specificity, intraplate and interplate variabilities. For instance, the optimised protocol is

addition of 35-40 mcg of protein/well, radioligand (3H-8-OH-DPAT, 0.4 nM), incubated for 90 minutes at pH 7.4 and 25(C. The screening window, Z' value of 0.67 indicates the assay is reliable as a high throughput assay, whilst the Ki values of known ligands indicate the assay is highly specific for 5-HT1a receptor activity.

The traditional method of separating individual components in complex mixtures poses enormous problems for natural product research. However, the separation process now involves a degree of automation to expedite the process. More recently, the introduction of new automated chromatographic separation such as 'Sepbox' is able to separate each component of a complex mixture in a single run. This coupled with high throughput bioassay-guided fractionation has expedited the entire process. The incorporation of dereplication process with the use of LC-MS, LC-PDA and LC-NMR, based on retention time, uv and molecular weight to recognize and to eliminate compounds that have no potential for exploitation from the discovery pathway has also help to accelerate the process.

Technology

A wide range of technologies has been used for screening programmes, which can be classified into receptor-based, cell-based and enzyme-based targets. For receptor-based targets, filtration assays, scintillation proximity assays (SPA) and time resolved fluorescence (TRF) have been adopted. For cell-based targets, cell-signalling and reporter gene assays have been widely used.

In general, screening technology is moving towards the use of assays with a minimum number of steps, and amenable to automation. SPA is a homogeneous radiometric technique, which relies on incorporation of solid scintillant into the bead or the microplate itself. The biological reagent (antibody, receptor, protein or hapten) is attached to the surface of the bead or the microplate via a linker. Upon completion of the screening reaction, the bound radioligand on the biological reagent in close proximity to the bead emits beta particles, which travel through the aqueous media with a limited path range. If the beta particles collide with the scintillant, energy is transferred and light is emitted. This makes the technique applicable to a wide range of assays including in situ receptor binding assays, enzymic assays and others. In addition, it can be fully automated, and hence is suitable for HTS.

Time resolved fluorescence (TRF) utilises the properties of lanthanides to overcome the problems such as background fluorescence and quenching that is often seen with other fluorescence techniques. The main application of TRF is dissociation enhanced lanthanide fluorescence immunoassays (DELFIA), where, a lanthanide such as europium (Eu) is attached to one of the biological reagents (antibody, protein or hapten) via a chelating agent. The bound biomolecule is practically non-fluorescent as the surrounding water molecules quench the fluorescence. Upon completion of the binding reaction, fluorescence is developed by the addition of an enhancement solution. The low pH (pH < 4) of this solution efficiently dissociates the Eu from the labelled biomolecule within a few minutes. The free Eu3+ rapidly distribute itself inside a micelle with components of the enhancement solution. As a result of the exclusion of water by the micelle, this entrapped Eu3+ fluoresces with a high intensity with amplification of 1-10 million times. In addition, it has a long decay time and a large stoke shift. These inherent properties allow the fluorescence to be measured after the background has decayed and the assays are highly sensitive and has a wide dynamic range. DELFIA can be applied to enzyme, receptor, cytotoxicity and immunoassays. The stable signal generated, together with low fluorescence background makes the technology ideal for automation.

Other fluorescence techniques including delayed fluorescence resonance energy transfer (DEFRET), fluorescence polarization and fluorescence imaging plate reader (FLIPR) are now available. Both DEFRET and FLIPR have been applied to screening in pharmaceutical industry. One of the main platform for inhouse screening in industry is FLIPR, as the assays are homogeneous, more rapid, enable kinetic studies and miniturization to be carried out, whilst outsourced screening, radiometric is still the preferred technique.

Conclusion

The combination of advanced technologies in HTS screening and automated separation has now enabled natural product research and identification of leads to be carried out more efficiently. For example, our inhouse research for the past one year has led to the identification several natural product leads for CNS and antimicrobial activities. To enhance the productivity of new drug discovery from natural products, partnerships with governmental and cooperate organisations are essential. This approach will reduce the cycle time of natural product research programme and maintain the unique chemical and pharmacophoric diversity of the natural product library.

IMAGING STUDIES IN CANCER DIAGNOSIS AND STAGING

Abdullah BJJ
Department of Radiology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Introduction

We have taken for granted our ability to see inside the human body in non-invasive ways which have allowed diseases such as cancers to be detected. The change from planar to sectional imaging modalities; changes from assessment of structure to functional; to cellular imaging to currently looking at molecular changes have revolutionized the role of imaging in every realm of medicine. From screening, diagnosis, treatment planning, to instituting the actual treatment and follow up responses. There has also been a move to use imaging in post-mortem studies for those with religious objections.

Computed tomography and magnetic resonance imaging along with ultrasound are currently the major players in sectional imaging. This has mainly allowed the acquisition to be done digitally as well as volume data-sets rather than slices. The ability to store, share and send images anywhere in the world has made the dissemination and exchange of patient care. This is based on the development of new standards in the way medical images such as DICOM and IHE are characterized. DICOM is used or will soon be used by virtually every medical profession that utilises images within the healthcare industry. These include cardiology, dentistry, endoscopy, mammography, ophthalmology, orthopaedics, pathology, paediatrics, radiation therapy, radiology, surgery, etc. DICOM is also used in veterinary medical imaging applications. DICOM also addresses the integration of information produced by these various specialty applications in the patient's Electronic Medical Record (EMR). It defines the network and media interchange services allowing storage and access to these DICOM objects for EMR systems. IHE is an initiative by healthcare professionals and industry to improve the way computer systems in healthcare share information. IHE on the other hand, promotes the coordinated use of established standards such as DICOM and HL7 to address specific clinical needs for optimal patient care. Systems developed in accordance with IHE, communicate better with one another, are easier to implement, and enable care providers to use information more effectively. Physicians, medical specialists, nurses, administrators and other care providers envision a day when vital information can be passed seamlessly from system to system within and across departments and made readily available at the point of care. IHE is designed to make their vision a reality by improving the state of systems integration and removing barriers to provide optimal patient care.

The advent of faster scanning techniques in all three modalities, along with better software have allowed the functional assessment to determine the tumour kinetics, e.g., blood flow, blood volume, permeability as being surrogate markers for tumour angiogenesis. These can then be used to characterize the malignant potential of lesions, the response to chemotherapy, etc. In addition, the developments of newer MRI sequences have allowed the demonstration of the white matter tracts in the brain so that the location of tumours on vital structures can be seen and this would help the surgeon to avoid them or choose a different approach.

The trend towards fusion of two or more imaging modalities has facilitated the exploitation of synergies between them. The hot modality in this group is PET/CT which has allowed a more accurate assessment of functional aspects of tumour but localized very accurately to an underlying structure with little misregistration. Once trapped in the cell, the radioactive fluorine decays, emitting a positron that undergoes annihilation, releasing two photons in exactly opposing directions that coincidence detectors record as an event. Using FDG, the activity of lesions can be determined and generally malignant tumours have a higher metabolic activity compared to normal benign tissue (with the exception of inflammatory processes). These events are summed over the course of imaging the body, and a 'functional' glucose map, or 'PET' scan, is developed. This functional map is superimposed over an 'anatomical' map of the body, such as CT, to create a combined functional-anatomical image (PET/CT). With PET/CT, the CT scan is an integral and integrated part of the PET scanner. PET/CT offers significant advantages over PET alone, including accurate spatial localization of PET-detected abnormalities as well as the determination of the location of questionable PET findings (normal tissue with

FDG uptake vs. tumour). This advantage is important, especially when characterizing head and neck structures as well as differentiating normal bowel activity from metastatic lymph nodes in the abdomen. Additional advantages include more rapid scans with less patient motion, higher quality transmission scans using CT (vs. external germanium sources) and fewer visits to the imaging specialist for multiple tests (since the patient can have a PET and a diagnostic quality CT in one scan). In several tumour types PET/CT using FDG is the modality of choice for staging and follow-up including the characterization of a solitary pulmonary nodule and the diagnosis, staging and restaging of non-small cell lung cancer (NSCLC), colon cancer, Hodgkin's disease (HD) and non-Hodgkin's (NHL) lymphoma, melanoma, head and neck cancer (HNC), esophageal cancer and specific indications for breast cancer, excluding axillary staging. However, there are other radiopharmaceuticals based on oxygen, nitrogen and carbon which can be used to follow other biological processes.

The twenty-first century has witnessed an explosion of molecular biology techniques, amazing advances in imaging, and the design of unique imaging probes. On the horizon are newer imaging technologies which are moving further into the cell cycle and looking at the specific pathways in the metabolic process and even looking at specific protein or gene markers e.g., vascular endothelial growth factor, annexin V, etc. Cancer is a complex disease and the apparent impenetrability of the disease is largely due to the multiple, often redundant pathways, which appear to evolve through the genetic instability of cancer cells. The ability to identify and image key common pathways specific to cancer cells, and the ability to image the effectiveness and outcome of strategies designed against these targets is critically important in the treatment of this disease. This process would even allow detection of the presence of predisposition. These changes would be visualized using MRI, PET or even ultrasound.

A discussion on advances in imaging would not be complete without examining the increasing role of minimally invasive image-guided therapy from simple biopsies to drainages to more complicated insertion of temporary inferior vena cava filters to radiofrequency ablation of tumours and chemoembolisations. The use of vertebroplasty and kyphoplasty have been used extensively in the management of patients with osteoporosis as well as those with vertebral collapse secondary to tumour infiltration. All these have been shown to reduce the morbidity as well the recovery times, thus improving the recovery times for most of the terminally ill patients. The advent of MRI guided high intensity focused ultrasound will further extend this role. By focusing the energy of an ultrasound beam, temperatures in excess of 100°C can be generated and this can be followed by using heat specific MR sequences. Localized radiotherapy using catheters and radioactive particles is being explored in the treatment of liver metastases and hepatomas. There are already trials in place looking at gene therapy for a variety of diseases and this is only going to expand further.

Medicine is also becoming increasingly image-centric and the volume data-sets generated from either CT, MRI and even US are being used for surgery. The basic concept of image-guided surgery (IGS) is that the surgical procedure is facilitated by a real time correlation of the operative field to a monitor, which shows the precise location of a selected surgical instrument to the surrounding structures. Although first developed for neurosurgery, its adaptation to sinus surgery is rapidly becoming the leading indication for this technology. In neurosurgery, the primary use of IGS is to locate an intracranial lesion for resection or biopsy. In sinus surgery, the main advantage is to avoid entering vital areas, such as the brain and the orbit. Its development and rapidly growing popularity in sinus surgery are directly attributable to such misadventures. It is rapidly becoming the standard of care for these procedures. Robotic surgery is set to revolutionize surgical procedures even further. The application of computer-aided planning, navigation and robotics in surgery provides significant advantages due to today's sophisticated techniques of patient-data visualization in combination with the flexibility and precision of novel robots. Augmented with 3D image-guidance technology these tools give finer control over sensitive movements in diseased areas and therefore allow more surgical procedures to be performed using minimally invasive techniques.

Conclusion

Even radiotherapy is not immune to these changes and there is technology which will allow the real-time assessment of radiotherapy as it is being delivered.

TUMOUR MARKERS: DEVELOPMENT AND CLINICAL UTILITY

Yap SF
Department of Pathology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Tumour Marker Development

Tumour markers are substances present in or produced by a tumour, or substances produced by the host in response to the tumour, that can be used to identify the presence of the tumour. Such substances can be present in cells/tissues or body fluids and are measured by chemical, immunological or molecular biological methods. The first tumour marker was described more than 100 years ago by Sir Henry Bence Jones. This marker, the Bence Jones Protein (BJP), represented the main diagnostic marker of multiple myeloma for more than a hundred years until its identity as a monoclonal immunoglobulin light chain was discovered. The next era in tumour marker development was from 1929 - 1962, when numerous hormones and enzymes were recognized to be associated with various neoplastic growths. Important landmarks during this period included the description of ectopic hormone syndromes and discovery of hormones such as hCG and ACTH which are associated with specific endocrine tumours. Numerous enzymes and iso-enzymes were also described during his period. However, the general utility of enzymes in tumour diagnosis was subsequently found to be relatively limited. The major breakthrough in tumour marker development came with the discovery of the oncofetal proteins, AFP and CEA in the mid-1960s. The practical use of these markers was realized some 10 years later with the advent of sensitive immunoassays brought about by the invention of the RIA and the successful production of momoclonal antibodies. With these technological developments, a new group of tumour markers known as 'Tumour Associated Antigens' were recognized; examples of these markers are CA125 and CA153, both of which have proven to be useful biochemical markers for the management of ovarian and breast cancer respectively.

More recent advances in the development of tumour markers came with a better understanding of cancer biology, particularly, at the cellular and molecular level. In the 1970s and 1980s, several oncogenes and anti-oncogenes were recognized. This was followed in the 1990s by advances in molecular techniques including PCR and high-throughput array technology. With the availability of these tools, it became possible to look at these genes in more detail, including their physiological functions, and the effect of mutations on these functions. The application of molecular techniques also led to the discovery of molecular markers in plasma and body fluids. These include tumour derived oncogenes, microsatellites, chromosomal translocations, viral DNA and mRNA. The potential use of these plasma nucleic acid as tumour markers have been reported by several workers in recent literature.

Currently, the range of tumour markers include :

1. Naturally secreted substances such as hormones, enzymes and iso-enzymes
2. Oncofetal proteins, the most well-known being AFP, CEA
3. Tumour-associated Antigens like CA125, CA19-9 and CA15-3
4. Secretory proteins and cell membrane bound proteins
5. Oncogene and oncogene products
6. Suppressor gene mutations

Clinical Utility of Tumour Markers

The clinical utility of enzymes as tumour markers, with the notable exception of PSA, is extremely limited. In the case of hormones, the use is mainly restricted to the definitive diagnosis and management of specific endocrine tumours. Several oncofetal antigens that are associated with various malignancies have been described; the more widely known of these are AFP, CEA and the Squamous Cell Antigen. These antigens are produced during fetal life and reappear in cancer patients as a result of reactivation of their encoding genes during malignant transformation. AFP is a 70 kDa glycoprotein that is associated with HCC and germ cell tumour. It is used in association with hCG for classifying, staging and monitoring germ cell tumours. It has also been used, in association with ultrasonagraphy, for the early detection of HCC in high risk individuals. CEA, also a glycoprotein, is a marker for a variety of cancers which include colorectal, gastrointestinal, lung and breast cancer, while SCC antigen, as the name implies, is elevated in a number of squamous cell cancers.

The tumour associated antigens are high MW mucins such as CA125 and CA15-3, which are commonly associated with cancer of the ovary and cancer of the breast respectively, or blood group antigens such as CA19-9 which is associated with cancer of the pancreas. These markers are present on the surface of tumour cells or are secreted by tumour cells. Therefore, they are more specific than naturally secreted markers like enzymes and hormones. Examples of proteins as tumour markers are the nuclear matrix protein, NMP22, and bladder tumour antigen, both of which are associated with transitional cell carcinoma of the urinary tract, and monoclonal immonoglobulins which are pathognomonic of multiple myeloma.

The most recently discovered tumour markers are proto-oncogenes and tumour suppressor genes. Briefly, proto-oncogenes are normal genes that encode products involved in cellular processes, in particular the signal transduction pathways. Overall, they act as positive regulators of cell proliferation and cell survival. Tumour suppressor genes, on the other hand, can be regarded as negative regulators of cell cycle proliferation. Together, these genes are responsible for the maintenance of normal tissue homeostasis. Oncogenes are basically proto-oncogenes that have undergone 'gain of function' genetic alterations that result in deregulation of the cell cycle and increased cell proliferation. The main types of changes that affect proto-oncogenes are:

1. Point mutations, which are generally missense mutations that activate the gene product, eg. the Ras mutation.
2. Amplification such as that of N-myc and c-erb B-2.
3. Translocations that place the gene under the control of active sequences or that generate a fusion product with new constitutive functions, for example the bcr/abl translocation associated with CML.

Mutations of tumour suppressor genes, in contrast to oncogenes, result in 'loss of function', that also result in unregulated cell cycling and proliferation. The most well known of the tumour suppressor genes is p53, which is mutated in a wide variety of cancers. The native (or wild type) p53 is believed to control cell division at the entry into the S phase, and loss of this function will result in uncontrolled cell cycling. However, alterations of p53 occur late in tumorigenesis, thereby limiting its usefulness as a marker for early detection of cancers. The clinical usefulness of tumour suppressor gene mutation appears to lie in the prediction of cancer susceptibility when the mutation is carried in the germline, eg. the BRCA1 and BRCA 2 genes in the case of inherited forms of breast and ovarian cancer, or the RB1 gene in the case of familial retinoblastoma.

The potential clinical applications of tumour markers include :

1. Population Screening
2. Disease Diagnosis
3. Prediction of Prognosis
4. Monitoring of Disease Course
5. Prediction and Monitoring of Therapeutic Response

In terms of screening, tumour markers suffer from lack of sensitivity, specificity and predictive value, particularly when applied to rare diseases in population screening programs. However, it may be applicable for selective high risk groups. For example AFP for detection of HCC in subjects with chronic hepatitis B infection and PSA for prostate cancer in males over 55. Notable examples of tumour markers used for disease diagnosis are monoclonal immunoglobulin for diagnosis of multiple myeloma, and hCG together with AFP for diagnosis of germ cell tumour.

The rationale for the use of tumour markers for the prediction of prognosis lies in the belief that serum level may be reflective of tumour burden; therefore, quantification of tumour markers may aid in 'clinical staging'. Further, the rate of decrease of the tumour marker following treatment may give an indication whether the treatment was successful or not.

The most useful applications of tumour markers are in (i) the monitoring of the disease course and (ii) the patient's response to therapy. As a general rule, markers increase with progress of disease and recurrence, decrease with remission and remain unchanged with stable disease. With respect to therapeutic monitoring, an uninterrupted increase in the tumour marker level indicates lack of response while an uninterrupted decrease indicates response to treatment. A surge followed by a decrease is also indicative of a therapeutic response. An immediate decline followed by an increase, on the other hand is indicative of non-response. A guideline published by the 'Working Group on Tumour Marker Criteria of the International Society for Oncodevelopmental Biology and Medicine' provides useful information on the interpretation of tumour marker values for patient monitoring.

RECENT ADVANCES IN PAEDIATRIC INTENSIVE CARE

Booker PD
Royal Liverpool Children's Hospital, Liverpool, United Kingdom

Paediatric intensive care units (PICUs) make a substantial and highly cost-effective contribution to child health in developed countries. The overall mortality rate of children requiring care in a PICU is now less then 5%, and, in contrast to preterm neonates and adults requiring intensive care, nearly all survivors go on to lead long, high quality lives. There is now considerable evidence that critically ill children have a better chance of survival if they are looked after in large PICUs: the most important single factor that has improved mortality and morbidity rates in children requiring intensive care has been the introduction of independent PICUs, staffed by specialist doctors and nurses. This premise is exemplified by the decline in mortality in patients with severe meningococcal disease over the past two decades, despite the absence of any significant change in therapy.

Nevertheless, the field of paediatric intensive care continues to evolve rapidly, with advances in drug and adjunctive therapies, ventilatory care, monitoring, and mechanical cardiovascular and renal support. The focus of care for many conditions that previously had a high mortality rate is now shifting towards reducing morbidity. Many important changes in ventilatory therapy have been instigated in response to increasing knowledge about ventilator-induced lung injury. Innovative practices of ventilatory support include high frequency oscillatory ventilation, prolonged prone positioning, lung recruitment strategies, inhaled nitric oxide, and permissive hypercapnia. New cardiovascular therapies include inodilators such as levosimendan, adjuvants such as triiodothyronine, and new monitoring methodologies that allow continuous assessment of cardiovascular status. The use of extracorporeal techniques, such as membrane oxygenation (ECMO) and haemofiltration, in the treatment of critically ill children has expanded dramatically in the past decade, their increasing success serving to emphasise the importance of centralisation of resources and staff expertise.

HUGHES' SYNDROME : A NEW DIMENSION TO RECURRENT PREGNANCY LOSS

Osborn ACV
Universiti Malaysia Sabah, Kota Kinabalu, Sabah, Malaysia

Introduction

The association between antiphospholipid antibodies and thrombosis is not new. Conley first drew attention to phospholipid-dependent coagulation inhibitors in 1952. Since then associations have been drawn between the presence of circulating antiphospholipid antibodies and a plethora of medical conditions resulting in the syndrome being given a variety of names. It was only in 1995 when the complex and probably indirect links between antiphospholipid antibodies and thrombosis was given the name 'Hughes Syndrome' after the London based rheumatologist. The condition has manifestations that transgress virtually every medical specialty but in Reproductive Medicine, it is the most important treatable cause for recurrent pregnancy loss. For these reasons, the condition has been identified as one of the two most important diseases of the twenty-first century – the other being AIDS. From the world literature to date, Hughes Syndrome accounts for approximately; 1 in 5 Deep Vein Thromboses ('DVTs'), 1 in 5 young strokes (under age 45) and 1 in 5 recurrent miscarriages – commonly referred to as the '1 in 5' rule. If one adds to this the as-yet unknown number of migraine, 'Alzheimers' and Multiple Sclerosis sufferers who actually have Hughes Syndrome, then the prevalence figure in the population could be as high as 1 in 500 individuals - truly one of the 'new' diseases of the late twentieth century.

Whilst an alteration of the homeostatic regulation of blood coagulation is understood, the precise mechanism of thrombosis remains unclear. Perhaps the most plausible hypothesis is the one that postulates a defect in cellular apoptosis, which exposes membrane phospholipids to the binding of various coagulation proteins. Once bound, a phospholipid-protein complex is formed and a neoepitope is uncovered, which subsequently becomes the target of autoantibodies. Several other hypotheses exist so that treatment options remain largely empirical and their responses often inconsistent.

Furthermore, given that all modalities of treatment carry inherent risks, it is crucial to restrict such therapy to those patients most likely to benefit although there is no currently available method of identifying this subset of patients. It is also important to note that disease activity and outcomes are not related to antiphospholipid antibody levels and that there is no evidence to support an aggressive and obsessive approach aimed at lowering these titres. Given that placental thrombosis may be responsible for recurrent pregnancy loss, there is plausible evidence for the successful use of low dose aspirin and fractionated heparin in selected patients with Hughes Syndrome. Indeed such therapeutic interventions have resulted in a significant improvement in the incidence of successful pregnancies in sufferers of the disease. The current management of pregnancy in women with Hughes Syndrome may be outlined as follows.

Prepregnancy Counselling

This is often possible as the diagnosis is usually known before pregnancy. At this meeting, it is imperative that the economic and emotional costs are discussed with the patient and her spouse. It is also important to draw her attention to recurrent hospitalizations and the possibility of adverse outcome. The obstetrician must also stress the need for compliance with medication despite the small risk of congenital defects occurring.

Antenatal Care

This centers around early booking and the incorporation of pharmacotherapy in appropriate cases. Ultrasound imaging with Doppler assessment of placental vasculature remains the key to good antenatal surveillance. It enables accurate dating, intrauterine growth, indicators of fetal normality assessment and, most importantly, a good account of placental perfusion.

Intrapartum Care

This must be undertaken at a tertiary institution equipped to offer a high level of intrapartum and neonatal intensive care. As the incidence of premature delivery is high, operative delivery is also frequent so that a multidisciplinary approach is likely to bring best results.

Postpartum Care

All patients must be given some form of thromboprophyllaxis. Issues of family size and contraception must be discussed and the need for long-term treatment with aspirin must be considered.

As there are currently no laboratory tests available to identify the subset of patients with antiphospholipid antibodies at risk for thrombosis or abortion, the issue of who to treat remains contentious. In essence, treatment should be restricted to those with recurrent obstetric problems and those with other medical complications such as thrombocytopenia. The range of treatments include *Immunosuppressants* (steroids, azathioprine, cyclophosphamide), *Anticoagulants* (warfarin, heparin – fractionated and unfractionated, aspirin), *Immunoglobulin infusions, plasmapharesis* and *antimalarials*. However, the potential risks and benefits of all these treatment regimes must be appreciated before exposing patients to them. These risks are outlined below:

Maternal Risks: venous and arterial thrombosis, operative delivery rates of as high as 35%, osteopenic fractures involving the femoral neck and vertebrae and placental abruption.

Neonatal Risks: Low birth weight caused by prematurity and intrauterine growth restriction, severe neonatal thrombocytopenia and congenital deformities secondary to drug administration, e.g., warfarin, prednisolone.

In a recent edition of the Australian and New Zealand Journal of Obstetrics and Gynaecology (2nd April, 2005), Tuohy and Harrison reported a case of ***Fetal Risk***. They describe a case of perinatal transfer of anticardiolipin antibodies associated with fatal neonatal aortic thrombosis.

Conclusion

In closing, it would incomplete if medicolegal implications of thid disease were not alluded to. With the practice of high risk obstetrics in a climate of high litigation, it is important to remember that the management of patients with Hughes Syndrome is unfortunately also bedeviled by medicolegal consequences. An obstetrician will be culpable in the following circumstances:

1. Failure to recognize Hughes Syndrome when suggested by history or clinical examination findings, especially thrombosis in a relatively young individual.

2. Failure to warn female patients about potential complications with pregnancy.

3. Failure to discontinue oral contraceptives or other estrogen preparations.

Clearly, this is a disease whose entire ramifications remain unquantified and elusive.

Given the information above, it would be reasonable to allocate treatment to patients after separating them into three categories as shown in Table 1 below.

Table 1

Clinical Situation	Management
History of pregnancy loss	Aspirin plus heparin (APTT in therapeutic range)
History of thromboembolism but no pregnancy loss	Heparin alone (APTT in therapeutic range)
No history of adverse events	Heparin alone 5000 IU twice daily close observation

Despite knowledge of this condition for more than half a century, the management of Hughes Syndrome remains an enigma. The way ahead lies in the development of a greater awareness of the condition, improved identification of the subset of women at greatest risk and the evolution of better antithrombotic regimens of treatment. To achieve this, a multidisciplinary approach is imperative.

UPDATE ON MATERNAL MORTALITY IN MALAYSIA

Ravindran J
Department of Obstetrics & Gynaecology, Seremban Hospital, 70300 Seremban, Malaysia

Introduction

Maternal mortality is often used as a proxy indicator of the care provided during the antenatal, intrapartum and postpartum periods. It is profoundly influenced by many socio-economic and cultural determinants. In the 1950s, Malaysia had a relatively low gross national product per capita. At that time, female literacy was low (17%) and the male-female literacy ratio was 0.32. Maternal mortality ratio was halved within seven years between 1950 to 1957. It took another 13 years to slice the MMR in half again. During this period, access to basic health care, including critical elements of maternal health care was improved for the bulk of the rural population through a widespread rural health network. In subsequent decades, Malaysia applied stepwise strategies to improve organizational and clinical management to reduce the MMR by 50% every six to 12 years (1). Apart from the initial capital investment in building facilities that were accessible to rural communities, the major expenditure in maternal health care was the operational cost associated with the human resources needed to provide services. Malaysia used a judicious mix of health personnel. The bulk of maternal health care was provided by well-trained but relatively low cost midwives, who were adequately supplies and equipped and were closely supervised and supported by nurse-midwives and much smaller numbers of medical doctors. A confidential system of enquiry into maternal deaths, based on that used in England and Wales was introduced in Malaysia in 1991 with a view to identifying deficiencies in care and recommending remedial measures (2).

Main Messages and Findings

The maternal mortality ratios have reduced from 44 per 100000 live births in 1991 to 28.1 in 2000. The MMR doubled in 1991 from 20 to 44.1 due to better data capture. Maternal deaths are certified by medical personnel as well as the police. This doubling was termed the paradox of increased rates and formed the basis of a publication in 1996 (3). In 1996 it was decided to calculate national maternal mortality ratios based on cases involving citizens and direct as well as indirect maternal deaths only.

The principal causes of maternal death remain postpartum haemorrhage with or without retained placenta, hypertensive disorders of pregnancy, obstetric embolisms and associated medical conditions. Medical conditions especially heart diseases in pregnancy have increased in proportion to 15.8% in 2000 compared with 7% in 1991 and hypertensive disorders in pregnancy has reduced from 16% in 1991 to 8.9% in 2000. The proportion of direct maternal deaths has reduced from 70% in the initial years to 55.7% currently. Concurrently the proportion of fortuitous deaths has increased to 33.3% in 2000.

An analysis of the deaths that occurred showed that the maternal mortality ratio was 53 per 100 000 live births for deliveries performed at home, whereas it was 36 per 100 000 in government hospitals and 21 per 100000 in private institutions.

Care was initially categorized as substandard if the National Technical Committee considered it inappropriate or deficient, taking into account the standards of care applicable in the year when death occurred. Where it was considered that death would have been preventable if the patient or her family had acted appropriately, or where there were other sociocultural, physical or geographical factors contributing to the outcome which were beyond the control of physicians, the term 'substandard care' was not applied. As from 1994, the term 'remediable factors' was introduced for factors previously referred to under the heading of 'substandard care' and the terms 'remediable patient factors' and 'personnel and facility factors' were introduced as categories of contributory factors. Remediable factors continue to be identified in up to 50% of patients. Contributory factors were associated with 27% of the deaths. Remoteness or inaccessibility was a factor in 7.2% of cases.

A lack of clinical acumen was detected in several cases in both the public and private sectors, involving failure to diagnose, failure to appreciate the severity of a patient's condition, therapy that was inadequate, inappropriate or delayed and failure to adhere to protocols. A significant proportion of these problems occurred in the postpartum period.

There is a clear need for continuing education of staff in the public and private sectors in order to improve clinical acumen and the management of difficult cases. Protocols were developed for the management of postpartum haemorrhage, hypertensive disorders of pregnancy and heart disease in pregnancy. Training courses were held throughout the country to familiarize staff in the management of these conditions.

It is worth underlining the significance of the confidential nature of the investigations for both patients and care-givers. In this type of enquiry, it is important to guarantee that no punitive action ensues, otherwise there would be little prospect of obtaining complete information.

Deaths from postpartum haemorrhage were often associated with remediable factors, and in most cases there was a delay in providing suitable care. Almost half of these cases were in mothers who delivered at home, often in areas where access was difficult. Many of the women who delivered at home were in the high risk category and many refused hospital care. The establishment of facilities for staying in hospital before delivery and of alternative birthing centres in rural areas has been recommended. Some women delivered in private centres where the facilities for resuscitation were inadequate. Review of the legislation governing such centres has occurred as a result of these findings.

Because many mothers were managed by relatively inexperienced doctors who either did not institute treatment early enough or failed to consult senior colleagues till it was too late, a red alert system was established nation wide for rapidly calling on personnel including blood bank and anaesthetic staff. Obstetric trauma contributing to postpartum haemorrhage and uterine inversion often arose because staff were inexperienced and failed to observe standard practice. In many cases of hypertensive disorders a more active or aggressive management of the mothers would have prevented deaths.

Although sudden collapse was frequently attributed to obstetric embolism, the number of deaths actually confirmed by postmortem examination as being linked to this condition was small. It was recommended that a distinction be made between confirmed cases of the condition and those clinically suggestive of it. Death form puerperal sepsis were usually associated with risk factors, among them instrumental or complicated delivery, manual removal of the placenta or diabetes mellitus. In several instances the occurrence of persistent fever during the puerperium was not accorded the significance it merited for patients, family members or health personnel.

In the Confidential Enquiries, it emerged that few women at risk because of medical conditions were offered pre-conception contraceptive counseling or early pregnancy termination. Health professionals sometimes failed to recognize obvious medical conditions and inappropriate or late intervention took place in certain cases. Because the risk of death would have been diminished in some cases had there been collaboration between physicians and obstetricians, it was recommended that combined management be adopted for patients with such conditions.

The confidential reports have been circulated to all institutions and organizations providing maternity care and to medical schools, postgraduate trainees and midwifery schools. Articles and case histories have been published in the newsletter of the national medical association. Regional seminars have been organised on the investigation system and the dissemination of its findings, and training modules have been distributed to all involved in the provision of maternity care.

Conclusion

The Malaysian experience illustrates one model for reducing maternal mortality in a developing country using mainly public financing and provision of maternal health services. MMR reduction has been rapid and sustained. Health policies and programmes evolved through successive phases of health systems development and were facilitated and supported by related policies in education, rural development and poverty reduction. Success has been achieved with modest public expenditures on health and on maternal health services have been largely free to clients who wanted them. An outstanding feature has been the success in making critical services accessible to the poor. The Confidential Enquiry system in the last decade has been instrumental in ensuring further gains in sustaining the reduction in maternal mortality.

References

1. Pathmanathan I, Liljestrand J, Martins JM, et al. Investing in maternal health-Learning from Malaysia and Sri Lanka. Human Development Network. Washington DC: The World Bank, 2003; 61-103.
2. Suleiman AB, Mathews A, Ravindran J, et al. A strategy for reducing maternal mortality. Bull WHO, 1999; 77(2): 190-193.
3. Ravindran J, Mathews A. Maternal mortality in Malaysia 1991-1992: The Paradox of increased rates. J Obstet Gynaecol 1996; 15 (4) : 86-88.

THE IMPACT OF DOMESTIC VIOLENCE ON WOMEN'S HEALTH

Othman S[1,2], Goddard C[2], Piterman L[2]
[1] Department of Primary Care Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia
[2] School of Primary Health Care, Monash University, Australia.

Introduction

Domestic violence (DV) cuts across all countries, cultures and religions. The prevalence of DV was reported in The World Health Organization Report on Violence to be from 10% to 60% in all the countries in the world (1). In Malaysia, 39% of women were reported to have previous experience of physical violence (2). In Malaysian clinical setting, 1 in 6 of adult female patients attending one outpatient clinic has reported of having DV experience within the past one year (3).

When comparing between women victims and non-victims presenting to health facilities, domestic violence patients were found to have had 3.74 more primary care visits, 1.75 more mental health visit and 7.2 more total visits per year than those without abusive background (4).

DV issues are initially seen as a human rights problem but have been accepted as a major public health problem because of the health consequences brought by it [5]. Although men could be victims of domestic violence also, studies have shown that women made the majority of the victims and it is usually women who are more prone to suffer severe consequences of domestic violence compared to men (5).

This article discusses the health consequences of DV on women who are victims of this kind of violence. There would also be discussion on children of these women victims also as there is close relationship of DV with child abuse.

What is domestic violence?

DV is also known as intimate partner violence, wife battering and spouse abuse. It signifies abuse of power of one intimate partner against another leading to coercion, intimidation and controlling behaviour. DV can be in the form of physical violence, psychological violence and sexual violence. Most of the time, victims face more than one type of violence and the violence acts escalate with time (6).

Fatal health consequences

Mortality of abused women occurs in cases of homicide and suicide. In one study, 57% of deaths in women resulting from homicide or violence were perpetrated by an intimate partner (7). It is also reported that women are five times more likely than men to be killed by an intimate partner (8). Stress of the abusive relationship causes women to be five times more likely to commit suicide as compared to women who are not in a violent relationship. The mean prevalence rate of suicidality among women victims is 17.9% (9). Other fatal health consequences come from AIDS-related mortality and maternal mortality (5).

Physical injuries

The direct effects of DV on women's health through repeated physical assaults result in physical injuries. DV contributes to the most common cause of non-fatal injury to women in the United States (10). The victims usually present with injuries of multiple sites of the body; commonly at the face, neck, trunk and abdomen with either soft tissues injuries or bony injuries. Most of these victims will present to casualty department for treatment especially if the injury is serious. However, injuries like maxillofacial, eye and ear trauma; and other mild injuries will lead these victims to present to other health facilities apart from casualty such as to the ophthalmology, ear and dental clinics. The victims usually will present late to the health care facilities, with explanations that do not fit the injuries, with injuries that have various stages of healing.

Mental health effect

Shock, fear and feeling numb are common psychological responses to DV (WHO 2002). However, the mental health effects persist long after a violent episode. One meta-analysis of DV studies found that PTSD is one of the most frequent mental health consequences of DV, followed by depression (11). It was also found that

severity of abuse was significantly correlated to severity of depression (11, 12). Victims are more likely to have alcohol problems as well as smoking and use of non-prescription and prescriptive drugs, amphetamines, tranquillisers, sleeping pills and anti-depressants than those who are not (11, 13, 14). It was found that among DV victims, half of them suffer some sort of psychiatric disorder. Among psychiatric disorder patients, a third of them have a background of abusive intimate relationship (15).

Victims of violence have more somatic symptoms related to musculoskeletal, genito-urinary, skin and respiratory system. Patients with gastrointestinal functional disorders were more likely than those with organic disease diagnoses to report a history of forced intercourse, frequent physical abuse and chronic or recurrent abdominal pain with more lifetime surgeries (16). Most of the abused women are restricted in the way they gain access to services, take part in public life, and receive emotional support from friends and relatives (5). Their self-esteem has been affected by their abusive relationship causing difficulty for them to participate outside the relationship.

Gynaecological and Pregnancy problems

Abused women who were exposed to both sexual and physical abuse as compared to physical abuse only are more likely to have contracted multiple and recent sexually transmitted diseases (STDs). They are more likely to be physically threatened by their partner when condom usage is requested and having the worry of contracting HIV (17).

Women who are pregnant may be more vulnerable to abuse. Simply being pregnant can exacerbate a domestic violence situation, causing physical trauma to escalate and even result in maternal death (18, 19). It was shown that 42 % of women victims experienced violence during the pregnancy and around 20 % of the victims have abuse for the first time while pregnant (20). Abuse in pregnancy is up to 11% in industrialized countries and up to 31.7% in developing countries (19). Abuse is reported to be recurrent during pregnancy, with 60% of abuse women reporting two or more episodes of assault during pregnancy (21).

Studies related to domestic violence and pregnancy found that women victims are more likely to report of having unwanted or unplanned pregnancy (19). These come from their inability to choose or practice contraceptive methods. Pregnant victims are also vulnerable to physical injuries during pregnancy and homicide. In United Kingdom and United States where maternal mortality is very low, domestic violence has been a noteworthy cause of maternal mortality (19).

The ill effects to the foetus come from direct effect of domestic violence such as spontaneous abortion, foetal injury and death of the mother. A lot of health complications correlated to abuse during pregnancy such as depression, substance abuse, smoking, anaemia, first and second trimester bleeding, less optimal weight gain and unhealthy eating patterns and reduction in birth weight. The ill effect on the foetus can also come indirectly from maternal stress, smoking, alcohol or drug use (19, 22). Abused women are also reported to have late prenatal care booking. Compared to non-abused women, abused women were twice as likely to begin prenatal care during the third trimester of their pregnancy (21).

Impact on children

Children of the victims also get affected from domestic violence. Children who witness violence between their parents are noted to have internalized behaviour such as anxiety and depression; externalized behaviour such as fighting, bullying, lying or cheating; being more disobedient at school and at home; have problems with social competence and more willing to use violence themselves (23). These children can be injured while attempting to intervene in a fight between their parents (24). Most of them have direct abuse on them and have subsequent intergenerational continuity of domestic violence (23, 25). It is estimated that in 30% to 60% of families with domestic violence is a factor, child abuse is also occurring (26).

Conclusion and Recommendations

DV causes a lot of health consequences in women and their children. While some may come to health facilities specifically for the management-related injuries, others may just appear for other reasons such as routine health check-up, ante-natal follow-up or subtle symptoms related to effect of abuse. It is crucial for health care providers not to overlook these cases. Failure to identify and manage their abusive background will lead them to continue being abused.

Many studies have highlighted the barriers to identify and manage these victims (27-29). However, most of them are from developed countries and none from Malaysia. The first author is currently conducting a study that examines the management of DV by the Malaysian general practitioners. Preliminary results show that lack of training caused low level of confidence in management of these cases by health care providers. Considering

the health consequences brought by DV, violence management should be integrated not only into undergraduate medical curriculum but also as a continuous medical education.

References

1. WHO. Violence: A Global Public Health Problem. World Health Organization 2002; 16-21.

2. Abdullah R. Raj-Hashim, Schmitt G, eds. Women's Aids Organization, Battered Women in Malaysia: Prevalence, Problems and Public Attitude,1995.

3. Norashikin M., *Keganasan rumahtangga terhadap wanita: Prevalen dan faktor-faktor yang mempengaruhinya di kalangan wanita di jabatan pesakit luar*. Malaysian Journal of Public Health Medicine 2002; 2(1): p. 58-64.

4. Ulrich YC, *et al*., Medical care utilization patterns in women with diagnosed domestic violence. Am J Prev Med 2003; 24(1): 9-15.

5. WHO, Violence by Intimate Partner. World Health Organization 2002; 89-121.

6. Tjaden P, Thoennes N., Extent, nature and consequences of intimate partner violence: Findings from the National Violence Against Women Survey. National Institute of Justice, Centres for Disease Control and Prevention, 2000.

7. Mouzos J. Homicidal Encounters: A Study of Homicide in Australia 1989-1999. Australian Institute of Criminology: Canberra 2000; 115.

8. Fischbach, R, Herbert B, Domestic violence and mental health: correlates and conundrums within and across cultures. Soc Sci Med 1997; 45(8): 1161-1176.

9. Stark E. and A. Flitcraft, Spouse Abuse, M. Rosenburg and M. Fenley, eds. In Violence in America: A Public Health Approach, New York: Oxford University Press 1991.

10. Kyriacou DN. et al., Risk factors for injury to women from domestic violence. N Engl J Med 1999; 341: 1892-8.

11. Golding, JM., Intimate Partner violence as a risk factor for mental disorders: A meta-analysis. J Fam Violence, 1999; 14(2): 99-132.

12. Pico-Alfonso MA. Psychological intimate partner violence: the major predictor of posttraumatic stress disorder in abused women. Neurosc Biobehavior Rev, 2005; 29: 181-193.

13. Coker AL. et al. Missed opportunities: Intimate partner violence in family practice settings. Prev Med 2002; 34(4): 445-454.

14. Campbell JC. Health consequences of intimate partner violence. Lancet 2002; 359(9314): 1331-1336.

15. Danielson K.K. et al., Comorbidity between abuse of an adult and DSM-III-R mental disorders: Evidence form an epidemiological *study*. Am J Psychiatry 1998; 155(1): 131-133.

16. Drossman DA, et al., Sexual and physical abuse and gasterointestinal illness: Review and recommendation. Ann Intern Med 1995; 123(10): 782-794.

17. Wingood GM, DR. J, Raj A, Adverse consequences of intimate partner abuse among women in non-urban domestic violence shelter. Am J Prev Med 2000; 19(4): 270-275.

18. Richardson J. et al., Identifying domestic violence: cross-sectional study in primary care. BMJ 2002; 324: 1-6.

19. Campbell J.C, Garcia-Moreno C, et al., Abuse during pregnancy in industrialized and developing countries. Violence Against Women 2004; 10(7): 770-789.

20. Australian Bureau of Statistic, Women's Safety Survey: Canberra. Australian Bureau of Statistic: Canberra 1996.

21. McFarlane J. et al., Assessing for abuse during pregnancy: severity and frequency of injuries and associated entry into prenatal care. JAMA 1992; 267(23): 3176-3178.

22. Coker AL. et al., Physical health consequences of physical and psychological intimate partner violence. Arch Fam Med 2000; 9(5): 451-457.

23. Stiles MM, Witnessing domestic violence: The effect on children. Am Fam Physician 2002; 66(11): 2052-2066.

24. Christian CW., et al., Paediatric injury resulting from family violence. Paediatrics 1997; 99(2): 81-84.

25. Kessler RC., et al., Patterns and mental health predictors of domestic violence in the United States: Results from the National Comorbidity Survey. Int J Law Psychiatry 2001; 24: 487-508.

26. Edleson JL., The overlap between child maltreatment and women battering. Violence Against Women 1999; 5(2): 134-154.

27. Sugg NK, Inui T, Primary care physician's response to domestic violence: Opening pandora's box. JAMA 1992; 267(23): 3157-3160.

28. McCauley J., et al., Inside 'Pandora's Box': Abuse women's experiences with clinicians and health services JGIM, 1998; 13(8): 549-555.

29. Hegarty KL, Taft AT, Overcoming the barriers to disclosure and inquiry of partner abuse for women attending general practice. Australian New Zealand Public Health 2001; 25: 433-437.

FROM ASPIRIN TO ANTIBODIES : DEVELOPMENTS IN THE MANAGEMENT OF RHEUMATIC DISORDERS

Irani MS
Ashford and St Peter's Hospitals, England

Introduction

. . . and in the beginning there was taxonomy. The accurate diagnosis of rheumatic disorders was paramount in subsequent development of appropriate treatments. Originally, taxonomy hinged on what evidence there was that a particular rheumatic disorder fell within a particular group of illness. However, much doubt was cast upon new developments although it should be remembered that 'the half life of medical knowledge is a scant five years' (King, 1982). Although this is the case 'all good things which exist are the fruits of originality' (John Stewart Mill 1806-1873). This conflicted with Alphonse Karr's (1849) statement that '*plus ça change, plus c'est la même chose*'. Therefore, there was adequate confusion which was prevalent.

Classification of disease

Both ancient and modern classification can be put as both historic descriptions such as Chronic Arthritis which was either 'atrophic', in other words, inflammatory or 'hypertrophic' degenerative such as osteoarthritis with formation of Heberden's and Bouchard's nodes.

Subsequently, anatomic descriptions on clinical and pathological grounds were developed.

The term rheumatism (reuma 'Gk. 'stream/flow') was coined by Galen in the C2nd BC. The idea of humour which flowed around the body affecting various joints was considered to be the case.

The term synovium was coined by the Swiss Paracelsus in the C16th AD. Syn- (Gk for 'with'). Ovum (Latin 'egg") described the appearance of synovial fluid. Fortunately, this was not a particularly robust classification of the various arthropathies.

Diagnosis

Subsequently, improvements in diagnostic tools with imaging, tests for assessing the inflammatory process, immunology and, latterly, molecular biology have made diagnosis more accurate. These developments would not have been possible without parallel improvements in technology.

Imaging with x-rays (Roentgen 1895, scintigraphy (McCarty 1970), ultrasound in 1990, computerised tomography (Hounsfield and Cormack 1972) and magnetic resonance imaging (Lauterbur, Damadian and Mansfield 1970s) and most recently, SPECT have improved imaging techniques for identifying the various arthropathies and appearances of joints.

Improvements in laboratory techniques with reagents such as sera for identifying rheumatoid factor and HLA groups has further refined diagnosis.

Laboratory techniques such as DNA amplification with 'blots', phage injection, cell fusion and chimera formations have helped not only in diagnosis but also in developments in treatment.

Therapy

The translation of technology to therapy has been a major step in the development of biological therapies for treatment of rheumatic disorders.

With advances in therapy, research in evidence based medicine has been vital. Clinical trials using age, sex and race matched controls, double blinded, randomised with placebo using large samples and when not available employing meta-analysis techniques with robust statistical methods have confirmed the efficacy of

modern therapies. However, with new knowledge, come problems. Publication bias of clinical studies has to be avoided and vetting ethics of clinical trials has to be borne in mind at all times. Currently, tumour necrosis factor inhibitors are being developed but it must be borne in mind that on their own, they are not as effective as when used when tried and tested agents such as methotrexate.

With pharmacological developments has come improvements in surgical techniques with arthroscopic and joint replacement as well as knowledge in rehabilitation.

Conclusion

The transition from purely anecdotal and empirical descriptive terms through to modern scientific technological advances can be summarised by Thomas Saenz's statement:

'When religion was strong and medicine was weak, man looked to God for magic. Now that medicine is strong and religion weak, man looks to medicine for magic.'

Undoubtedly, further developments will continue to come on line with modification of existing knowledge and in the hundred years of the University of Malaya's existence, many changes have happened and in the years to come the University of Malaya will see many more and be part of the developments easing the suffering from musculoskeletal disorders.

THE AGEING PATIENT : HOW TO MANAGE THE INEVITABLE?

Irani MS
Ashford and St Peter's Hospitals, England

Introduction

The only thing that we can be sure of when we are born is that we are going to die. On this happy note we can point out that morbidity among persons aged 65 and over shows that arthritis is the most significant factor. It far exceeds hypertension, cardiac conditions or orthopaedic impairment. The relative frequency of musculoskeletal disease in young and old age reconfirms this fact by showing that there is Still's disease, ankylosing spondylitis, Reiter's disease, rheumatic fever and idiopathic systemic lupus erythematosus is more prevalent in youth (2-25 years). Deficiencies in bone mineralization, polymyalgia rheumatica and giant cell arteritis and of course degenerative joint disease.

With ageing comes white hair, wrinkles and wisdom. However, the most frequent symptoms in elderly patients are from musculoskeletal disorders. As there is a wide range of conditions that may account for these symptoms, diagnosis is complicated particularly by the presence of other diseases.

In contrast to children's disease, diseases affecting elderly patients manifest themselves in different ways to that of patients in their middle years. Although prevention of disease is an ideal, the ultimate aim is preservation of functional capacity and independence. As there are differences in metabolism in an aged population, pharmacological intervention must be kept to a minimum and more reliance should be placed on physical medicine and rehabilitation, if prevention has failed.

With development of safer anaesthetic techniques, more adventurous surgery is now possible, however quality of life must always be borne in mind rather than mere prolongation of existence.

Taking a broader view, the spiritual beliefs and personal ethics of an individual and their relatives have to be borne in mind when treating those patients who have had many life experiences.

With an aging population and reduction of new live births, government departments are all too conscious of the fact that fit and able elderly would be looking after each other as there may not be many young able carers in years to come!

The physician's role in the rehabilitation of older adult patients

The goal of physical therapy is to maximise safe and independent mobility. The objectives being to build strength and endurance particularly lower extremity joint range of motion and function, thereby improving balance and coordination. This, in turn, increases the ability to transfer and walk.

These objectives are achieved by improving safety awareness and managing orthotic/prothetic and assistive devices. Selection of appropriate wheelchair seating is also essential.

The modalities that are available are superficial heat or cold, deep heat, electrical stimulation and massage to reduce pain and spasm and promote stretching. Hydrotherapy for wound care also assists.

What about the home environment?

Modifications to improve safety yet enabling barrier free access ability should be borne in mind.

The role of occupational therapy

The goal is to maximise safe and independent self care. The objectives are achieved by building upper extremity strength and improving fine motor skills, coordination and dexterity by increasing upper extremity joint range of motion and maximising visual-perceptual and cognitive skills. Optimising home and financial management and promoting safety awareness are to be integrated into the rehabilitation process.

And how are these objectives achieved?

Techniques available are those which encourage clothing and foot wear modification for ease of use. The use of appropriate assistive and adaptive equipment to compensate for self-care deficits such as built-up handles, long-handled reacher, etc. Designing and managing upper extremity orthotics to stabilise and protect painful or weak joints or to facilitate holding and using utensils should also be focused on. Energy conservation techniques for efficient self-care and ambulation should not be overlooked.

The home environment

Modifications have to be implemented so as to improve self-care (ADLs and IADLs).

Communication

Speech and language problems should be tackled by having objectives to improve neurological communication deficit and evaluating swallowing and training for dysphagia. Speech training following laryngectomy and training of the family to communicate is vital.

The problems to be targeted should be: dysphagia, dyspraxia, dysarthria and aphasia. The means by which this is achieved is by the incorporation of a speech therapy in a multidisciplinary therapy group and the use of augmentative communication devices.

The use of recreational therapy

Recreational therapy is employed to develop and enhance leisure activity skills by developing structured leisure time planning, which fosters socialisation skills. This is best achieved by group and individual activities.

Return to work

Vocational therapy explores alternatives to maximise the vocational potential for the older worker. Evaluating a worker's barrier to continue their current job and skills whilst remembering attitudes, functional capacities and matching this profile to the job requirements, physical and other demands is essential.

But, what are the options to returning to work?

Either the patient returns to their previous job or starts transitional work. Alternative jobs and retraining or ultimately retirement must be considered too.

The Multidisciplinary Therapy Team

Besides the physician, physiotherapist, occupational therapist, speech therapist, medical social work input, psychologist nurse and physician's assistant must not be overlooked.

Such individuals, together with problem orientated programmes, are to be considered.

Phases of rehabilitation

Rehabilitation has to be considered in tandem with the available facilities for acute, post acute and maintenance therapy. The medical issues for rehabilitation patient are control of pain, thromboembolic phenomenon, urinary retention or incontinence, constipation, orthostatic hypotension and cardiovascular deconditioning.

Conclusion

As dismal as growing old may seem, catastrophic events occurring early in life can incapacitate an individual to a degree of dependence which otherwise might occur in fullness of time. It is vital to remember that no one group of therapists can rehabilitate and that it is a multidisciplinary approach that has to be adopted with phases of utilisation of skills of various individuals within that therapy group.

Medical educators particularly at undergraduate level should focus on how to make rehabilitation an exciting and essential part of management of patients in any discipline whether it be cardiology, neurology or orthopaedics. It is a challenge that one has to embrace and develop through one's postgraduate and practising professional clinical life.

Although one cannot avoid the inevitable, we may optimise the journey there.

THE BURDEN OF DEPRESSION IN THE ASIA-PACIFIC REGION

Ng CH
Department of Psychiatry, University of Melbourne, St Vincent's Mental Health Service and The Melbourne Clinic, Australia

Introduction

Mental disorders represent five of the ten leading causes of global burden of disease, accounting for 12% of all disability in the world. The prevalence of depression in Western populations is up to 10% whereas lifetime risk is up to 26% in females and 12% in males. Chronicity of illness is common with about 50 to 85% recurrence rate and 20 to 35% having persistent symptoms. By the year 2020, WHO projects that depression will be the second leading cause of disease burden worldwide (1). Due to cultural differences influence diagnosis prevalence rates of depression in Asia may not be directly comparable. Surveys conducted in Asia indicate approximately 5% of population have depressive disorder and up to 15% suffer from depressive symptoms (2). Epidemiological studies on depression in this region remain lacking despite being much needed. In Australia, the 12 months prevalence of depressive disorders in adults was 5.8%, being higher in females (7.4%) than males (4.2%) (3).

Main messages

Although depressive disorders are a growing public health problem in the Asia-Pacific region, they have generally received low priority in health funding and policy. Clinical depression are mostly unrecognised and untreated. Consequently the socio-economic burden of depression is significant in terms of suffering, disability and financial loss. Direct health costs consist of medications, GP and specialist consultations, public and private hospital admissions, community and ambulatory services. Indirect costs are less obvious and may include unemployment, absenteeism, loss of productivity and distress on marital, parental and social roles and relationships. Both the direct and indirect economic costs due to depression are substantially high. Tragically, it is also associated with a suicide rate of about 10% and the majority of those who committed suicide suffered from major depression. In 2000, WHO estimated about 815,000 suicides occurring worldwide and the rate of suicide attempts is up to 20-fold higher. However, official suicide data tends to under estimate true suicide rates.

A way of estimating the socioeconomic costs of depression is using disability adjusted life years (DALYs), years of life lost (YLL) and years lived with disability (YLD). These measures supplement the monetary value of morbidity and mortality of illnesses. For China WHO in 2000 estimated that for depression 14.2 million DALYs (9 million for female; 5.2 million for male), whereas for Asia-Pacfic a total of 22.7 million DALYs. Due to suicide cases, China had 2.6 million YLL and Asia Pacific had 5 million YLL. Despite few epidemiology and service use studies, cost of depression in Asia is therefore likely to be very high. Nevertheless, the medical fee schedule (ranging from $1-$16 for outpatients; $17-$40/day for inpatients) is relatively affordable for general population. Most health care systems and insurance coverage in Asia-Pacific, however, follow medical care scheme and have no special provisions to reimburse treatment for depression (4). To avoid major costs burden, policy makers need to increase public awareness to seek early treatment, improve affordability of treatment and invest in appropriate mental health services.

Obstacles to identifying and treating depression include lack of public awareness, persistent stigma of mental illness, poor access to care, inadequate protection of social rights, and insufficient financial and human resources. Guidelines for the diagnosis and treatment of depression in Asia need to include both pharmacological and psychological approaches, and take into account local cultural factors and practices. Future development of appropriate mental health services and healthcare system as well as community-based treatments are necessary. Efforts to remove barriers to early identification and intervention would include raising awareness that depression is common and treatable, improving referral pathways, optimising screening methods, promoting best clinical practice, working with traditional health systems and training in relapse prevention.

'Beyondblue' is a national depression initiative established by federal and states of Australia to increase community awareness of depression and anxiety (5).

Its successes have been based on a coordinated national depression strategy, investment in primary care education programs, population-based prevention, early intervention and reform in mental health services and insurance schemes. Participation by key political, media and community leaders to raise profile and partnerships between health and education, business and community areas are also other key strategies.

Conclusion

Depression is prevalent worldwide and is associated with significant burden in terms of disability and socio-economic loss for countries and communities. In spite of this, it remains largely under-recognised and under-treated. There is an urgent need to increase public awareness to present for medical and psychological assessment. Continue training and support for GPs/ primary care clinicians to improve provision of effective treatments are necessary to ensure quality care. Health care reimbursement policies and mental health services need to ensure that the treatment of depression is relatively affordable and accessible to the vast majority of the population.

References

1. Murray CJL, Lopez AD. The global burden of disease: A comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020. Cambridge: Harvard University Press, 1996.

2. Chiu E. Epidemiology of depression in the Asia-Pacific region. Australasian Psychiat 2004; 12: S4-S10.

3. Henderson S, Andrews G, Hall W. Australia's mental health: an overview of the general population survey. Australia and New Zealand Psychiat 2000; 34: 197-205.

4. Hu TW. The economic burden of depression and reimbursement policy in the Asia Pacific region. Australasian Psychiat 2004; 12: S11-S15.

5. Hickie I. Can we reduce the burden of depression? The Australian experience with beyondblue: the national depression initiative. Australasian Psychiat 2004; 12: S38-S46.

OBSTRUCTIVE SLEEP APNOEA AND CARDIOVASCULAR COMPLICATIONS

David Hui SC
Division of Respiratory Medicine, Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

Introduction

Obstructive sleep apnoea syndrome (OSAS) is a common form of sleep disordered breathing (SDB) characterized by repetitive episodes of partial or complete upper airway obstruction causing sleep fragmentation and symptoms (1). It is equally common among the middle-aged male Caucasian and Asian populations with a prevalence of at least 4% (2, 3). OSAS may cause disabling daytime sleepiness, impaired cognitive function, poor quality of life, and increases the risk of road traffic accidents (1). Sleep-induced loss of upper airway muscle tone and obesity are the major factors in the pathogenesis of OSAS. However, craniofacial abnormality may play an important role especially in the Asian populations. While Asian patients with OSAS are generally less obese than the Caucasian counterparts, craniofacial abnormalities such as a low hyoid bone and retro-position of the maxilla or mandible are common predisposing factors in the Asian populations (4, 5). Other predisposing factors in the pathogenesis of OSAS in adults include inappropriate use of benzodiazepine or alcohol (further reduction in muscle tone), endocrine causes such as hypothyroidism (macroglossia, mucopolysaccharide deposits in upper airway, myopathy, neuropathy) and acromegaly (macroglossia, central sleep apnoea), smoking (airway inflammation), and enlarged tonsils and adenoids (mechanical obstruction) in paediatric cases (6).

Evidence and possible mechanisms

In recent years, there are growing data linking SDB to cardiovascular complications. Several epidemiological studies have shown an independent association between SDB and hypertension after controlling for confounding factors such as age, body mass index (BMI), sex, alcohol and smoking (7-9). Patients with OSAS have increased ambulatory diastolic blood pressure (BP) both day and night and increased systolic BP at night compared to controls matched for age and BMI (10). The US Sleep Heart Health Study cohort has shown the effects of SDB on various manifestations of cardiovascular diseases, and relatively SDB was more strongly associated with reported stroke and heart failure than with coronary artery disease (11). A recent observational study has shown that from midnight to 6 a.m., sudden death from cardiac causes occurred in 46% of people with OSAS, as compared with 21% of people without OSAS (P=0.01), 16% of the general population (P<0.001), and the 25% expected by chance (P<0.001) (12). For people with OSAS, the relative risk of sudden death from cardiac causes from midnight to 6 a.m. was 2.57 (95% CI, 1.87 to 3.52) compared to those without OSAS.12 A 7-year longitudinal study of otherwise healthy patients with OSAS has shown a higher incidence (56.8%) of at least one cardiovascular complication in patients incompletely treated than those effectively treated, who have a low incidence (6.7%) similar to the normal controls (13). Another prospective study of over 10 years has shown that untreated severe OSA increased the risk of fatal (OR 2.87, 95%CI 1.17-7.51) and non-fatal cardiovascular events (OR 3.17, 95%CI 1.12-7.51) compared with healthy controls (14).

Cerebrovascular disease is an important cause of morbidity and mortality worldwide. Several studies have reported a high prevalence of SDB predominantly of obstructive nature in patients following stroke in the acute phase and rehabilitation phase (15, 16). A case-controlled study in Hong Kong has shown a high prevalence of OSA in Chinese patients admitted with acute ischaemic stroke (49% vs 24% in a control group) (17). Two recent studies in Europe have shown that patients with both OSA and stroke have lower survival rates than those with stroke alone (18, 19). Atherosclerosis of the carotid arteries is an important cause of ischaemic stroke. In recent years, carotid artery intima-media thickness (IMT), measured by B-mode ultrasound, has been shown to correlate with traditional vascular risk factors and may predict the likelihood of acute coronary events and stroke (20). In a study of 167 Japanese patients referred for the screening of OSAS, it showed that the severity of OSA is independently related to the carotid artery IMT, and the severity of OSA-induced hypoxaemia is more important than the frequency of obstructive events (21). The findings have been corroborated by similar findings of a case-controlled study in Germany (22).

In addition to hypertension, other mechanisms for the association between SDB and cardiovascular complications are not fully understood but there is strong evidence indicating a role for the sympathetic nervous system in the pathophysiological process. OSA-related arousals are closely linked to increases in sympathetic activity. A case-controlled study recently conducted in HK has shown that OSAS, through repeated episodes of arousals, may lead to platelet activation. Platelet activation is an important step in the pathogenesis of ischaemic stroke but its activity can be reduced by nasal continuous positive airway pressure (CPAP) treatment (23). Multiple, potentially intertwined mechanisms are proposed to link OSA with chronic cardiovascular diseases, and these include tonic elevation of sympathetic neural activity, vascular endothelial dysfunction, oxidative stress, inflammation, and metabolic dysregulation (24). In addition to cascades of increased vasoactive peptides and proinflammatory factors, repetitive surges of sympathetic activity may directly promote endothelial/vascular injury and enhanced coagulability. Platelet aggregability and increases in haematocrit, fibrinogen levels, and blood viscosity may also predispose to clot formation and atherosclerosis in patients with OSAS (24).

Treatment

Nasal CPAP is the most effective treatment for OSAS with robust evidence in support of its efficacy in improving symptoms, cognitive function, and quality of life (1). Several randomized placebo-controlled studies have shown that nasal CPAP can reduce day and night BP in patients with OSAS (25, 26). It was shown that a 3.3 mmHg reduction in a 24-hour mean systemic BP among sleepy patients with OSAS in the therapeutic versus the sub-therapeutic CPAP arm, and the beneficial effect of CPAP on BP was seen mostly in those with more severe OSAS (25). More recently, it was noted that patients with severe OSAS in the active CPAP treatment arm achieved a reduction in mean systemic BP of 9.9 mmHg over a period of nine weeks (26). This magnitude of reduction in mean BP with nasal CPAP is predicted to reduce coronary heart disease event risk and stroke risk by 37% and 56% respectively (26). Other favourable effects of CPAP include reduction of sympathetic activity and hypoxic/oxidative stress (27, 28), with improvement of vasodilator response and endothelial function (29).

In patients who are not able to tolerate nasal CPAP, dental appliance in the form of mandibular advancement device can improve symptoms (30), and reduce mean 24-hour diastolic BP by 1.8 mmHg after four weeks of treatment (31).

Conclusion and Recommendation

These data have important therapeutic implications, and compliance with nasal CPAP or dental device may reduce the risk of cardiovascular complications associated with OSAS.

References

1. Engleman HM, Douglas NJ. Sleepiness, cognitive function, and quality of life in obstructive sleep apnoea/hypopnoea syndrome. Thorax 2004; 59:618-622.

2. Ip MS, Lam B, Lauder IJ, et al. A community study of sleep-disordered breathing in middle-aged Chinese men in Hong Kong. Chest 2001; 119:62-69.

3. Hui DS, Chan JK, et al. Prevalence of snoring and sleep-disordered breathing in a group of commercial bus drivers in Hong Kong. Intern Med J 2002; 32:149-157.

4. Hui DS, Ko FW, et al. Cephalometric assessment of craniofacial morphology in Chinese patients with obstructive sleep apnoea. Respir Med 2003; 97:640-646.

5. Lam B, Ooi CG, Peh WC, et al. Computed tomographic evaluation of the role of craniofacial and upper airway morphology in obstructive sleep apnoea in Chinese. Respir Med. 2004; 98:301-307.

6. Hui DS, Choy DK, Ko FW, et al. Obstructive sleep apnoea syndrome: treatment update. HK Med J 2000; 6:209-217.

7. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea as a risk factor for hypertension: population study. Br Med J 2000; 320:479-482.

8. Nieto FJ, Young TB, Lind BK, et al. Association of Sleep-disordered breathing, sleep apnoea and hypertension in a large community-based study. JAMA 2000; 283:1829-1836.

9. Peppard P, Young TB, Palta M, et al. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000; 342:1378-1384.

10. Davies CW, Crosby JH, Mullins RL, et al. Case-control study of 24-hour ambulatory blood pressure in patients with obstructive sleep apnoea and normal matched control subjects. Thorax 2000; 55:736-740.

11. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001; 163:19-25.

12. Gami AS, Howard DE, Olson EJ, et al. Day-night pattern of sudden death in obstructive sleep apnoea. N Engl J Med 2005; 352:1206-1214.

13. Peker Y, Hedner J, Norum J, et al. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnoea: a 7-year follow-up. Am J Respir Crit Care Med 2002; 166:159-165.

14. Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005; 365:1046-1053.

15. Wessendorf T, Teschler H, Wang YM, et al. Sleep-disordered breathing among patients with first-ever stroke. J Neurol 2000; 247:41-47.

16. Parra O, Arboix A, Bechich S, et al. Time course of sleep-related breathing disorders in first-ever stroke or transient ischemic attack. Am J Respir Crit Care Med 2000; 161:375-380.

17. Hui DS, Choy DK, Wong KS, et al. Prevalence of sleep-disordered breathing and continuous positive airway pressure compliance. Results in a group of Chinese patients post first-ever ischemic stroke. Chest 2002; 122:852-860.

18. Turkington PM, Allgar V, Bamford J, et al. Effect of upper airway obstruction in acute stroke on functional outcome at 6 months. Thorax 2004; 59:367-371.

19. Parra O, Arboix A, Montserrat JM, et al. Sleep-related breathing disorders: impact on mortality of cerebrovascular disease. Eur Respir J 2004; 24:267-272.

20. O'leary DH, Polak JF, Kronmai RA, et al. Carotid artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. N Engl J Med 1999; 340:14-22.

21. Suzuki T, Nakano H, Maekawa J, et al. obstructive sleep apnoea and carotid artery intima-media thickness. Sleep 2004; 27:129-133.

22. Schulz R, Seeger W, Fegbeutel C, et al. Changes in extracranial arteries in obstructive sleep apnoea. Eur Respir J 2005; 25:69-74.

23. Hui DS, Ko FW, Fok JP, et al. The effects of nasal continuous positive airway pressure on platelet activation in obstructive sleep apnoea. Chest 2004; 125:1768-1775.

24. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnoea- Implications for cardiac and vascular disease. JAMA 2003; 290:1906-1914.

25. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and sub-therapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomized prospective parallel trial. Lancet 2002; 359:204-210.

26. Becker HF, Jerrentrup A, Ploch T, et al. Effect of nasal continuous positive airway pressure on blood pressure in patients with obstructive sleep apnoea. Circulation 2003; 107:68-73.

27. Ohga E, Tomita T, Wada H, et al. Effects of obstructive sleep apnoea on circulating ICAM-1, IL-8, and MCP-1. J Appl Physiol 2003; 94:179-184.

28. Yokoe T, Monoguchi K, Matsuo H, et al. Elevated levels of C-reactive protein and IL-6 in patients with OSAS are decreased by nasal continuous positive airway pressure. Circulation 2003; 107: 1129-1134.

29. Ip MS, Tse HF, Lam B, et al. Endothelial function in obstructive sleep apnoea and response to treatment. Am J Respir Crit Care Med 2004; 169:348-353.

30. Gotsopoulos H, Chen C, Qian J, et al. Oral appliance therapy improves symptoms in obstructive sleep apnoea: a randomized, controlled trial. Am J Respir Crit Care Med 2002; 166:743-748.

31. Gotsopoulos H, Kelly JJ, Cistulli PA. Oral appliance therapy reduces blood pressure in obstructive sleep apnoea: a randomized, controlled trial. Sleep 2004; 27: 934-941.

PET RADIOPHARMACEUTICAL PRODUCTION: DESIGN AND REQUIREMENTS OF THE FACILITY

Peter Eu
Department of Nuclear Medicine and PET Centre, Peter MacCallum Cancer Centre, East Melbourne, Australia.

The requirements for the production of a radiopharmaceutical include having sufficient quantities of the radionuclide of interest in a pure and suitable chemical form, highly pure chemical starting materials, suitable remote synthesis methods, along with good product clean up and quality assurance methods to ensure suitability for clinical use. Production should be in an environment compliant with local safety and regulatory affairs for both pharmaceutical production and radiation safety. The developmental work involved in bringing F-18 Fluoro-deoxy glucose, 18FDG, to its present production form highlights some of the complexity associated with producing positron emission tomography, PET, radiopharmaceuticals.

During the early days of our PET Centre, 18FDG was initially sourced from a neighbouring hospital that produced this radiopharmaceutical. An 18FDG radiochemistry synthesis unit was later installed in our centre and the in-house production of 18FDG was initiated with fluorine-18 sourced from the National Medical Cyclotron facility in Sydney. With the increase in 18FDG PET scans, it became apparent that to be able to meet this workload, a self-reliant system of producing 18FDG was required. A cyclotron was installed to meet this need.

A PET radiopharmaceutical production facility's design and requirements would depend upon the level of manufacture intended. At our facility, we have a 12 MeV superconducting cyclotron that only allows the production of a proton beam to a maximum current of 80 uA thereby limiting us to proton only nuclear reactions. The radionuclides of which we have targets for suited to this reaction include Carbon-11, Fluorine-18, Yttrium-86 and Iodine-124 of which Carbon 11 is a gas target, Fluorine-18 is an aqueous target while Iodine-124 and Yttrium-86 are solid targets. Carbon-11 is not utilised in our facility, as we currently do not have the equipment to handle this gaseous radioisotope or its chemistry.

While there are many ways in which Fluorine-18 can be produced, our facility is limited to the (p,n) reaction. This reaction is now the most commonly accepted method for producing F-18. The starting material, 18O-H2O, to this nuclear reaction has to be highly enriched in O-18 atoms, preferably greater than 95 %. This water should also be highly pure, chemically, with minimal contaminants, organic or otherwise. Low O-18 enriched water may result in unwanted radionuclides produced such as Nitrogen-15 that may result in unwanted radiation emissions as well as potentially lower yields in the chemistry synthesis. The use of impure water in the production of F-18 may damage the target body during irradiation resulting in unnecessary down time and possibly expensive repairs. Contaminants in the F-18 water will also give very low, if any, chemical reaction yields in these sensitive fluorination chemistry reactions. It is now common practice to receive a certificate of analysis with every batch of O-18 water from the supplier as well as perform occasional analysis of the water to ascertain its quality.

In 1990, there were several hundred F-18 radiopharmaceuticals recorded where the F-18 atom was either substituted for a hydroxy group or placed in a position where its presence does not significantly alter the biological behaviour of the molecule. There is usually more than one way to fluorinate a compound as evidenced by the production of 18FDG where there are more than half a dozen published methods. Most of these methods to a facility would be limited to the physical type of F-18 produced, gas or liquid, type of chemistry synthesis and hence the available starting precursors, radiochemistry synthesis module available and purification methods employed.

In our facility, we produce the following F-18 radiopharmaceuticals including, sodium (18F) fluoride, 2-deoxy-2-(18F)-fluoro-D-glucose (FDG), (18F)Fluorothymidine (FLT), (18F)Fluoroazomycin arabinoside (FAZA), (18F)Fluoroethyltyrosine (FET), and (18F)Fluoroethylcholine (FCH) for clinical use. We have three different types of radiochemistry modules that can be and are modified to suit the production purpose to give the best optimal yields with minimal impurity. These are all housed in lead shielded hot cells which bathe the modules in Class A air under negative pressures to protect the pharmaceutical product while

protecting the environment from potential radiation hazards. These are located within our clean room that has a terminal HEPA air filtration system under positive pressure with the appropriate air changes that should satisfy the local authorities for the manufacture of pharmaceuticals while the ante room is under negative pressure to satisfy the local radiation safety authority. Quality assurance studies are performed on each production to look for the radiochemical purity of the product as well as for the absence of any other materials, which may be untoward in a patient.

The other radionuclides produced in our facility are Iodine-124 and Yttrium-86. These are made using solid target technology. While the production of these can be rather straightforward with the right equipment and starting material, the recovery of the radionuclide produced in the proper chemical form with high radionuclidic purity can be challenging.

Yttrium-86 is produced here using greater than 95% enriched Stontium-86 carbonate as the starting target material. Recovery of Yttrium-86 as the chloride salt form from the target starting material is made possible by utilising the electrochemical differences of strontium and yttrium followed by dissolving the isolated Yttrium-86 in hydrochloric acid. Yttrium-86 will be used to label proteins as well as being a PET substitute radionuclide for Indium-111 to enable Indium-111 labelled single photon emission tomography (SPET) type radiopharmaceuticals to be imaged with PET technology.

Iodine-124 is produced from the proton bombardment of the target starting material, enriched Tellurium-124 oxide, in our cyclotron and recovered as the sodium salt. Recovery the radionuclide from the target is performed by utilising the difference in volatility of iodine and tellurium. The Iodine-124 will be used to replace some of the SPET Iodine-123 in the labelling of radioiodinated pharmaceuticals.

A radiopharmacy facility would require a source of radioactivity whether the product is brought in as a ready made radiopharmaceutical, as the raw radionuclide obtained from an external supplier, or from an in-house production source such as a particle accelerator or generator system if available. To manufacture the radiopharmaceutical it would require the appropriate chemistry synthesis and remote modules as well as the appropriate product clean up methods and equipment. The proper quality assurance program should also be in place. All these have to be performed in accordance with the requirements of the local authorities especially, Good Manufacturing Practice for medicinal products and radiation safety procedures. The productions of a radiopharmaceutical, especially for research, from basic starting materials do require a few disciplines of science and pharmacy before it can be considered for clinical use. The success to a functional Radiopharmaceutical Production facility lies mainly in having the appropriate personnel available.

THE PURSUIT OF AN IDEAL IMAGING PROTOCOL IN PET AND PET-CT : THE HONG KONG EXPERIENCE

Kevin Tse KM
Nuclear Medicine Department, St.Teresa's Hospital, Hong Kong.

Introduction

The PET centre at St.Teresa's hospital was established in early 2000 when we purchased the ADAC C-PET scanner and a GE. Minitrace cyclotron. We have upgraded our PET scanner to a Philips Gemini PET-CT in June 2004. We have performed over 6000 clinical cases during this period and would like to share our experience with the audience.

What is the ideal imaging protocol in PET-CT? This is not a simple question to answer. PET-CT is a relatively new imaging modality that combines both functional and anatomical information. In most advanced countries, this technique is conducted mainly by nuclear radiologists with vast clinical experience on PET imaging. On the other hand, many of the newly established PET centers are run by general radiologists who are specialized in conventional anatomical imaging such as CT and MRI. Different groups of radiologists may have different opinions on the protocol. Some people put more emphasis on the functional aspect whereas some people do CT guided PET. Well, is there an ideal PET-CT protocol for us?

Findings

We have experience with the older generation PET scanner and the new PET-CT machine equipped with new crystal detectors. There is no doubt that the newer crystals such as GSO or LSO outperform the older crystals such as NaI and BGO. The images in my talk clearly confirm this statement. PET was once considered an almost perfect imaging modality in oncology. This was a true statement few years ago, and was supported by many research and clinical data. PET scan has shown superior accuracy when compared with CT or MRI in many tumours. The problem is that there is no detail anatomical information in the PET images. This is probably not a major problem in some cancers such as lymphoma. Nevertheless, without the detail anatomical information, interpretation of PET scan is difficult in many situations. For example, physiological uptake in brown fat had been misinterpreted as lymph node involvement prior the PET-CT era. If you want to establish a new PET centre, there is no point to purchase a PET only scanner. PET-CT is the only option.

Before we can improve an imaging technique, we should know some of its limitations. In PET-CT, we may encounter problems related to motion, misregistration between PET and CT, false positive reading due to inflammation and limitation in spatial resolution.

Patient preparations are critical for achieving the best imaging result in PET-CT. All patients should fast for at least 6 hours. Good hydration is necessary during the uptake phase. In some patients, we give intravenous fluid supplement. The control of blood glucose is very important. Intravenous insulin could be administered to bring down the blood glucose level before administration of FDG. The patient should avoid exercise before the examination. We should keep the patient warm and relax during the uptake phase to avoid unnecessary uptake in the muscles and brown fat. The use of valium is controversial. We have not find any significant advantage of using valium during the uptake phase after the introduction of PET-CT, as we can clearly identify the muscles in the head and neck regions to avoid false reading. Use of duspatalin is a routine in all our patients. This is an antispasmodic with a direct action on the smooth muscles of the G.I. tract, relieving spasm without affecting normal gut motility. With the usage of this drug, we can reduce false reading result from G.I. tract excretion.

Motion-related artifacts could be due to respiration, heart movement, bowel movement, bladder filling or patient movement during acquisition. This will result in misregistration between the PET and CT scan images. Shallow free breathing gives us the best result for image registration. Many of the elderly patients could not cooperate with the end expiratory method or any breath holding methods. When there is a significant discrepancy of the level of diaphragm between the PET and CT images, we would perform a delayed regional scan of the thorax using Cs rod source as the method for attenuation correction. Gating of the respiratory and cardiac cycles is probably not easy and could be

extremely tedious. Some centres are doing research on respiratory gating. Nevertheless, there is no commercially available software in the market up to date. During the examination, proper patient positioning is important. We should use appropriate support and immobilization band to decrease patient movement. Arm up position is always recommended if possible. Potential artifacts could be seen when we image the patient with arms down.

Intense urine activity may result in streak artifacts in the adjacent regions. Adequate hydration is important to decrease the concentration of radioactivity in the urine. In general, urine with low radioactivity would not cause any problem. The use of lasix, bladder catheter, bladder irrigation and delayed imaging are useful techniques in special circumstances. New software technique such as the 3D RAMLA can reduce the artifacts related to urine with high radioactivity.

Most of the PET-CT scan use CT as the attenuation correction method. This is a useful, fast and cost effective technique. Our machine is also equipped with the Caesium rod source. This has an added advantage in some situations; for example, presence of metallic implants or pacemaker, presence of high concentration IV and oral CT contrast, or significant misregistration of diaphragm.

The use of IV and oral CT contrast will definitely improve the diagnostic accuracy of PET-CT scan. We find that the presence of low concentration CT contrast will not significantly affect the PET images and SUV measurements. The presence of high concentration CT IV or oral contrast could result in false positive "hot spot" on the final reconstructed PET scan. For better assessment of G.I. tract, we may use water as a negative G.I. contrast. IV contrast is recommended for most of the head and neck tumors, liver tumors and pre-operative lung cancers cases.

Delayed imaging is important and can enhance the diagnostic sensitivity of PET-CT scan. The nuclear radiologist should check all the scans before discharging the patients. When in doubt, delayed scanning is conducted. Small or subtle lesions with low uptake could be better visualized on delayed scanning due to improve contrast. We can also differentiate false reading resulted from urine and G.I. tract excretion from genuine pathology on the delayed images.

The interpretation of non-attenuated PET images is important for those who use CT for attenuation correction. This is especially true in the presence of high concentration CT contrast or radiodense materials such as metallic implants or pacemaker. Some people believe that the non-attenuated PET images will help to detect small superficial lesion.

Conclusion

PET-CT is the most exciting imaging modality in the world of imaging. As we accumulate more and more experience, we understand this technique better. The pursuit for an ideal imaging protocol will never cease.

A MEDICAL MANAGEMENT OF INTERSTITIAL ECTOPIC PREGNANCY: A 5-YEAR CLINICAL STUDY

Tang A, Baartz D, Khoo SK
Royal Brisbane and Women's Hospital, and University of Queensland, Brisbane, Australia

Introduction

An ectopic pregnancy in the interstitial portion of the fallopian tube is rare, occurring in 2% to 3% of all ectopic pregnancies. Because of its location, such a pregnancy poses a challenge in diagnosis and management. Transvaginal ultrasound is now able to delineate the gestation sac. The available treatment options include resection by laparotomy or laparoscopy, or methotrexate by direct injection into the gestation sac or systemic use. Limited evidence on intramuscular use of methotrexate showed variable success. For this reason, we report a 5-year audit (2000-2004) of 11 consecutive interstitial pregnancies in a series of 346 ectopic pregnancies.

Findings

Of the 11 cases, two required urgent surgery for rupture on presentation. In the remaining nine cases, IV methotrexate (300mg) was used, with oral folinic acid rescue (15 mg x 4 doses). There were no side-effects. Our criteria for treatment included a stable clinical condition, no ultrasound evidence of rupture, normal liver/renal function and patient reliability for follow up. No restriction was placed on serum HCG level, size of gestation sac, gestational age and presence of fetal heart motion so that they could be tested for their influence on treatment success. Complete HCG resolution was achieved in eight cases (89% success rate), requiring 30-129 days. None of the variables tested was found to affect outcome; successful outcome was seen with HCG level as high as 106,000 U/L and gestation sac as large as 6 cm and a live fetus.

Conclusion

The methotrexate/folinic acid regimen used as a one-dose treatment in this study is safe and effective for unruptured interstitial pregnancy, with no side-effects and the advantage of avoiding invasive surgery. Subsequent tubal patency and reproductive function are yet to be ascertained.

CURRENT PERSPECTIVE ON CERVICAL CANCER IN INDONESIA

Herman S
Department of Obstetrics and Gynaecology, Padjadjaran University Faculty of Medicine, Hasan Sadikin Hospital, Bandung, Indonesia

Introduction

Since two decades ago, cancer has received more attention in Indonesia as its position has soared from the 12th to the 6th rank of the cause of death. Hospital-based data reveal cancer of the uterine cervix to be the most common malignancy, possibly associated with the existence of various risk factors that can be encountered throughout the country. Each year as many as approximately 40,000 new cases of cervical cancer are calculated to arise. Besides the quantity, another problem in the management of cervical cancer is the late stage of disease when patients first appear in the health centres. The patient characteristics seem to have slightly changed lately; the cancer is reported to be found more frequently in younger age with higher stage.

Treatment modalities vary from one hospital to another depending upon the qualification of medical specialists and therapeutic equipment available. Chemotherapy and modern radiotherapy facilities as well as radical surgery are offered mostly by governmental teaching hospitals and those specializing in cancer treatment.

Prevention efforts have not shown a significant result yet, basically due to financial and knowledge constraints of the community group at risk of developing the cancer.

Downstaging measures that have been initialised in some areas by practicing visual inspection with acetic acid might be an alternative approach to lower the number of advanced cases.

Sophisticated laboratory examination using molecular biology principles is utilised in big cities mostly for research purposes. Ongoing collaborative studies with outstanding universities in developed countries are aimed at developing vaccines against cervical cancer in the years to come.

Cancer of the uterine cervix remains the most frequent malignancy found in developing countries like Indonesia. This fact might be explained by the existence of considerable social-economic risk factors nationwide. Yet it does not automatically imply a comprehensive management of cervical cancer. Lack of a national cancer registry is an influencing negative factor, which may be caused by the geographical constraint.

The purpose of writing this paper is to present a personal description on the current situation of cervical cancer in Indonesia based on several studies and data on patients admitted to the Hasan Sadikin Hospital in Bandung as the only referral gynaecological oncology centre in the West Java province.

Results

With its 13,000 islands and 220 million population, Indonesia faces remarkable difficulties on communication matters. It is thus understandable that data on cancer are inconsistent according to the source and method of survey.

National data reveal cancer as an important cause of death as it has soared from the 12th in 1986 to the 6th rank in 1992 (Table 1).

Table 1. Most frequent causes of death in Indonesia*

1.	infectious diseases
2.	accidents
3.	cardiovascular diseases
4.	cerebrovascular diseases
5.	other degenerative diseases
6.	cancer

* data per 1992

Geographic and communication obstacles render accurate population-based cancer registry in this country impossible. Like in other developing countries cervical cancer comprises the most frequent malignancy in Indonesia (Table 2).

Table 2. Incidence of 10 most frequent cancers in Indonesia, 1988-1994 (pathology-based)

No	Site of cancer	Number of cases
1	Uterine cervix	26,200
2	Breast	16,642
3	Skin	11,053
4	Nasopharynx	8,060
5	Lymphgland	7,144
6	Ovary	6,955
7	Rectum	6,487
8	Thyroid	5,254
9	Soft tissue	4,594
10	Colon	4,277

The above data were retrieved from the 13 governmental medical education centres, while the number of cervical cancer cases is described as follows (Figure 1).

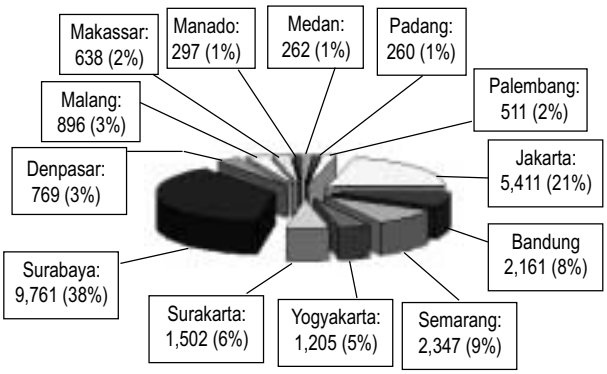


Figure 1. Number of cervical cancer patients in 13 government teaching hospitals in Indonesia 1984-1994 (pathology-based).

Being a top referral centre, the Hasan Sadikin Hospital receives patients from places over the province, including cancer patients. Proportion of those cancers according to the anatomic location is shown below (Table 3).

West Java is known as the most populous province, dwelled by approximately 20% of the whole people of Indonesia, around 40 million. Consequently, data of the province may represent the national figure.

Table 3. Ten most frequent cancers in the Hasan Sadikin teaching hospital

No	Site of cancer	Percent
1	Uterine cervix	20.09
2	Breast	11.26
3	Skin	9.03
4	Lymphgland (primary)	8.47
5	Nasopharynx	8.05
6	Lymphgland (secondary)	4.69
7	Ovary	4.45
8	Soft tissue	4.41
9	Colorectal	4.23
10	Secondary tumour (unspecified)	3.21

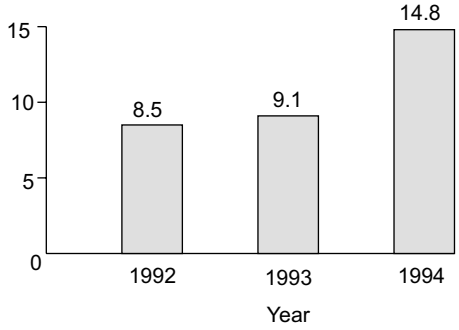


Figure 2. Percentage of cervical cancer (outpatient) compared to all cancer patients at the Hasan Sadikin Hospital

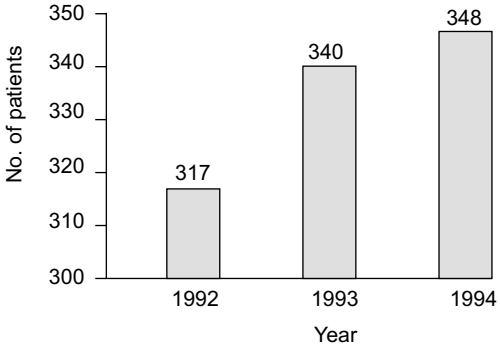


Figure 3. Number of cervical cancer patients (in-patients) at the Hasan Sadikin Hospital

The number of cancer patients in the Hasan Sadikin Hospital has shown a tendency to increase: in 1992 there were 1,153 cancer patients (5.14 % of total number of patients), climbing up to 1,352 (5.91%) in 1995. Both the total number and the proportion of cervical cancer also indicate an increase (Figures 2 and 3).

Using a formula issued by the Ministry of Health the incidence of cancer in Indonesia is calculated to be 100 of new cases per 100,000 population, 20% out of which is due to cervical cancer. Based on the formula the number of new cases of cervical cancer in West Java would then yield a number of 8,000 annually. The number of cervical cancer patients documented in the Hasan Sadikin Hospital annually is approximately 400, meaning that the great majority of those patients are not admitted to this hospital. It is assumed that most of them are not reported, while some would go to health centres in Jakarta and other provinces, and rich patients might use health facilities abroad.

Around two thirds of the patients treated in our hospital were already in late stages (Figure 7). Similar figure was reported from other teaching hospitals in Indonesia. A general impression expressed by other gynaecological oncologists in Indonesia is that they recently found younger patients with increasing stage at their first visit.

Other findings encountered in our previous study include those related to social factors (Figures 4-6).

The average age at first marriage was 16.6 years. As many as 33.3% of patients and husbands married twice, and 12.3% married three times. The average number of patient's marriage was 1.7, while the average parity was 4.6.

Prophylaxis and early detection

Prophylactic measures are carried out in both governmental health facilities and private sectors, usually by conducting Pap test. This means of early detection – available at almost all health centres – is applied only on limited coverage of community due to financial reasons.

A big discrepancy in the prophylactic practice occurs between big cities and rural areas. In big laboratories new technologies are available in the form of automated cytology (Papnet) or liquid-based cytology (ThinPrep); both are used mostly for research purposes.

The report of cytological examination is generally done by the conventional Pap system, however there has been an increasing tendency to replace or combine it with the Bethesda system; which was started in the teaching hospitals.

Another screening program available in big cities is that using a biomolecular approach. Two methods are used, detecting individual human papillomavirus (HPV) DNA type by PCR and finding the oncogenic types of HPV by Hybrid Capture. Again, they are generally used in research.

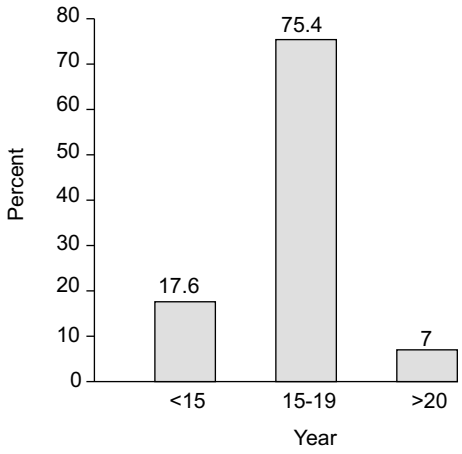


Figure 4. Age at first marriage of patients

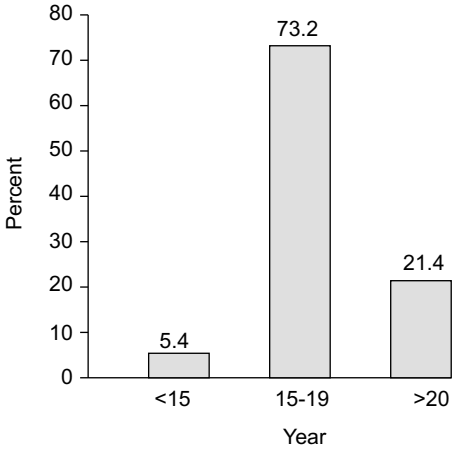


Figure 5. Age at first pregnancy

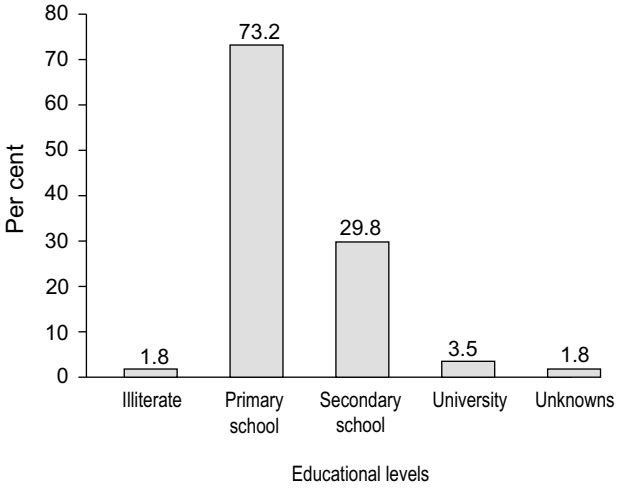


Figure 6. Educational level of patients

Being challenged by the failure of cytological examination in preventing cervical cancer it was recently introduced a method to look for cases of cervical cancer at earlier stages. This down staging approach is aimed at finding precancerous and early lesions of cervical cancer by

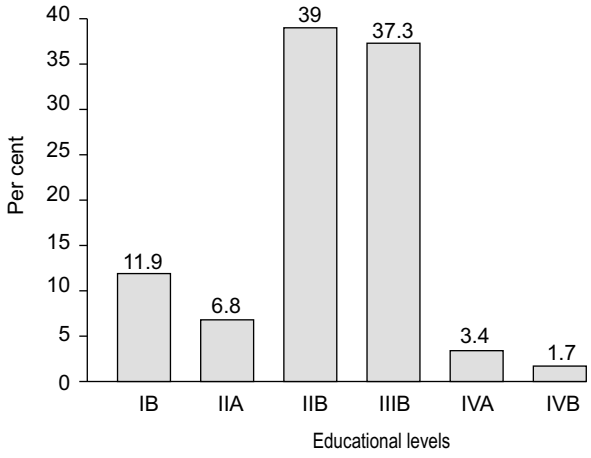


Figure 7. Stage of disease of patients

applying acetic acid on the uterine cervix, hence it is called 'visual inspection with acetic acid' (VIA).

A collaborative research between the Leiden University Medical Centre and the Padjadjaran University in Bandung, the University of Indonesia in Jakarta, the Udayana University in Denpasar, and the Siliwangi University in Tasikmalaya under the Female Cancer Programme is still going on to find and treat precancer and early stage of cervical cancer ('see and treat') by applying the VIA and treating the lesions by cryotherapy on the spot.

The down staging approach is said to be more feasible to conduct in developing countries like Indonesia due to its advantages over the Pap test.

Treatment

For the treatment of cervical cancer radical surgery, chemotherapy and radiation therapy are available at all governmental teaching hospitals and cancer hospitals. Besides, they are also offered in private hospitals where gynaecological oncologists from teaching hospitals serve as visiting doctors and in some private hospitals provided with radiation facilities. Special operative technique like trachelectomy is carried out rarely in some teaching hospitals.

Research

Multicentre studies, also those with colleagues from neighbouring countries, were performed mostly to evaluate the results of treatment of cervical cancer by chemoradiation.

Research studies by hybrid capture (HC) have been conducted on limited number of cases in several university hospitals.

Studies on HPV typing have produced two important findings. In the 1995, series the prevalence of HPV type was found to be constituted by HPV 16 in 31.9% and HPV 18 in 48.9% of cases. In 2002, the study revealed the HPV typing as follows: HPV 16: 44%, HPV 18: 39%, and HPV 52: 14%. The study was conducted with the Leiden University in the Netherlands, in the attempts to produce the vaccine against cervical cancer in the future.

PET/CT CLINICAL IMAGE INTERPRETATION : LYMPHOMA, BREAST CARCINOMA, COLORECTAL CARCINOMA, MELANOMA, HEAD-NECK, THYROID AND ESOPHAGEAL CARCINOMAS

Partha G
Asia Pacific Nuclear Medicine Group, Siemens Medical Solutions, Singapore

Clinical image interpretation in PET/CT should consider factors like exact localization of lesion, degree of malignancy, differentiation of benign and malignant lesions and influence of PET findings in disease staging and management. In Lymphoma, the critical question is disease staging and careful evaluation of borderline lesions and differentiation from infective pathology is necessary to determine proper stage. In NHL extranodal disease is common, especially in Spleen, Marrow and Waldeyer's ring. Post-therapy assessment should consider FDG uptake levels in residual masses which often harbour disease. Post-chemotherapy status should take into consideration uptake of FDG in Thymus and marrow which is normal after therapy. PET is especially helpful in characterizing small lymph nodes which appear normal on CT but may harbour residual disease or recurrence. Mismatches between CT and PET findings are common primarily related to small nodal size or central necrosis leading to poor FDG retention. Cerebral Lymphoma is associated with immunosuppressive states and often present with periventricular FDG avid hyperdensities on PET/CT. Physiological uptakes in stomach, ureter, colon, etc. should be considered carefully while interpretation of PET in Lymphoma. Brown fat also show FDG uptake often mistaken for lymphadenopathy. Infective pathologies like Infectious Mononucleosis often mimic PET picture of Lymphoma.

Primary Breast cancer is usually FDG avid but tumours smaller than 1cm in size is often difficult to pick up. SUV levels are a good indicator to differentiate malignant from benign lesions. FDG uptake is low in slow growing well differentiated tumours like Tubular and Lobular CA and CA in situ. Increased FDG uptake suggests more aggressive tumour type. The major role of PET is in staging especially for Axillary nodes and distal mets. Sensitivity is lower for nodes smaller than 8 mm so a negative PET/CT in patient with aggressive primary breast tumour mandates further investigation like Sentinel node biopsy. PET is useful in assessment of tumour and metastases response to therapy since SUV levels reflect tumour burden. Bone metastasis is the commonest and shows avid FDG uptake usually in Osteoblastic metastases. Osteosclerotic mets may be positive on bone scan but negative on FDG. PET is also most sensitive to evaluate for recurrence both in the primary site as well as in axillary nodes.

Esophageal cancer is usually FDG avid. PET/CT is useful in delineation of extent of primary disease as well as nodal and distant metastasis. Primary objective is to assess respectability of primary lesion. SUV values reflect tumour aggressiveness. Some tumours like Gastric Lymphoma are especially FDG avid. Post-operative PET/CT should carefully evaluate uptake in the surgical margins and anastomoses since inflammatory changes may mimic or mask residual tumour or recurrence. Gastrointestinal Stromal tumours (GIST) show response to Glivec therapy and FDG PET is useful in monitoring therapeutic response.

Role of PET in Colorectal cancer is primarily for assessment of local, lymph node and distant spread. Metastases are usually FDG avid. Primary mucinous tumours show low FDG uptake. Colonic adenomas often show FDG uptake and may appear as primary tumours. FDG PET is also highly sensitive to demonstrate tumour recurrence from post operative changes. Thus PET is recommended in cases with rising CEA levels following primary tumour resection. Metastases in the mesenteric and retroperitoneal lymph nodes and in liver are most common. Chronic inflammatory changes, post operative inflammation and disease like Crohn's also may cause diagnostic difficulties. Tumour recurrence at anastomotic site following resection is common and shows FDG avidity.

Most head-neck cancers are squamous cell cancers and show high FDG avidity. Larger primary tumour suggests bad prognosis. Local nodal metastases are common at presentation. There are 20%-30% patients who develop second tumour in upper aerodigestive tract-esophagus and bronchi common sites. Distant metastasis (lung, liver, bone) common with tumours of hypopharynx and tongue. Five percent of the cases present with Cervical

node metastases of unknown primary. FDG PET useful in delineating primary tumour, local and distal met as well as response to treatment and tumour recurrence. Fusion of PET and CT images delineate necrotic changes within tumour to assist planning for radiation therapy as well as surgical margins. FDG PET also very useful to differentiate tumour recurrence from post surgical and radiation fibrosis which is common and alters normal anatomy significantly. Extent of FDG uptake and SUV level response are critical for assessment of therapy usefulness. Post-surgery inflammatory changes complicate PET evaluation.

Melanoma shows avid FDG uptake and PET is useful in delineating regional lymph nodal and distant metastasis. PET not highly sensitive for early local nodal metastasis and Sentinel node biopsy is the preferred method.

SCREENING FOR COLORECTAL CANCER

David JG
Department of Surgical Gastroenterology, Gartnavel General Hospital, 1053 Great Western Road, Glasgow, United Kingdom

Introduction

Control of cancer is one of the significant challenges facing the developed world in the 21st century. While there has been evidence of significant progress in staging, treatment planning and modest improvements in the results of management there is also is an understandable emphasis on detecting the disease before it advances to a stage that is beyond the scope of curative treatment.

Diagnostic technology offers a range of new options. Clinicians are no longer dependant on traditional methods such as clinical examination, standard contrast radiology and endoscopy. New endoluminal methods are gaining ground and CT, MRI, PET, SPECT and immuno-scintigraphy have all been investigated. In particular, CT colonography and 3D virtual colonoscopy may well offer particular advantages for screening future generations of patients.

There are some important general principles which apply when assessing the potential value of screening for a given cancer site. For example it is important to focus on cancers which produce a substantial disease burden in the community. Furthermore a screening programme would really only be of practical value if there was demonstrable advantage to early detection and if target population were shown to be compliant with the screening techniques. It is also vital to consider the characteristics of the available screening methods. Safety and accuracy are major concerns and for population screening the cost effectiveness and specificity of a selected technique are of particular importance. Accumulating a large proportion of false positive screening test results places an intolerable strain on the more refined and detailed diagnostic work which is required as well as creating unnecessary psychological morbidity in the individuals so identified.

Large bowel cancer is one of the most threatening and epidemiologically important cancer sites in the Western world and it qualifies as an attractive screening option in view of the fact that the results of treating early forms of the disease are associated with much less morbidity and far better results.

The mainstay of colorectal cancer screening so far has made use of several simple chemical or immunological methods of detecting occult blood in the stool. These investigations are far from ideal. The sensitivity of the standard chemical tests for occult blood can be enhanced by re-hydrating the slides but only at the cost of increasing the number of false positive cases recorded. The tests are however easy to apply to large populations and even without re-hydration, they are acceptably sensitive although specificity remains a significant problem. Range of dietary and related factors can also be responsible for false positive tests but providing certain restrictions and precautions are followed the accumulated evidence does support the suggestion that large bowel cancers can be detected early. Not only so but there is now clear evidence in the literature that (for two distinct European populations) even these somewhat imperfect tests can be associated with significantly improved mortality from colorectal cancer. To illustrate the impact of such screening the detected disease characteristics it is of interest to note that in the English study (1), which comprised 152,850 subjects, the proportion of T1 lesions in the screen detected group was 52% compared with 13% in the control group. For distant disease - only 5% of the screen detected cases had demonstrable liver metastases whereas the incidence was 22% in the cancer control group. The reduction in colorectal cancer mortality was 15% in the English study and 18% in a similarly designed Danish study (2) published at the same time.

Results of this nature do need to be examined in the light of different forms of bias which can distort the interpretation of screening studies. In particular lead time bias which may be considered as early detection in those who may well succumb to the disease irrespective of the screening intervention and length bias which preferentially allows the selective detection of slow growing tumours with an associated good prognosis.

There have been some suggestions that the single application of a sigmoidoscopic or colonoscopic examination may be a sufficient screening investigation to apply on a large scale population basis. These

suggestions have, however, been based on uncontrolled data and results of properly designed trials are awaited.

While there is no clear cut candidate technique which is likely to sweep away the inexpensive albeit sub optimal FOB test it is nevertheless evident that a range of emerging technologies (3) offer potential for the future. Modifications of occult blood testing methods to utilise immunochemical tests which have been demonstrated to retain good levels of sensitivity (e.g., 87% for carcinoma; 47.4% for adenomas which are more than 10 mm in diameter) but with a significant improvement in specificity (e.g., 97.9% in a 'normal' population) thus enhancing their utility in population screening look promising.Alternative approaches to measure porphyrin spectro-fluorometrically or to screen stool for specific molecular markers such as point mutations on specific regions of certain genes e.g., K-ras, APC and p53, are also being investigated. Such methods are highly accurate and consistent but are very expensive and not automated at present.

Other imaging techniques have been developed such that they should now be considered as possible screening methods. CT colonography or virtual colonoscopy has gradually come of age over the past few years and offers real potential in the identification of small pre-cancerous lesions. Similarly, as experience with capsule video endoscopy increases there may be some value in exploring this as a tool to use in certain populations. The main difficulties with these non or minimally invasive methods relates to their expense and at the present time, this would prohibit their application.

Conclusion

For the foreseeable future, it is not unreasonable to suggest a slightly different approach to early detection of colorectal cancer. Rather than applying an imperfect test to large populations where the actual prevalence of the disease is small or modest it would be logical to confine surveillance to groups of subjects where there is good evidence that the risk of colonic neoplasia is substantially higher than the background level. Such targeted colorectal surveillance could reasonably be considered in individuals in the categories outlined below:

- During follow-up after resection of an adenoma or carcinoma
- Where the family history reveals that a subject has either:
  - Two first degree relatives or
  - One first degree relative <45 years with a history of colorectal cancer.
- Inflammatory bowel disease
- Hereditary non-polyposis colon cancer (HNPCC), Familial adenomatous polyposis (FAP), juvenile polyposis or Peutz-Jeghers syndrome
- Ureterosigmoidostomy
- Acromegaly

The challenges which remain include the need to improve both risk assessment and the screening techniques such that a cost effective practical solution can be presented as a viable option amongst the conflicting demands in any health economy.

References

1. Hardcastle JD, et al. Randomised controlled trial of faecal-occult blood screening for colorectal cancer. Lancet 1996: 348;1472-77.

2. Kronborg O, et al. Randomised study of screening for colorectal cancer with faecal-occult blood test. Lancet 1996; 348:1467-71.

3. Levin B, et al. Emerging technologies in screening for colorectal cancer: CT colonegraphy, immunochemical faecal occult blood tests and stool screening using molecular masters. CA Cancer J Clin 2003; 53:44-55.

THE EVOLVING ROLE OF ENDOSCOPY IN THE MANAGEMENT OF GASTROINTESTINAL CANCERS

Goh KL, Leong KK
Department of Medicine, University of Malaya Medical Centre, 50603 Kuala Lumpur, Malaysia

Introduction

Men's innate curiosity to look into the insides of his own body probably dates back to the dawn of western medicine in the time of Hippocrates. But it was only in using the early 19th century that speculums of various sorts were used to examine the urethra, throat, the ears and the vagina. Philip Bozzini of Frankfurt described candle light in 'lichtleiter' or light conductor and illuminated a speculum to examine the urethra and bladder in 1806 (1). Antonin Desormeaux of Paris (1853) described a modification of this original instrument and called his device (for the first time) an endoscope (2). The first gastrointestinal endoscopes were open hollow tubes that were inserted through the throat. Adolf Kussmaul and others took the cue from sword swallowers, at that time being popular entertainers and fashioned the first esophagoscope and then a gastroscope (3). Edison's discovery of the electric bulbs and incandescent light and the subsequent miniaturization of light source enabled a great advancement in the visualization of the 'viscera'. Rigid instruments and then semi flexible instruments were then introduced and used in patients (3). Rudolf Schindler above anyone else in the early 20th century contributed to the 'popularization' of the upper GI endoscopy using his semi flexible endoscope (4). Basil Hirschowitz made use of the technology of fiberoptics and invented the first flexible gastroscope in 1957 (5).

However, it was not that long ago that Sir John Eriksen, Surgeon Extraordinary to Queen Victoria in 1873 said that 'the abdomen, the chest and the brain will forever be shut from the wise and humane surgeon'. In the 21st century not only can we see the insides of the human body with amazing clarity, endoscopy has allowed us to perform numerous procedures in the GIT which was previously unimaginable.

Endoscopy has played an important role in the management of GI cancers, which has involved broadly progressively better diagnostics, palliative therapy of obstructive lesions and resection of endoluminal cancers (Figure 1). GFI endoscopy has evolved from just purely diagnostic endoscopy to therapeutic endoscopy and now to endoscopic surgery. Along the way this has necessitated the need for close cooperation with surgeons, radiologists and pathologists.

Diagnostic endoscopy

The advent of fibreoptic endoscopy in the early 1960s ushered in a new era in GI endoscopy. Soon after the production of the first practical upper GI endoscope in 1961 (6), relentless research and development of newer and better instruments have allowed the endoscopist unsurpassed views both the upper and lower GIT. Accurate diagnosis of GI malignancies and assessment of extent and location has allowed optimal management of these cancers.

Videoendoscopy

Technical advances in electronic allowed the invention and introduction of the video endoscope in the early 1980s (6). An electronic sensor or charged couple device was placed at the end of a 'fibre scope'. This allows images to be captured in a digital format which is then transmitted to a computer processor which then translated images into a television monitor or screen. Glass fibres that were used to transmit images in the early fiberscopes were then only used to transmit light to illuminate the GI mucosa. Video endoscopy has been a durable and robust technology and has enabled accurate imaging of the GI mucosa. Additionally, it has allowed instant image acquisition and storage. Video endoscopy is the standard system that is used in all GI endoscopy units throughout the world today.

Therapeutic endoscopy Polpypectomy

GI endoscopy has evolved from a purely diagnostic to a therapeutic role. Soon after the introduction of fiberoptic colonoscopy, Wolff and Shinya from Beth Israel Hospital, New York carried out perhaps the first therapeutic endoscopic procedure- polpypectomy using a wire diathermy snare (7). While the early polyps

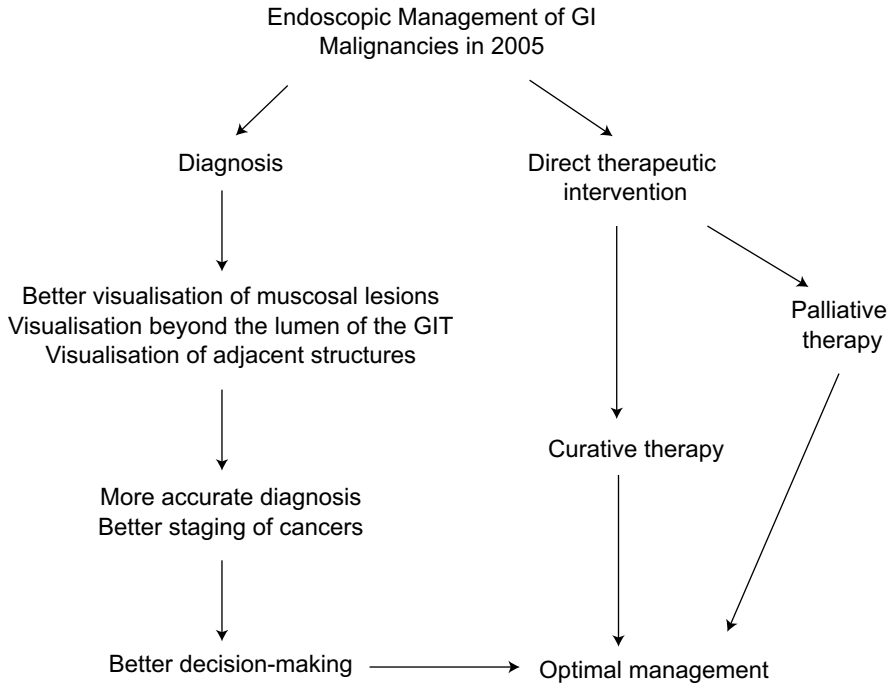


Figure 1. Endoscopic management of GI malignancies in 2005

removed were small, experience and expertise and newer accessories soon allowed removal of large polyps, sessile polyps and in recent years development of endoscopic mucosal resection where early mucosal cancer can be removed essentially still, with a diathermy snare.

Palliation of obstructing tumours

Palliations of obstructing esophageal cancers were amongst the early therapeutic endoscopic procedures. Dilation of a narrowed lumen with bougie and subsequently balloon dilators and insertion of fixed lumen plastic tubes have allowed a clear passage to the tumour (8). Disobliteration therapy using alcohol injection, lasers and more recently argon plasma coagulation have been used and often complements placement of endoprosthesis as endoscopic therapy.The biggest advance in recent years has been the invention of self-expanding metallic stents (SEMS) (9).These stents are placed over a catheter when undeployed and has a small diameter, which allows the whole device to be placed through a narrowed lumen. The stent can then be deployed when the metallic wire mesh will expand once placed in an optimal position. SEMS has allowed a larger lumen stent to be placed with much greater ease and safety. Esophageal stents placed over a wire are considered (OTW) devices. Newer SEMS devices have even a smaller diameter and can be placed through the scope (TTS). What it means now is that SEMS can be placed where the scope can reach. This has allowed placement of colonic (even to the proximal colon) and enteral stents (10).

Endoscopic retrograde Cholangiop-nacreatography (ERCP)

With the development of UGI endoscopy, attempts were made firstly at visualising the ampulla of Vater, which was located in the second part of the duodenum and thereafter canulation and opacifying the bile ducts and the pancreatic duct. Walter McCune (11) was the first to achieve this and this was followed quickly by the Japanese, Oi, *et al* (12). Soon a tremendous amount of ERCP work was developed and carried out by innovative and enterprising endoscopists including Nib Soehendra, Peter Cotton and Kees Huibregtse. Biliary sphincterotomy was carried out and placement of stents in the bile duct to relieve jaundice from malignant biliary obstruction followed soon after. Fixed lumen plastic stent of 7FG and 10FG diameters were placed. Again in recent years with the advent of SEMS technology such stents have also been placed in the biliary tree. Similar work although more difficult, has been carried out in the pancreatic duct where removal of stones, dilation of strictures and placement of stents in cases of chronic pancreatitis has been also carried out.

Looking beyond the GI lumen

Endoscopic ultrasound or endosonography is a novel diagnostic method where an ultrasound probe is place at the tip of a conventional endoscope. What this has allowed us is to image using sonography to image structures outside the GI lumen and in the wall of the GI tract (13). It has allowed us to image with great accuracy structures adjacent to the GI lumen such as the pancreas, bile duct and the liver. In recent years, with the use of the linear array scope, needle biopsies can be taken from the pancreas and contiguous lymph nodes. Drainage of pancreatic pesudocsyst under sonographic guidance is now possible as is neurolysis injection of the celiac plexus for pain relief.

The last frontier – the small intestine

Conventional upper GI endoscopes allow the operator to reach at the most the third part of the duodenum. Longer and more flexible scopes called enteroscopes allow the operator to traverse the duodenal-jejunal junction to enter the upper jejunum and further downwards (14). Enteroscopy is, however, a technically difficult procedure and it is almost impossible to examine large tract of the small intestine. The invention and use the double balloon enteroscopy has overcome some of the technical difficulties and patient endoscopists can now traverse the whole of the small intestine past the ileocecal valve (15).

The invention of a micro-camera in the form of a swallowed capsule allowed views of the small intestine. The first and only one still to date was invented by the Israeli company, Given Inc. The first report of its use was by Iddan, *et al* (16). Capsule endoscopy has allowed fairly accurate imaging of the small intestine. With this device images are continuously picked up by the swallowed camera, which then transmits images to a digitrapper, which then stores images, which can then be downloaded in to a computer.

Even better visualization of the mucosa

Magnifying scopes bring images to $\times$ 10 to $\times$ 100 with higher mega pixels have allowed accurate observations of the GI mucosa. Detection of early tumors has also been further enhanced with the use of several dyes in what has been lapelled chromoendoscopy. Together with magnifying scopes, chromoendoscopy allows detection of very early lesions allowing endoscopic mucosal resection or ablative therapies (17,18). Narrow band imaging where filters confine the visual spectrum to very narrow band has provided greatly enhanced images of the mucosa including depth of invasion of tumours (19).

Optical biopsies

Even greater magnification of the mucosa allows what has been termed as optical biopsies. In essence, the tip of the scope is like a microscope. Confocal microscopy technology has allowed very good images, as are the new endo cytoscopy scopes where even cellular structures can be discerned (20, 21).

Endoscopic surgery

Endoscopic mucosal resection (EMR) and submuocsal dissection (ESD)

EMR allows resection of early cancers in the esophagus, stomach and colon which are confined to the mucosal layer. Following sub mucosal injection with saline, lifting the mucosal layer from the sub mucosal layer a polypectomy snare is lopped around the lesion and then subsequently 'cut off'. Modifications of this basic method using a tube and a cap fitted at the end of the endoscope have been used (22). More recently, dissection of the GI mucosa around the lesion and submucosally is carried out using a modified 'needle knife'. This technique is known as endoscopic submucosal dissection and has been carried out by several experts in Japan where early gastric cancer is common (23).

Trans-gastric peritoneoscopy and surgery

This is a novel method of accessing the peritoneal cavity using a flexible endoscopy through the gastric wall. This is achieved by creating a 'hole' in the gastric wall with a needle knife and entering the peritoneal cavity with a flexible scope. The 'perforation' is subsequently closed with endoclips. Experiments have been carried out in pigs where ligation of the fallopian tubes has been carried out (24). Whether this will evolve into a practical procedure is left to be seen but underlines new approaches to abdominal surgery.

Conclusion

There is no limit to man's ingenuity. Advances in medicine have brought great relief to suffering from cancers. As Sir Winston Churchill said in another context but apt with respect to GI endoscopy- '*Now is not the end. Now is not even the beginning of the end. Now is perhaps the end of the beginning*'. We look forward to further exciting ideas and developments in the field.

References

1. Bozzini P. *Lichtleiter, eine Erfindungzur Anschauung innerer Theile undh Krankheiten nebst der Abbildung. Huefelands neues Journal der pract Heilkunde* 1806; 17: 107-24.

2. Desormeaux AJ. *De l' endoscope, instrument proper a eclairercertaines cavites inetensely de l'econimie. Comptes rendues de l'Academie des Sceinces* 1855; 40:692-3.

3. Edmonson JM. History of instruments for Gastroinetsinal Endoscopy. Gastrointest Endosc 1991; 37: S27-56.

4. Gordon ME, Kirsner JB. Rudolf Schindler, pioneer endoscopist. Glimpses of the man and his work. Gastroenterology 1979; 77: 354-61.

5. Hirschowitz BI, Curtiss LE, Peters CW, et al. Demonstration of a new gastroscope, the 'fiberscope'. Gastroenterology 1958; 35: 50-53.

6. Sivak MV. Video endoscopy. Clin Gastroenterogy 1986; 15:205-34.

7. Wolff WI, Shinya H. A new approach to the management of colonic polyps. Adv Surg 1973; 7:45-67.

8. Atkinson M, Ferguson R. Fibreoptic endoscopic palliative intubation of inoperable oesophagogastric neoplasms. Br Med J 1977, Jan 29; 1(6056):266-7.

9. Mergener K, Kozarek RA. Stenting of the gastrointestinal tract. Dig Dis 2002; 20(2):173-81.

10. Knyrim K,Wagner HJ, Bethge N, et al. A controlled trial of an expansile metal stent for palliation of esophageal obstruction due to inoperable cancer. N Engl J Med 1993 Oct 28; 329(18):1302-7.

11. McCune WS, Shorb PE, Moscovitz H. Endoscopic cannulation of the ampulla of vater: a preliminary report. Ann Surg 1968 May; 167(5):752-6.

12. Oi I, Takenoto T, Kondo T. Fibre duodenoscope: direct observation of the papilla of Vater: a preliminary report. Endoscopy 1970; 3: 101-3.

13. Tio TL, Tytgat GN. Endoscopic ultrasonography in the assessment of intra- and transmural infiltration of tumours in the oesophagus, stomach and papilla of Vater and in the detection of extraoesophageal lesions. Endoscopy 1984 Nov; 16(6):203-10.

14. Lewis BS, Waye JD. Total small bowel enteroscopy. Gastrointest Endosc 1987 Dec; 33(6):435-8.

15. Yamamoto H, Sekine Y, Sato Y, et al. Sugano K. Total enteroscopy with a nonsurgical steerable double-balloon method. Gastrointest Endosc 2001 Feb; 53(2):216-20.

16. Iddan G, Meron G, Glukhovsky A, et al. Wireless capsule endoscopy. Nature 2000 May 25; 405(6785):417.

17. Tada M, Misaki F, Kawai K. A new approach to the observation of minute changes of the colonic mucosa by means of magnifying colonoscope, type CF-MB-M (Olympus). Gastrointest Endosc 1978 May; 24(4):146-7.

18. Fleischer DE. Chromoendoscopy and magnification endoscopy in the colon. Gastrointest Endosc 1999 Mar; 49(3 Pt 2): S45-9.

19. Machida H, Sano Y, Hamamoto Y, et al. Narrow-band imaging in the diagnosis of colorectal mucosal lesions: a pilot study. Endoscopy 2004 Dec; 36(12):1094-8.

20. Inoue H, Igari T, Nishikage T, et al. A novel method of virtual histopathology using laser-scanning confocal microscopy in-vitro with untreated fresh specimens from the gastrointestinal mucosa. Endoscopy 2000 Jun; 32(6):439-43.

21. Kumagai Y, Monma K, Kawada K. Magnifying chromoendoscopy of the esophagus: in-vivo pathological diagnosis using an endocytoscopy system. Endoscopy 2004 Jul; 36(7):590-4.

22. Inoue H, Fukami N, Yoshida T, et al. Endoscopic mucosal resection for esophageal and gastric cancers. J Gastroenterol Hepatol 2002 Apr; 17(4):382-8.

23. Kato M. Endoscopic submucosal dissection (ESD) is being accepted as a new procedure of endoscopic treatment of early gastric cancer. Intern Med 2005 Feb; 44(2):85-6.

24. Kalloo AN, Singh VK, Jagannath SB, et al. Flexible transgastric peritoneoscopy: a novel approach to diagnostic and therapeutic interventions in the peritoneal cavity. Gastrointest Endosc 2004 Jul; 60(1):114-7.

EMERGING ROLE OF INTERVENTIONAL RADIOLOGY IN CANCER TREATMENT

Abdullah BJJ
Department of Radiology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Introduction

Minimally invasive image guided interventional procedures (MIIGIP) are increasingly important in the management of patients with cancer. This is mainly due to the lower costs in terms of morbidity as well as shorter recovery times and hospital stays (1). More importantly, these interventions typically represent the least invasive definitive diagnostic or therapeutic options available for them. The primary goals of the interventional radiology procedures can be categorized as the diagnosis of cancer or cancer-related diseases, the treatment of cancer and the treatment of complications arising from cancer.

For those related to cancer diagnosis or complications related to cancer, the advent of newer and faster scanning techniques e.g., multi-detector CT which allows better assessment of size, location and extent of disease involvement with a much shorter scan time; the development of better MRI sequences which allow demonstration of white matter fibers, ability to localise brain function, indirect demonstration of tumour neoangiogenesis; PET/CT with its ability to determine the functional aspects of tumour viability immaterial of size and other structural characteristics. The development of novel tissue specific contrast agents targeted to localise to specific tissues is increasingly being used to not only detect but also characterize the abnormalities found.

For the treatment of cancers using MIIGIP, the list is ever expanding. These extend from the simpler but nonetheless important access of central veins by insertion of peripherally inserted central lines, chemoports, etc., imaging-guided biopsies (to obtain samples for cytological or pathologic testing without affecting adjacent structures), aspiration and drainage of collections, obstructed renal or biliary systems to the more complicated and demanding transcatheter chemoembolization (delivering chemotherapeutic agent & embolic material to a tumour), tumour ablation (using radiofrequency, cryotherapy or even high intensity focused ultrasound). The development of focused radiotherapy with injection of radioactive embolic material and gene therapy are options being explored.

The complications that may occur in cancer can also be treated with interventional techniques with an increased role of MIIGIP in pain control, vertebroplasty and kyphoplasty. All these advances have occurred in a background of greater sensitivity and accuracy occurring in imaging allowing better characterization and localization.

Conclusion

With regards to the treatment of cancer, the role of MIIGIP has extended beyond traditional radiology into the areas of surgery. MRI-guided brain surgery is now common place in leading centres around the world to facilitate better and more definite surgery for brain tumours; use of CT to localize and treat tumours real-time for radiotherapy; use of images from CT or MRI used for robotic surgery are new development on the horizon.

References

1. Noh HM, Kaufman JA, Rhea JT, *et al*. Cost comparison of radiologic versus surgical placement of long-term hemodialysis catheters. AJR Am J Roentgenol 1999; 172:673-5

NEW STRATEGIES IN VENTILATION

Mok QQ
Paediatric Intensive Care Unit, Great Ormond Street Hospital, London, United Kingdom

Introduction

Major advances have occurred in the provision of respiratory support since the advent of the iron lung ventilators during the polio epidemic in 1952. This has resulted in new types of ventilators, new modes and strategies, and the use of other adjuncts to optimize gas exchange.

Main messages

The main aim of respiratory support is to improve oxygenation and ventilation with increased patient comfort but at the same time causing minimal lung injury. Newer ventilators have numerous modes and the ability to measure and deliver the required pressure, tidal volume or breaths to meet the patient's demands and to prevent fatigue. Synchronising the patient's attempts to breathe with the ventilator breaths result in better tolerance and improved weaning. These modes are available in sophisticated ventilators used in intensive care units, as well as in simpler portable ventilators for home use. Spontaneous or non-invasive ventilation results in better gas distribution and less complications resulting from intubation and invasive ventilation.

In addition to increased sophistication and improved choice of modes, significant improvement in survival has resulted from adopting modern strategies in ventilation. Minimising lung injury was shown to be more important than achieving normal gas exchange, and permissive hypercarbia is becoming an increasingly acceptable strategy. Recent multicentre studies have shown that recruitment of alveolar volume to open up the lung, limiting peak pressures and ventilating with small tidal volumes, cause less barotrauma to the lung units, resulting in better outcomes (1,2). A large multicentre trial reported by the ARDS network showed there was a significant reduction in mortality in patients managed with tidal volumes of 6 ml/kg body weight compared to the traditional volume of 12 ml/kg (3). The patients in the small tidal volume group had less lung inflammation, more ventilator free days, and more days without organ failure. It has also been shown that opening up the alveoli and keeping them open with a positive end expiratory pressure above the inflection point results in improvement in oxygenation. High frequency oscillatory ventilation (HFOV) uses this principle to the maximum, and is now widely used in paediatric and neonatal patients. Many studies have shown an improved outcome in patients with diffuse alveolar disease and air-leak syndromes treated with HFOV using adequate alveolar recruitment manoeuvres (4-7). The patients on HFOV are extubated earlier and are less likely to require supplemental oxygen, compared to patients treated with conventional ventilation (8). Recent studies have been carried out using HFOV in adults.

Various adjuncts are also used to improve ventilation perfusion matching in order to limit barotrauma from the use of high ventilator pressures or oxygen. These include exogenous surfactant to reduce surface tension, steroids to reduce the inflammatory response, prone positioning to recruit atelectatic lung units, and pulmonary vasodilators. Surfactant replacement is well established in respiratory distress in preterm babies. Recent trials have described its use in paediatric patients with acute lung injury, resulting in improved oxygenation and reduced mortality (9). Studies have shown that short courses of steroids at high doses are not effective, but prolonged courses at lower doses have been associated with improvement in unresolving ARDS (10). Placing patients with acute respiratory failure in the prone position improves their oxygenation but not their survival (11). The addition of pulmonary vasodilators results in an improvement in oxygenation by reducing ventilation perfusion mismatch. Inhaled nitric oxide causes relaxation of the smooth muscles by stimulation of guanylate cyclase and an increase in cyclic GMP. This leads to vasodilatation and a reduction in pulmonary artery pressures, with little effect on systemic pressures. Many studies have shown that the use of inhaled nitric oxide has led to a reduction in the need for more aggressive ventilator strategies and extracorporeal support, as well as a reduction in chronic lung disease, although it has not had an effect on the mortality rate (12-14). However, the cost of inhaled nitric oxide is exorbitant and out of the range of many intensive care units in developing countries, thus trials of other

vasodilators (sildenafil, nitric oxide donors and phosphodiesterase inhibitors) are being carried out in the acute situation (15). Various ventilator strategies and adjuncts can also be used in combination, and this has been shown to produce better results (16). Extracorporeal oxygenation using artificial membranes (ECMO) is an established adjunct in paediatric practice, providing lung rest in reversible lung conditions. The results for lung recovery are good in neonates with cardio-respiratory failure supported with ECMO, with a survival rate of 85% to hospital discharge. However the survival rates of 50-60% in paediatric or adult patients are less impressive. Other novel methods of providing lung rest by using perfluorocarbons as the liquid interface in the alveolar spaces for gas exchange have not replaced traditional methods of gas ventilation, despite numerous trials.

Conclusion

In conclusion, it has been shown that the use of protective ventilator strategies and other adjuncts to ventilation has resulted in minimizing lung injury and better patient outcomes.

References

1. Amato MB, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 1998; 338:347-54.

2. Tobin MJ. Advances in mechanical ventilation. N Engl J Med 2001; 344:1986-96.

3. The ARDS network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342:1301-8.

4. Arnold JH, et al. Prospective randomized comparison of high-frequency oscillatory ventilation and conventional ventilation in paediatric respiratory failure. Crit Care Med 1994; 22:1530-9.

5. Rettwitz-Volk W, et al. A prospective randomised multicentre trial of high-frequency oscillatory ventilation compared with conventional ventilation in preterm infants with respiratory distress syndrome receiving surfactant. J Paediatr 1998; 132:249-54.

6. Johnson AH, et al. High-frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity. N Engl J Med 2002; 347:633-42.

7. Froese AB, et al. High-frequency oscillatory ventilation: lessons from the neonatal/paediatric experience. Crit Care Med 2005; 33:S115-21.

8. Courtney SE, et al. High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. N Engl J Med 2002; 347:643-52.

9. Willson DF, et al. Effect of exogenous surfactant (calfactant) in paediatric acute lung injury. JAMA 2005; 293:470-6.

10. Meduri GU, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome. JAMA 1998; 280-159-65.

11. Gattinoni L. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 2001; 345:568-73.

12. The Neonatal Inhaled Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. N Engl J Med 1997; 336:597-604.

13. Clark RH, et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. N Engl J Med 2000; 342:469-74.

14. Mok Q, et al. Persistent pulmonary hypertension of the term neonate. A strategy for management. Eur J Pediatr 1999; 158-825-7.

15. Lowson S. Inhaled alternatives to nitric oxide. Crit Care Med 2005; 33:S188-95.

16. Dobyns EL, et al. Interactive effects of high-frequency oscillatory ventilation and inhaled nitric oxide in acute hypoxemic respiratory failure in paediatrics. Crit Care Med 2002; 30:2425-29.

IMPACT OF THE NEW VACCINATION SCHEDULE

Hussain Imam Hj MI
Paediatric Institute, Hospital Kuala Lumpur, Jalan Pahang, 50586 Kuala Lumpur, Malaysia

Introduction

Immunization is recognized as one of the most cost beneficial health interventions. Hence almost all countries have some form of immunization schedule, generally targeted at the paediatric population, with aim of reducing the burden of selected infectious diseases.

In Malaysia, the last antigen introduced into the national immunization schedule was Hepatitis B in 1989. Despite the introduction of many new vaccines since then, it was only in 2002 that the Expanded Program of Immunization(EPI) was changed with the introduction of universal two dose Measles, Mumps, Rubella(MMR) and three doses Haemophilus influenzea type B(Hib) in combination with Diptheria, Pertussis and Tetanus(DPT). Why did the Ministry of Health(MOH) choose these two antigens in particular?

In 1982, mass immunization measles was introduced with a monocomponent vaccine given at nine months. This timing was chosen to avoid interference with maternal antibodies while still hoping to give protection to infants vulnerable to the disease. This resulted in a diminishing incidence from 32.8 per 100,000 in 1987 to 2.6 per 100,000 in 1997.

In 1998, 565 cases were reported as follows:
- 206 cases in Peninsular Malaysia (1.3/100,000)
- 269 cases in Sabah (13.5/100,000)
- 90 cases in Sarawak (4.5/100,00)

There were five measles deaths in 1998, all in Sabah and in children below one year old (1).

In 1999 going into 2000, there was a national epidemic with 1452 reported cases. This came as a surprise to many given our good presumed coverage. However, on further in depth study, there were pockets of low coverage, especially in urban areas like the Petaling District. This was not the only reason for the outbreak. A single dose of measles vaccine at nine months gives only 85-95% protection (2). This in combination with a measles coverage that averages at 86% means that there is an accumulation cohort of susceptibles in the population. Experience in other countries shows that when the number of susceptibles equals the birth cohort, which in Malaysia is 500,000 there will be an outbreak of measles (3). Assuming that only 80% of children achieve protection from our immunization program for reasons stated earlier, we can expect an outbreak every five years in Malaysia. Other countries implementing single dose measles have had a similar experience and many have since switched to a two-dose regime. The second dose in this case is strictly not a booster, but rather to mop up those not protected from the first dose.

Hence, the Ministry decided to introduce a two-dose regime.

Routine immunization against Rubella for girls in Standard 6 was introduced in 1986. This was based on the philosophy that since only girls get pregnant, only they need protection from an otherwise mild disease. However, this strategy has failed to prevent the occurrence of congenital rubella syndrome as the virus continues to circulate among the susceptibles in the community passing the disease to pregnant mothers who were not immunized or had a poor uptake. The only way to eliminate congenital rubella is to eradicate the virus from the community. This means that both boys and girls need to be immunized (3).

Mumps is an important cause of acquired deafness and appears to be linked with childhood diabetes. Like Varicella, the disease is more severe in adults. It is incorporated into a vaccine with measles and rubella making up MMR.

Based on the above considerations, the Ministry of Health Malaysia decided to introduce universal MMR for all children at 12 months and at school entry at six to seven years. In addition monocomponent measles was given at six months to children in Sabah only.

This would not, however, avert the next outbreak of measles from the accumulating population of susceptibles. Hence, the Ministry of Health Malaysia decided to have a mass immunization campaign with a

monocomponent measles vaccine for all children from Standard 1 (seven years old) to Form 3 (15 years old) in 2004.

Meningitis is a debilitating disease of children with a 10% mortality and 30-40% of survivors suffer permanent neurological deficits.

In Malaysia, many studies have shown that Haemophilus inflnenzea type B(Hib) is the cause of about half the cases of bacterial meningitis in children under five years (4, 5). Unfortunately Hib is a particularly expensive vaccine and its introduction will increase the Ministry of Health's vaccine budget many fold. However a cost benefit analysis showed that this would be cost beneficial (6). Hence, Hib was also introduced as a combination vaccine with DPT to be given at two, three and five months. Boosters in the second year are not presently part of the EPI.

In order not to create too much confusion on the ground, it was decided to introduce MMR and DPT-Hib at the same time that is July 2002.

Unfortunately, due to various logistic reasons the supply of DPT-Hib has been erratic and the program was only fully enforced from mid-2004. It is hence difficult to judge vaccine efficacy as this time.

Conclusion

The mass immunization against measles succeeded in averting an outbreak on measles in 2004. If the two dose MMR regime is effective, we should not have any more measles outbreaks (7). At present there is nation wide surveillance on measles and congenital rubella, in addition to Hib cases. The results of this surveillance has been encouraging for measles. However, the data on Hib is pending, given the initial teething problems with this vaccine.

References

1. Ministry of Health Malaysia. Information Documentation Unit:Annual Report 1999.

2. MMWR advances in global measles control and elimination: summary of the 1997 International Meeting. 1998/47(RR11) July 24; 1-23.

3. Peltola H, The elimination of indigenous measles, mumps and rubella from Finland by a 12 year, two-dose program. N Engl J Med 1994; 331:1397-402.

4. Choo KE, Ariffin WA Ahmad T, et al, Pyogenic meningitis in hospitalized children in Kelantan, Malaysia. Ann Trop Paediatr 1990 Mar; 10(1):89-98.

5. Hussain IHMI, Sofiah A, Ong LC, et al, Haemophilus influenzae meningitis in Malaysia. Pediatr Infectious Dis J 1998 Sep; 17(9 Suppl): S189-90.

6. Hussain IHMI, Syed AlJunid, Sofiah A, et al, Cost benefit analysis of Haemophilus influnza vaccination programme in Malaysia. *Bulletin Kesihatan Masyarakat University Kebangsaan Malaysia,* 5, 1999; 79-89.

7. Infectious Disease Unit, Public Health Division Ministry of Health Malaysia, Internal Report on Mass Measles Immunization Campaign (unpublished).

REDUCING THE IMPACT OF GENETIC DISEASES: CURATIVE AND PREVENTIVE ASPECTS

Thong MK
Department of Paediatrics, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.

Introduction

As we reflect on the University of Malaya's Centennial Celebration, let us take the opportunity to remember that we celebrated the 50th anniversary of the elucidation of the DNA double helix structure by Watson and Crick, and witnessed the successful completion of the Human Genome Project in 2003. It is not surprising that there are a lot of expectations that this revolution in genetics will pave the way to genomic medicine and gene therapy (1).

Over the next few decades, new information will emerge how individual genes, or groups of genes interacting together with external factors, increased our predisposition certain diseases such as birth defects, cancers, coronary heart diseases, infertility and psychiatric illnesses. It is also expected that identification of 'good' genes may protect us from diseases. Pharmacogenetics will lead to prescribing which is more effectively tailored to the needs of the individual. Genetic testing may become an integral part of health care, becoming faster and more accurate and cheaper and easily available to general practitioners. In short, genetics permeates all fields in medicine (2, 3).

What is the best way to reduce the impact of genetic diseases in the population?

The treatment of genetic disorders required the characterisation of the mutations of the genetic diseases and the understanding of the pathophysiology process of these changes. Therapeutic options included specific dietary manipulation for inborn errors of metabolism, drug therapy to augment gene function such as hydroxyurea in sickle cell anaemia, enzyme or protein replacement therapy and the replacement or removal of abnormal tissues. Recombinant DNA technology has enabled biosynthetic materials such as Factor VII, vaccines and insulin to be produced in large quantities. Stem cell transplantation was successfully used to cure a number of genetic disorders, such as β-thalassaemia major and childhood malignancy. While the curative options are steadily increasing, the number of conditions treated in this manner had remained small (4).

Somatic gene therapy was considered a promising curative option but had remained largely experimental due to a number of technical difficulties (5). Setbacks of gene therapy included the following reports:

1. The number of protein variants outnumbers the number of coding genes. One gene may affect expression of many other genes. For example in Duchenne muscular dystrophy, dystrophin gene mutation downregulates 327 other genes but upregulates 77 genes.

2. Insertional mutagenesis. For example, apparent successful gene therapy for severe combined immunodeficiency (SCID) resulted in 2 / 9 patients who died later of T-cell acute lymphoblastic leukaemia due to activation of an adjacent oncogene.

3. Immunological / toxicity issues. For example, gene therapy for urea cycle defect (ornithine transcarbamylase deficiency) using viral vector was associated with mortality.

4. Targeted delivery of the normal gene copy to all affected tissues, including brain and heart may not be successful.

On the other hand, prevention of genetic diseases (community genetics) was achieved through empowering individuals with information about their genetic risks and enabling them to make informed choices about their reproductive options. Genetic counselling is non-directive. It is a process whereby doctors educate their patients about genetic diseases, discuss whether an inherited disorder is a certainty or just a remote possibility for their future offspring, help patients and their families make informed decision about reproductive options and also help them come to terms with the relevant issues. Clinical geneticists are medical practitioners who, together with other professional colleagues such as social workers and genetic counsellors care for children and families with disorders with a genetic basis (6-9).

Reducing genetic morbidity and mortality would be a secondary goal of prevention. Preventive programmes for inherited disorders included maternal serum screening and ultrasonography (prenatal diagnosis), neonatal screening (glucose-6-phosphate dehydrogenase G6PD deficiency and inherited metabolic disorders) and infant screening (prelingual hearing loss, major birth defects), population screening for genetic diseases (thalassaemia carriers), perinatal strategies to reduce congenital malformations and familial cancer screening (using family history in general practise). All these strategies require a detailed understanding of the epidemiology and natural history of the disorders, genetic testing techniques and their limitations, equitable availability of the programmes to the target population, public education and the availability of genetic counselling (10-11).

Preventative programmes for genetic disorders have been widely used as it is considered clinical and cost-effective. The screening for G-6-PD deficiency is considered to be effective in reducing mental handicap by preventing kernicterus. In the past decade, newer technology has led to expanded newborn screening for 30 metabolic disorders using tandem mass spectrometry. This was advocated as the next step in prevention of genetic diseases. However, Health Technology Assessments on this new approach provided information that it is not cost and clinical effective apart from screening for phenylketonuria and MCAD deficiency in the United Kingdom. In Malaysia, plans are afoot to introduce this program by the Ministry of Health. However a number of issues are unresolved. For example, this newborn screening requires newborn heel prick blood sampling between 48 - 72 hours but most of our postnatal infants are discharged within the first 24 hours. Secondly, parental counselling services, logistic issues (contact tracing of at risk infants) and support services are not easily available (12-14).

The Center for Disease Control (CDC) Office of Genomics and Disease Prevention in collaboration with National Institutes of Health, USA have embarked on a public health initiative to evaluate on the use of family history information to asses risk for common diseases and to influence early detection and prevention strategies in 2002 (Family History Public Health Initiative). By using an easy to follow 'Family History Tool' to assess risk classification for each individual, it was feasible to stratify public health and personalised recommendations for each family. Therefore family doctors and public health practitioners have their roles to play in reducing genetic disorders in the community (15-17).

The ethical, legal, social and religious implications of this 'new genetics' must be carefully evaluated and debated. Recently it was announced that the Ministry of Health of Malaysia would screen the population for thalassaemic trait as part of the Thalassaemia Control program. While this is a laudable move, there are a number of the above considerations that must be taken into account before population screening can be done. For example, will genetic counselling be provided to the population? Which age groups will be screened? Will prenatal diagnosis and termination of pregnancy for affected fetuses be allowed in government hospitals if two thalassaemic carriers decided to start their family? (18-20).

Conclusion

It is recommended that both suitable curative and preventive aspects be utilised to reduce the impact of genetic diseases. Genetic counselling should remain the mainstay of all genetic services as empowering at-risk families and individuals should be a priority. Guidelines and regulations must be established to recognise the patient's fundamental rights of informed consent, informed choice, autonomy and confidentiality (21-24).

References

1. Guttmacher AE, Collins FS. Genomic medicine a primer. N Engl J Med 2002; 347: 1512-20.

2. World Health Organization. Services for the prevention and management of genetic disorders and birth defects in developing countries. Report of the joint WHO/WAOPBD meeting (WHO/HGN/GL/WAOPBD/99.1) 1999.

3. World Health Organization. Primary health care approaches for prevention and control of congenital and genetic disorders. (WHO/HGN/WG/00.1) 2000.

4. Juengst ET. What next for human gene therapy? Br Med J 2003; 326: 1410-11.

5. Emery AEH. Genetic medicine - today's perspective. J R Coll Physicians Edinb 2004; 34: 187-191.

6. The International Centre for Birth Defects (ICBD). Guidelines for the development on national programmes for monitoring birth defects. (World Health Organization, Hereditary Diseases Programme, Geneva), 1993.

7. Rosano A, Botto LD, Botting B, et al., Infant mortality and congenital anomalies from 1950 to 1994: an international perspective. J Epidemiol Comm Health 2000; 54(9): 660-666.

8. Thong MK. Epidemiology of birth defects in Malaysian births. Master of Paediatrics Thesis, Kuala Lumpur: University of Malaya. 1995.

9. Yoon PW, Olney RS, Khoury MJ, et al. Contribution of birth defects and genetic diseases to paediatric hospitalisations. Arch Paediat Adoles Med 1997; 151: 1096-1103.

10. Harper P. Practical Genetic Counselling 4th Edn. Wright: Butterworth and Co. Ltd. 2003.

11. Modell B, Kuliev AM. A scientific basis for cost-benefit analysis of genetic services. Trends in Genetics 1993; 9: 46-52.

12. Thong MK, Choy YS, Rowani MR. Inborn errors of metabolism. Malaysian Journal of Paediatrics and Child Health 2001; 13 (1&2) : 19-26.

13. Seymour CA, Thomason MJ, Chalmers RA, et al. Newborn screening for inborn errors of metabolism: a systematic review. Health Technol Assess 1997;1(11):195.

14. Pandor A, et al. Clinical effectiveness and cost-effectiveness of neonatal screening for IEM using tandem mass spectrometry: a systematic review. Health Technol Assess 2004; 8: No 12.

15. Yoon PW, Scheuner MT, Khoury MJ. Research priorities for evaluating family history in the prevention of common chronic diseases. Am J Prev Med 2003; 24.

16. Yoon PW, Scheuner MT, Gwinn M, et al. Awareness of family health history as a risk factor for diseases. United States, 2004. MMWR 2004; 53 (44) 1044-1047.

17. Scheuner MT, Yoon PW, Khoury MJ. Contribution of mendelian disorders to common chronic disease: Opportunities for recognition, intervention and prevention. Am J Med Genet 2004; 125C: 50-65.

18. Thong MK, Law HY, Ng ISL. Molecular heterogeneity of β-thalassaemia in Malaysia: a practical approach to diagnosis. Ann Acad Med Singapore 1996; 25: 79-83.

19. Ostrowsky J, Lippman A, Scriver C.(1985) Cost-benefit analysis of a thalassemia disease prevention program. Am J Public Health; 75(7):732-6.

20. Thong MK. Molecular heterogeneity of beta thalassaemia in Malaysian children. Doctor of Medicine (M.D.) thesis, Kuala Lumpur: University of Malaya, 2004.

21. Alwan A, Modell B. Recommendations for introducing genetic services in developing countries. Nature Rev Genetics 2003; 4, 61-68.

22. Davis MK, Khoury MJ, Erickson JD. Pregnancy experience after delivery of a child with a major birth defect: a population study. Paediatrics 1995; 95, 59-65.

23. Editorial. The Clinical Geneticist and the 'New Genetics'. Med J Aust 2003;178(9):458-462.

24. World Health Organization. International Guidelines on ethical issues in medical genetic and genetic services. Report of a WHO meeting on ethical issues in medical genetics. 1998 Geneva, 15-16 December 1997. Pub. WHO/HGN/GL/ETH/98.1.

CHALLENGES IN POSTGRADUATE MEDICAL EDUCATION:THE UK SOLUTION

Kenneth MC
Dean of Postgraduate Medical Education, University of Glasgow, NHS Education for Scotland, Scotland

Introduction

In 2003, the UK Health Department published a policy statement on Modernising Medical Careers. In this, they set out the principles underpinning major reforms of Postgraduate Medical Education and Training. This reform was driven by the belief that there was a lack of structure to much of the training, training for many was unnecessarily long, assessment methods were poorly developed, and there was an increasing expectation that service would be delivered by trained staff rather than trainees. In addition, the reforms were driven by the need for care based on more effective teamwork, a multi-disciplinary approach, and more flexible training pathways tailored to meet not only the service but the trainees' personal needs. Above all, the driver for change was a need to improve the care delivered to patients.

The key principles to be followed were -
- Programme-based training
- A broad-based training in the initial years
- Programmes that were time limited
- A facility to move between programmes
- Flexible training opportunities
- Improved career advice at all stages of undergraduate and postgraduate training

Following graduation from medical school, trainees will enter a two-year foundation programme. During this time they will be expected to develop core skills and achieve levels of competence that will be incremental, ie appropriate to their stage of training. There will be an emphasis on the ability to manage acute emergencies. The programme will allow in the two-year period an opportunity to experience six specialties, this including both community and hospital care.

At the end of this time, the trainee will have generic skills covering -
- Clinical skill
- Effective relationships with patients
- Clinical governance and safety
- Use of evidence and data
- Communication
- Teamworking
- Time management
- Effective decision-making
- Understanding different settings

Following two years of foundation, trainees will competitively enter specialty training programmes. For some specialties there will be direct entry following foundation programme, but for others there will be one or two basic specialty training years before sub-specialization.

In order to successfully deliver these changes, a curriculum has been published for foundation programme, and each specialty is producing its own curriculum which will have to meet strict criteria.

Best practice in selection programmes will be followed promoting equality and diversity within medicine.

For progression through the training programmes there will be in place robust assessment methods. These will include -
- A knowledge test specific to each specialty
- Work-based assessment, for example case-based discussion, directly observed procedures or skills and multi-source feedback
- Presented evidence, for example a personal development plan and reflective educational logbook
- Supervisor's report
- A summative record of training and assessment

These methods are either currently proven or are being piloted in advance of the start of the changes.

In order for such a radical change to be introduced, it is important that clinical and educational supervisors are understanding of the reasons for change and trained in the assessment methodology.

With these changes there are a number of implications. The current Consultant Workforce will not only need training but time to carry out the rigorous assessments described above. While training will be structured, more intensive, and of shorter duration, the contribution of the trainee to the delivery of care of the patients

(service) will be reduced. This has major implications for the health service, and the transition from the status quo to a point where the service is delivered by trained doctors rather than doctors in training needs to be carefully managed.

Questions, therefore, arise as to whom will backfill for trainees who are not contributing in the same way to service and for Consultant colleagues who will be training rather than delivering service.

Conclusion

There is, therefore, an opportunity for others within the healthcare system to take on new and extended roles. This has its own financial implications.

The rationale for change is accepted. The implications for the current workforce, for future trainees, for other healthcare workers, and for those responsible for financing the healthcare system has to be addressed.

Inevitably, the tensions that exist between training and education and service delivery remain.

THE UNIVERSITY OF MALAYA MEDICAL CENTRE NURSING SERVICES: RECOLLECTIONS AND DEVELOPMENT

Phan CY
In-patient Services, University of Malaya Medical Centre, 50603 Kuala Lumpur, Malaysia

Introduction

The University of Malaya Medical Centre (UMMC), formerly known as University Hospital is a classless teaching hospital situated in the Federal Territory of Kuala Lumpur.

The Hospital, an integrated part of the Medical Faculty of University Malaya, comes under the Ministry of Education. Its organization and administration is the responsibility of (a) the Hospital Director, (b) the Medical Staff Advisory Committee and (c) the Hospital Board of Management. The primary aim of the hospital is to provide facilities for undergraduate and postgraduate medical education, internship and resident programmes, basic and post-basic training of nurses as well as for research.

Development

Phase I of the Hospital, consisting of the main block of wards and the podium (operating theatres, radio-diagnostic, accident and emergency, policlinic, pharmacy, central sterile supply, cafeteria, administration and medical record) was completed in December 1966. The first block of wards was opened in March 1967. Gradually, more wards, the Polyclinic and the 24-hour Accident and Emergency unit, started to provide services for the public. Phase II, consisting of the paediatric, maternity and rehabilitation units became functional in March 1968. Three additional blocks, the Primary Medical Care (1992), the East Wing (1997) and the Trauma and Emergency (2004) were added to the complex.

In 2003, the Examination wards and the Infectious Disease wards were opened. Finally, the foundation for the Woman and Child Centre had been laid. A Rehabilitation Centre is on plan. The Hospital started with 336 beds and had reached 878 beds since 1989.

Responsibilities of nursing administration

The Nursing Service Department sets the nursing philosophy, objectives, standards of care and types of nursing care delivery. It plans the recruitment and placement of nursing personnel and provides orientation to new staff. It is also responsible for providing in-service training programmes for the existing staffs and for the competency of nurses.

The nurses deliver nursing care by using the Nursing Process, i.e., they assess, plan, implement and evaluate care given. Each nurse is assigned a number of patients and she is responsible for the total care of her patients.

Nursing service and nursing heads

The Nursing service has come a long way since 1967. As expected, the type of nursing care and services provided, depends very much on the philosophy and objectives of the chief matron as well as the resources available during her term in office.

University Hospital has four chief matrons since 1967 and each matron had left behind her stamp on the nursing administration.

Nursing heads of yesteryears

The four Nursing Heads were:

1. Mrs Beri (1966-1968)
   An American who was employed by University Hospital to recruit nurses and to help set up the hospital.

2. Late Madam A K Nooi (1968-1977)
   A retired matron from Tung Shin Hospital, was a firm and non-assuming lady who laid the groundwork for the nursing service in UMMC.

3. Mrs. Hajjah Sawiah A Rahman (1977-1990)
   A dynamic and bubbly matron, was a survivor who accepted all challenges in the course of her work. Implemented a shorter night-duty shift (from 7 to 4 nights) which greatly reduced absenteeism.

4. Ms. Sofiah Abd Rahman (1990-1999)
   A steady and unassuming matron who believed in training and upgrading nursing competencies. Nurses were sent for courses and attachments both locally and overseas. Faced with the crisis of an acute shortage of nurses due to huge resignations, a reduce number of intake of student nurses and the demand of extra nurses for new services (medical specialization), she took drastic but unpopular steps to correct the situation. A few wards were closed, staff nurses from Polyclinic were deployed to work in the wards. A new post, the clinical assistant, was created. School leavers were recruited and trained to perform simple nursing procedures. Also, special allowances were given to keep the existing nurses in service.

Restructuring of nursing services

In 1997, the nursing unit was restructured in the name of corporatization. The post of Chief Matron was abolished. Instead, four responsibility centres were set up and four nursing officers were appointed to take charge of the Ambulatory unit, the In- Patient, Critical and OT Services and Nursing Policy. They report to the deputy director (clinical) and are assisted by their assistants. The ward sisters take charge of the wards, supervise the assistant nurses/ midwives, the clerks and the attendants. Working together with the ward sisters are the clinical nurse specialists, to whom difficult cases such as big wounds, stoma care, etc., are referred. The clinical nurse specialist also has the duty to educate, supervise and prepare patients for home care.

Nursing workload

With the expansion of the hospital, the nursing workload has increased. In 1967, the number of admissions was 1600, now it is about 50,000 admissions annually.

Clinic attendance has increased tremendously over the years. In 1967, the number was 100,000, now it is 500,000 a year.

The number of nurses had increased from 30 in 1967 to 1336 in 2004.

Additional services

The Post-surgical Care Area (PASCA) functioned since 3rd August 1998 to monitor and observe post-surgery ill patients and the Day Care Surgery was started in 2002. Apart from the usual out patient activities, the ambulatory unit offers special services to TB patients, immunization services, staff health services, diabetes and podiatry counselling services. The unit also manages the patient information centre. The latest additional services are the admission and discharge unit, the wellness and occupational health clinics.

Challenges

The Nursing Service faces the challenge of having too many junior staff nurses (31.2 % with less than three years of experience; 37.6 % with less than five years of experience). They lack assessment and analytical skills and therefore are unable to recognize potential problems of patients. They need close supervision.

The second challenge is the frequent demand for expansion of services when there is still a shortage of facilities and manpower.

Conclusion and Recommendation

We hope the government will introduce a salary scheme for graduate nurses. This will make nursing more attractive as a profession. At present, the nursing education and training is hospital-base. This must be shifted to a university. In the university, nursing students will have the time, opportunity and the environment to grow socially, intellectually and to develop their potentials to the fullest. Nurses also need to develop the 'soft skills', such as communication, interpersonal and social skills in dealing with people. With better training, nurses should become more professional in the discharge of their duties. This will gain them the respect from the public. In this way, nurses can carry the image of nursing to a higher level.

PALLIATIVE CARE IN THE COMMUNITY

Ednin H
Hospis Malaysia, Kuala Lumpur, Malaysia

Introduction

Over the years, the medicalisation of dying has resulted in a loss of the capacity of our community to accept death and dying as meaningful aspects of life. Death is being fought at all stages of the life cycle with a devaluation of family care and the traditional rituals surrounding death and dying (1,2). The result is that dying patients are sometimes trapped between the two evils of technology that tries to keep bodies alive indefinitely and a clamour for physician assisted suicide as the only alternative to physician assisted suffering (3). The result is that homes have become adapted into not only an environment for living but also becoming constructed into places for healthcare needs. This may include values that may be incongruent with the inherent home culture. Where homes allow for social and spiritual growth, they may be transformed into a mini medical model complete with all the paraphernalia that identifies a hospital environment.

However, community based palliative care is increasingly becoming more relevant to the community due to failures of hospital based curative treatment, a desire for supportive care service to improve outcome and end-of-life care. This may be at the request of patients, families and recently, doctors. The paradox is that despite most dying patients preferring to remain at home, many die in institutions (4,5). Many are not consulted as to their wishes. Thus whilst many families may on one hand want comfort for their loved one in their final days, the lack of acceptance and fear of issues relating to death may produce an alternate ending.

Findings

The relevance of a community based palliative care service requires the understanding of end-of-life issues pertaining primarily to the patients and their families as well as the inherent resources within the community. It requires an appreciation into issues relating to diseases, communication, social circumstances, spirituality and ethics. The role of general practitioners (6), community palliative care services, hospital based community services, volunteer support groups and others should not be devalued. The role of government in providing guidance and legislation in end-of-life care is also relevant.

Much work has been done in evaluating the needs of patients and families. Caregivers themselves have a great deal to contend with in caring for patients at home. They have high needs and suffer from their own psychological morbidity. Assistance in problem solving, nursing care, social support as well as respite care are core areas which needs to be addressed (7,8).

Patients and families want information. This relates to the disease, psychological issues, social welfare, basic caregiving skills, palliative care and spirituality (9). Information; its timing, delivery and perceived attitude of practitioners, content and trust is important (10). This information is then often rechecked with other sources. In dealing with cancer, the communication between doctor and patient often relates to a scenario where false optimism about recovery is transmitted which later may recede as disease progresses (11).

It would certainly be very helpful if hospital clinicians adopt a more patient centred supportive care approach especially in dealing with situations requiring end-of-life care. Suggested questions could be 'what is the most important issues in your life right now?', 'What is your greatest worry?','How do you see the future?','Are there times when you feel down?' and 'What helps keep you going?' are a few suggestions that may help guide the clinician in what really matters.

Patients and families face a multitude of medical dilemmas. They need to be aware of not only the aims of medical investigations and disease interventions but only the uncertainty of the disease trajectory, the management of co-morbidities, the expressed wishes of the patient and other interested parties all within the social framework of the 'family' environment. In being referred for community based palliative care, patients and caregivers derive much information from secondary

sources and personal / related experiences. Hospital physicians do need to be more aware and up to date of community palliative care services and their available resources.

Palliative Care has evolved into a specialty that is based on improving quality of life for patients and families by early assessment and intervention of all aspects of suffering (12). Palliative care services are now starting to show a trend to patient satisfaction and therapeutic intervention (13). Many of the medical issues such as pain and symptom control, hydration and nutrition, dyspnoea, wound management, nursing care which may involve complex medical intervention are now entirely manageable in the home, assisted by palliative care services.

Dealing with psychological and spiritual concerns, role of alternative and complementary therapies, miscommunications and misconceptions and taboo topics such as sexuality and death may be areas that require intervention and responsible palliative care practitioners will engage actively to reduce fear, anxiety and promote well-being.

Conclusion

In order to be relevant to the needs of the community, a palliative care service needs to be adept at the assessment, identification and management of all symptoms pertaining to the illness experience. They should be accessible and provide a rapid response to patients and families. Information gathering and dissemination, education and training are a core function which requires excellent communication skills. Resources such as medication and equipment associated with symptom relief are also required. A multi-disciplinary team with varying levels of skills allows a palliative care service to adapt itself to the challenges in the community. Linkages with supportive services such as in-patient palliative care, oncology and specialist pain services where possible are useful. Some community palliative care services may also offer volunteer support and the provision of day care. As the death of the patient approaches, dealing with anticipatory grief and bereavement are also a crucial aspect of the needs of the family and should not casually overlooked.

The referral of patients for palliative care should be based on need rather than on prognosis as the ability of doctors to prognosticate in end-of-life care is poor (14). Difficult issues remain. Prognostication, difficult symptoms such as asthenia-cachexia, difficult communication issues, spirituality, legal and ethical issues will continue to challenge palliative care for some time. It is, however, a challenge to be relished.

References

1. Clark D. Between hope and acceptance: the medicalization of dying. Br Med J 2002; 324:905-907.
2. Illich I. Limits to medicine : medical nemesis: the expropriation of health. London : Marion Boyars, 1976.
3. Morris D. Illness and culture in the postmodern Age. London: University of California Press, 1988.
4. Thorpe G. Enabling more dying people to remain at home. Br Med J 1993; (307):915-8.
5. Palliative Care: Fourth Report of Sessions 2003-4 www.parliament.uk/parliamentary _committees/ health_committee.cfm.
6. Mitcell GK. How well do general practitioners deliver palliative care? A systematic review. Palliat Med 2002 Nov; 16(6):457-64.
7. Harding R, Higginson IJ. What is the best way to help caregivers in cancer and palliative care? A systematic literature review of intervention and their effectiveness. Palliat Med 2003 Jan; 17(1):63-74.
8. Hauser JM, Kramer BJ. Family caregivers in palliative care. Clin Geriatr Med 2004 Nov; 20(4):671-88.
9. Lin WC, Tsao CJ. Information needs of family caregivers of terminal cancer patients in Taiwan. Am J Hosp Pall Care 2004; 21(6):438-44.
10. Kirk K, Kirk I. Kristianson L. What do patients receiving palliative care for cancer and their families want to be told? A Canadian and Australian qualitative study. Br Med J 2004; 328:1343.
11. Anne-Mei T, Hak T, Koeter G, et al. Collusion in doctor-patient communication about imminent death: an ethnographic study. Br Med J 2000; 321:1376-81.
12. WHO definition of Palliative Care, 2002.
13. Higginson IJ, Finlay IG, Goodwin DM, et al. Do hospital based palliative care teams improve care for patients or families at the end of life? J Pain Symptom Manage 2003. Feb; 25(2): 150-68.
14. Christakis N, Lamont E. Extent and determinants of error in doctors' prognosis in terminally ill patients: prospective cohort study. Br Med J 2000; 320:469-473.

PAIN MANAGEMENT IN PATIENTS WITH ADVANCED CANCER

Vijayan R
Department of Anaesthesiology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Introduction

The number of cancer patients in the world is increasing. Of the estimated nine million new cancer cases every year, more than one-half occur in the developing world. The majority of these patients present with advanced disease, when pain management and palliative care are the only options available.

The incidence of pain at various stages of the disease trajectory is approximately 50%; it increases to 75% in patients with advanced cancer (1). Most patients with advanced cancer have two or more types of cancer related pain, sometimes with different aetiology (2) see box. It has been estimated that up to 90% of cancer pain could be effectively controlled using the World Health Organization (WHO) guidelines (3). However, evidence indicates that cancer pain is often under-diagnosed and under-treated even in developed countries (4, 5). The pain of malignant disease may have physical, psychological, social and spiritual dimensions, and this must be taken into consideration when planning treatments.

There is little doubt that failure to control cancer pain generally is due to a lack of careful assessment of the patient and the pain along with a failure to apply the cancer pain guidelines as outlined by the World Health Organization (WHO). The fundamental concept that underlies appropriate and successful management of cancer pain is:

Assessment and definition of the patient's pain

The origin of the pain must be identified along with its intensity and its impact on the quality of life.

The aetiology of cancer pain can be broadly classified as:

A. pain associated with direct tumour involvement.
B. pain associated with therapy.
C. pain associated with chronic illness.
D. pain unrelated to cancer and cancer therapy, and
E. combination of the above.

Assessment of cancer pain includes:

- ***Characterization of Pain***
  It includes assessment of location, radiation, onset, duration (constant or intermittent), quality (burning, dull, gnawing, lancinating or paroxysmal), aggravating factors (such as movement), relieving factors (including response to analgesics) and any neurological deficits. This detailed assessment usually assists in determining the pathophysiology of pain and facilitates the selection of appropriate drug therapy.
- ***Intensity of Pain***
  As pain is a very subjective sensation, assessment by the patient is generally considered to be the gold standard. It can be performed by any tool (Visual analogue or numeric rating scale or a five point verbal scale) depending on the level of the patient's understanding.
- ***Multidimensional assessment***
  In addition patients with cancer present with multiple symptoms such as fatigue, anorexia, nausea, vomiting, dyspnoea, drowsiness, depression, anxiety, sleep disturbance and a general sense of being unwell (6). Coexistence of other symptoms such as anxiety may alter the way a patient perceives pain.
  Multidimensional assessment is of great importance. Any system used particularly in debilitated patients must be quick, simple, valid, reliable, sensitive and clinically relevant. Either numeric rating or visual analogue scales (VAS) are simple and effective for many of these symptoms. An example of a simple, validated multiple symptom assessment tool that utilises VAS is the Edmonton Symptom Assessment System -ESAS (7).
- ***Other Factors***
  Factors such as individual patient's beliefs, cultural background should be taken into consideration. It is important to realize that fear of tolerance and addiction to opioid mediation, fear of treatment side effects and various beliefs and expectations can all contribute to patient's reluctance to report pain.

Management

Successful management of the cancer patient with pain depends on the ability of the clinician:

- To assess initial problems
- Identify and evaluate pain syndromes (see above)
- Formulate a plan for continuing care, both for the patient and family.

Comprehensive cancer care encompasses a continuum that progresses from disease-orientated, curative, life-prolonging treatment through symptom-orientated, supportive and palliative care extending to terminal hospice care. Pain management is, and should be, an integral component of comprehensive cancer care. Designing an effective pain control strategy for the individual patient requires knowledge of the ways in which a patient's cancer, cancer therapy and pain therapy can interact.

The guiding principle is to individualize the approach to the patient's needs depending on the stage of the disease, prognosis and life expectance.

- Primary therapy of the cancer is considered the first priority, i.e., surgery, chemotherapy or radiotherapy.
- Pharmacotherapy – for pain relief. Pain can be incorporated at every stage of the illness
  - pain due to the tumour,
  - pain due to therapy, and
  - pain unrelated to the cancer.

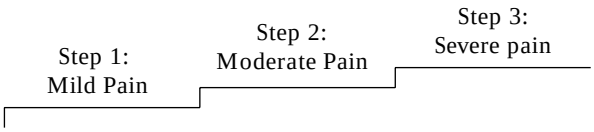
In 1982, the World Health Organization (WHO) initiated a programme, which aimed to improve the treatment of cancer pain worldwide. Their guidelines were published in 1986 (8). While these guidelines have been criticized as simplistic, they are in fact sophisticated but presented in a simplistic manner. To use the WHO guidelines involves:

1. a careful patient assessment (as indicated above),
2. appropriate choice of drugs,
3. careful drug titration with care to avoid or anticipate side effects, and
4. reassessment and appropriate adjustment of the regimen.

It must be remembered that these guidelines were never meant to be used as an alternative to other cancer pain management strategies, but as an integral part of the spectrum of treatments available. Radiotherapy, chemotherapy, surgery, physiotherapy, nerve block techniques, acupuncture, relaxation therapy are some of the common strategies used as appropriate in individual patients.

The core of these guidelines is a 3-Step analgesic ladder which, depending on individual pain intensity, progresses from Step 1 to 3.

W.H.O. Analgisic Step-ladder



Step 1	(Mild pain)	Non-opioids ± adjuvant
Step 2	(Pain persisting – Mild – moderate pain)	Weak opioids ± non-opioid ± adjuvant drugs
Step 3	(Pain persisting/ increasing – Moderate to severe)	Strong opioids ± non-opioid ± adjuvant

(Table 1 and 2)

These guidelines have been validated by Ventafridda, *et al* (9) and Zech, *et al* (10) who found that up to 88% of patients obtain satisfactory relief.

Table 1. Systemic analgesics used in Cancer Pain.

Type	Drug
Non opioid	Paracetamol NSAIDs / COX-2 inhibitors
Weak Opioid	Codeine Dihydrocodeine Tramadol
Strong Opioid	Morphine Hydromorphone Oxycodone Fentanyl (including Transdermal/ Transmucosal routes) Methadone

Palliative oncological therapy, adjuvant drugs and other symptomatic therapeutic measures may be integrated into every analgesic step.

Pethidine is not recommended for use in severe pain associated with cancer. It has a short half-life and its metabolite norpethidine is toxic (11). Partial agonists such as buprenorphine are best avoided because of their low maximal efficacy. Mixed agonist-antagonist drugs such as pentazocine and butarphanol and nalbuphine should be avoided as they also have the potential to precipitate withdrawal in patients receiving full agonists (12).

Guidelines for analgesic therapy

1. Pharmcotherapy forms the mainstay of cancer pain control and should as far as possible be given by the oral route. Treatment of cancer pain should begin with a straightforward explanation to the patient of the causes of the pain or pains. Many pains respond best to a combination of drug and non-drug measures.

2. The choice of analgesics depends on the intensity of pain, type of pain and their effectiveness depending on whether the pain is nociceptive or neuropathic in character or a combination.
   A. ***Nociceptive Pain.*** E.g., pain arising from:
   - Visceral structures such as the liver, pelvic organs, bowel, lung,
   - Deep somatic structures such as chest wall infiltration with tumour in Carcinoma of the breast,
   - Bone secondaries, and
   - Nociceptive pain is more responsive to opioids and NSAIDS.

   B. ***Neuropathic Pain.*** (Pain due to injury to nerves) e.g.,
   - Tumour infiltration of the brachial plexus / lumbosacral plexus.
   - Neuropathic pain is less responsive to opioids and is managed with anticonvulsant and antidepressant drugs.

3. Cancer patients frequently have more than one type of pain. A combination of analgesics is usually necessary to ensure maximum pain relief.

4. Drugs should be always given in a suitable dose on a time contingent basis and ***never on a PRN*** basis.

5. There should be rapid progression from Step 1 through to Step 3 of the ladder and early use of adjuvant drugs is recommended (Table 2).

6. If pain relief is inadequate despite Strong opioid therapy, reevaluate and reassess the patient

Which opioid for cancer pain?

There are a number of potent opioids that are currently available to control severe pain – Morphine, oxycodone, hydromorphone, fentanyl, methadone. However morphine remains the gold standard, as it is inexpensive, can be given by the oral route and is easily titratable. However, the choice of opioids depends largely on their availability in individual countries. Morphine and transdermal fentanyl are the two commonly used opioids in most developing countries of Southeast Asia. Unfortunately, due to strict regulations, morphine is not readily available in many countries and transdermal fentanyl is expensive. Difficult access to potent opioids is one of the reasons for inadequate cancer pain relief in many countries.

Table 2. Adjuvant drugs used in cancer pain.

Type	Drug	Main indications
Anticonvulsants	Clonezepam Carbamazepine Gabapentin	• Neuropathic pain, nerve injury dyaesthesia • Stabbing in quality
Antidepressants	Amitriptyline Nortriptyline	• Neuropathic pain - burning in quality
Corticosterioids	Prednisolone Dexamethasone	• Headache - raised intracranial pressure • Spinal cord injury
Spasmolytics	Butylscopolamine	• Colicky pain
Anxiolytics / hypnotics	Benzodiazepines	• Anxiety, insomnia
Laxatives	Lactulose, Senna alkaloids	• Constipation
Anti-emetics	Metaclopramide Ondansetron	• Nausea / vomiting
Topical agents	EMLA, lignocaine viscous	• Oral mucositis, oropharyngeal ulceration
Bisphosphonates	Pamidronate	• Multiple myeloma • Bone metastases - breast cancer
Calcitonin	Salmon-calcitonin	• Bone metastases
NMDA antagonist	Ketamine - low dose	• Neuropathic pain

Transdermal fentanyl (TTS Fentanyl) can be useful in patients who have swallowing difficulties or in the presence of vomiting. Since it has a 72-hour dosing schedule, there is better patient compliance and a tendency for less constipation. Oxycodone, when available, may provide an alternative to morphine if hallucinations and disturbed sleep are troublesome. However, physicians in many countries do not have the luxury of providing opioid rotation for their patients.

Strategies for cancer pain in patients who are poorly responsive to systemic opioid therapy

Even if under-treatment where to be eliminated, some cancer patients continue to experience an unsatisfactory balance between analgesia and side effects, despite efforts to optimize the dose. These patients must be considered for alternative analgesic strategies.

'Opioid responsiveness' may be defined as the probability that adequate analgesia (satisfactory analgesia without intolerable and unmanageable side effects) can be attained during gradual dose titration. Alternatively, responsiveness - either in an individual or population of patients - can refer to the degree of analgesia obtained at treatment-limited toxicity.

Difficult pain syndromes and poor prognostic factors

Main risk factors for poor pain control are (13, 14):

- Neuropathic pain - compression, invasion, destruction of the peripheral or central nervous system,
- Incidental pain - pathological fracture or movement pain,
- Tolerance - drug tolerance or increasing underlying disease,
- Psychological distress - major depression, hostility to the health care system, and
- Alcohol or drug abuse - past history of such an abuse.

It is important to identify patients with poor prognostic pain syndromes in order to optimize their management with more complex approaches.

Four distinct strategies (Table 3) should be considered when a patient is recognized as responding poorly during the trial of systemic opioid therapy (15).

Unfortunately, the selection of the best approach for the individual patient with poor responsive is hampered by the absence of clinical trials that have compared the

Table 3. Alternative strategies for poorly responsive pain

Approach	Therapeutic options
1. Opening the 'therapeutic window'	• More effective side effect treatment. E.g., a psychostimulant for sedation
2. Identifying an opioid with a more favourable balance between analgesia and side effects	• 'Opioid rotation'
3. Pharmacological techniques that reduce system opioid requirements	• Co-administration of a non-opioid analgesic and adjuvant • Neuraxial opioid (spinal opioid infusion) • Myofascial trigger point injections
4. Non pharmacological techniques to reduce opioid requirement	• Neurolytic procedures – Coeliac plexus block – Hypogastric plexus block – Epidural neurolysis • Neuro-ablative procedures – Cordotomy • Rehabilitative – Bracing – TENS • Psychological – Education – Cognitive behavioural therapy • Complimentary – Acupuncture – Traditional Massage

various treatments.The choice of one therapy over the other depends on the individual patient, the experience of the clinician and his judgment and the availability of the modality.

Invasive techniques

Pain associated with cancer can be adequately controlled in 75 - 80% of patients with the judicious use of drugs. In the other 20 - 25% of patients, invasive techniques may be required for optimum control of pain. It should be considered when side effects are intolerable such as severe sedation. It can reduce analgesic requirements and provide a better quality of life.

1. ***Nerve blocks***
   - Using local anaesthetics or neurolytic agents
   - Local anaesthetic blocks have a temporary effect but can be prolonged using continuous infusions via catheters.
   - Trigger point injections - myofascial pain

2. ***Neurolytic procedures***
   - Coeliac plexus block with alcohol for carcinoma of the pancreas, liver cancer
   - Hypogastric plexus block with phenol in water - pelvic malignancies
   - Intrathecal phenol / glycerol - carcinoma of the rectum, bladder
     (Neurolysis implies the destruction of neurons by placing a needle close of the nerve (or plexus or spinal cord) and injecting a neurodestructive chemicals or producing neural damage with cold (cryotherapy) or heat (radiofrequency coagulation -
   - Ethyl alcohol, phenol and glyercol in varying concentrations cause Wallerian degeneration of neurons, which usually spares the basal lamina around the Schwann cell tube. This permits regeneration that accounts for the return of function and pain some weeks after the block.
   - There is a renewed interest in neurolytic procedures (16, 17), particularly where the health care system cannot afford newer expensive technologies, such as spinal opioids (see below), or where medications are not available to utilize the WHO ladder. These procedures should be thought of as part of the pain therapy and not as a curative modality.

3. ***Spinal opioids (intrathecal or epidural) via a catheter***
   - Temporary or permanent catheters and pumps are placed and morphine continuously infused to provide pain relief.
   - Avoids the sensory and motor block associated with neurolytic blocks
   - Analgesic requirements are a fraction of the systemic dose and hence patients are not as sedated or confused as when systemic opioids are used.
   - However, it is an expensive procedure and requires good domiciliary nursing care to provide syringes of morphine regularly.

Effective pain relief can therefore be achieved by an organized approach.

a. treating the disease,
b. pharmacotherapy,
c. interrupting the pain pathways (if indicated), and
d. supporting the emotional and social well being of the patient.

Total pain

The concept of 'total pain' encompasses psychological, social and spiritual factors, as well as the physical aspects of pain. Patients experience overwhelming pain from all directions and the support of the whole team is necessary to help them cope with their immense distress.

These factors are similar regardless of the aetiology of chronic pain. However, the impact of cancer pain on the patient and the family is greater than that of non-malignant acute or chronic pain.

Conclusion

It is important to understand the various factors that alter (diminish or exacerbate) ones perception of pain when addressing cancer pain. Many of these issues should be addressed in tandem with other modalities.

References

1. Bonica JJ. Cancer pain. In: Bonica JJ, ed. The Management of Pain. Philadelphia: Lea and Febiger, 1990; 403.

2. Foley K. The treatment of cancer pain. N Engl J Med 1985; 313:93.

3. Schug SA, Zech D, Dorr U. Cancer pain management according to WHO analgesic guidelines. J Pain Symptom Manage 1990; 5: 27-32.

4. World Health Organization. Expert Committee Report 1990. Cancer Pain Relief and Palliative Care. Technical Series 804. Geneva: World Health Organization, 1990.

5. Von Roenn JH, Cleeland CS, Gronin R et al. Physician's attitudes and practice in cancer pain management. A survey from the Eastern Cooperative Oncology Group. Ann Intern Med 1993; 119: 121-126.

6. Bruera E. Research into symptoms other than pain. In: DoyleD, Hanks GW, Macdonald N (Eds). Oxford Textbook of Palliative Medicine. Oxford: Oxford University Press, 1998; 179-185.

7. Bruera E, Kuehn N, Miller MJ, et al. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care 1991; 7: 6-9.

8. World Health Organization. Cancer Pain Relief. Geneva, Switzerland: World Health Organization, 1986.

9. Ventafridda V, Tamburini M, Caraceni A, et al. A validation study of the WHO method for cancer pain relief. Cancer 1987; 59: 850 - 856.

10. Zech DF, Grond S, Lynch J, et al. Validation of World Health Organization guidelines for cancer pain relief: a 10 year prospective study. Pain 1995; 63: 65-76.

11. Kaiko RF, Foley KM, Grabinski PY, et al. Central nervous system excitatory effects of meperidine in cancer patients. Ann Neurol 1983; 13: 180-185.

12. Hoskin PS, Hanks GW. Opioid agonist-antagonist drugs in acute and chronic pain states. Drugs 1991; 41: 326-344.

13. Bruera E, Schoeller T. et al. A prospective multicenter assessment of the Edmonton staging system fro cancer pain. J Pain Symptom Manage 1995; 10: 348-355.

14. Mercandante S, Portenoy RK. Opioid poorly responsive cancer pain. Part 1. Clinical consideration. J Pain Symptom Manage 2001; 21: 144-150.

15. Mercandante S, Portenoy RK. Opioid poorly responsive cancer pain. Part 3. Clinical strategies to improve opioid responsiveness. J Pain Symptom Manage 2001; 21: 338-354.

16. de Leon-Casasola OA, Kent E, Lema MJ, et al. Neurolytic superior hypogastric plexus block for chronic pelvic pain associated with cancer. Pain 1993; 54: 145-151.

17. Plancarte R, Amescua C, Patt RB, et al. Superior hypogastric plexus block for pelvic cancer pain. Anesthesio 1990; 73: 236-239.

LEGAL AND ETHICAL ISSUES IN THE CARE OF TERMINALLY ILL PATIENTS

Norchaya T
Faculty of Law, University of Malaya, 50603 Kuala Lumpur, Malaysia

The legal and ethical issues surrounding the care of terminally ill patients include the extent of the doctor's duty to treat, consent to treatment, confidentiality issues, the making of advance directives and euthanasia. This short paper attempts to highlight very briefly, the elements involved in each of the issues above.

In the first place, there is a need to define what it means by the phrase 'terminally ill patient'. Although physicians do not necessarily agree on what the life expectancy should be before a person is deemed to be terminally ill, the general consensus is that a terminally ill patient is defined as someone whose illness is incurable and irreversible and whose prognosis indicates that he has no more than six months to live.

In such a situation when treatment is no longer curative but only palliative in nature, a broad issue which arises is the concept or definition of treatment, and on a more practical level is the issue of the scope of the physician's duty of care to treat. While under different circumstances the duty to treat is aimed at recovery, in the case of terminally ill patients the duty is aimed at the alleviation of pain. The question then arises - if pain-relieving medication does not alleviate pain, does the doctor have a duty beyond that stage? In the event that the terminally ill patient feels that he no longer wants to continue living, can he legally and ethically request for the doctor's assistance to end his life? Can it ever be argued (and defended) that the termination of his life is within the scope of 'caring' for him? Euthanasia as a 'choice' of treatment on the basis of patient autonomy and perhaps even 'right to die' has been and will continue, to be the subject of controversy and debate.

Although proponents of euthanasia generally hold the view that euthanasia can only be of one type, that being active voluntary euthanasia, euthanasia is conventionally divided into two types: active and passive euthanasia. The difference between the two lies in the method employed to bring about death. While active euthanasia refers to the deliberate ending of life, passive euthanasia refers to causing death through non-treatment or omission. The most relevant piece of law in Malaysia on this issue is the Penal Code. Active euthanasia would fall within the provision of Section 299 of the Code which provides that :

> *whoever causes death by doing an act with the intention of causing death, or with the intention of causing such bodily injury as is likely to cause death, or with the knowledge that he is likely by such act to cause death, commits the offence of culpable homicide.*

Culpable homicide is punishable with imprisonment for up to twenty years and fine. The bigger question is whether active euthanasia constitutes murder? Section 300 of the Penal Code provides that culpable homicide is murder in a few situations. Two of the situations are relevant, namely; if death is caused intentionally, or if death is caused without any excuse. Certainly in the case of active euthanasia death is caused intentionally and so it amounts to murder. However, it may be argued that death is caused with an excuse - mercy. Can mercy ever constitute an acceptable excuse? The principle is that mercy whether on the part of relatives or physician, does not negate the mental element required under the law to establish a crime. Interestingly however, the drafters of the Penal Code acknowledged that homicide by consent should not be equated with murder, and that where the motive for ending life is on grounds of humanity, the act does not give rise to murder.

Another question which arises is whether it can amount to murder when the patient himself requested for, and consented to his death. The general principle is that consent to die is an invalid consent. The Penal Code however, provides an exception to this. It is provided that where someone who is above 18 years of age consents to the risk of death through an act, it is not murder (culpable homicide is still made out). Thus it is argued that where continued treatment is futile, and palliation no longer benefits the patient and he consents to death, an assisting physician will not be committing murder. Yet another reason for not holding active euthanasia as murder is because in Malaysia murder carries the death penalty and so reflects the gravity and heinousness of the offence which perhaps might not be the case in euthanasia. All these are speculative however as there has been no test case in Malaysia.

Where the patient dies due to the withdrawal or withholding of artificial nutrition and hydration, this is termed as passive euthanasia. As with active euthanasia, the question is whether passive euthanasia is culpable homicide under section 299 of the Penal Code. It is submitted that passive euthanasia should not be caught by section 299 as it is not a culpable omission under the law.

Other important issues which arise almost simultaneously are issues relating to consent and confidentiality. These two issues impact on patient autonomy. Does a terminally ill patient who is on pain-relieving medication possess full decision-making capacity? How does one ascertain when the patient might not be in a position to make decisions and vice versa? Obtaining consent to proceed with (even) palliative treatment is a non-negotiable requirement. This can be difficult where the patient is unable to give consent. Although the 'best interest' test supposedly provides some sort of guidance to both relatives and the healthcare team on how to proceed next, this can be difficult where there are differing views among the relatives.

However, even in the case where the patient is mentally competent, his consent or more importantly refusal to give consent; should be 'considered' before it is acted upon because it is often the case that decision-making as well as information gathering by the healthcare team is made in the presence of relatives, and consequently it is not impossible that the consent or refusal does not truly reflect the wishes of the patient. This scenario is also contrary to the principle of patient confidentiality.

Advance directives as a reflection and celebration of patient autonomy is also another issue which is relevant in the care of terminally ill patient. Advance directives however, are not yet common practice in Malaysia, perhaps due to patients' reluctance to decide for their future treatment decision-making, preferring to leave the responsibility to relatives, as well as the physicians.

THE ROLE OF HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDHOOD CANCERS

Chan LL
Department of Paediatrics, University of Malaya Medical Centre, 50603 Kuala Lumpur, Malaysia

Introduction

Cancer is the second leading cause of death in children aged 1-14 years and accounts for 10% of all cancers diagnosed. In USA where records have been kept for the past 30 years, the Surveillance, Epidemiology and End Result programme has shown a steady rise in the incidence of childhood cancers where approximately 120 to 150 out of every million children get cancer. Thankfully this disturbing trend has also been accompanied by a remarkable progress in treatment resulting in a substantial decrease in mortality and morbidity from cancer. Leukaemias, brain tumours and lymphomas are the most commonly diagnosed malignancies followed by neuroblastoma, sarcoma and nephroblastoma. Improved survival from cancer is the result of many factors in particular improved treatment. Modern treatment is multi-modal incorporating chemotherapy, surgery, radiotherapy, immunotherapy and also high-dose chemotherapy with haematopoietic stem cell transplantation (HSCT).

Main Message

The role of HSCT has evolved from a last ditch attempt to save a patient to treatment of choice for certain malignancies. Mortality and mobidity related to HSCT have steadily been decreasing. Advances in various aspects of HSCT have contributed to this. Improved methods of histocompatibility testing using high resolution molecular methods and the matching of increased number of alleles have led to better selection of donors especially unrelated donors. Alternative sources of stem cells be it autologous or allogeneic, are now available ranging from bone marrow to peripheral blood and umbilical cord blood. The emergence of voluntary bone marrow and cord blood banks all over the world has widened patients' access to HSCT. Manipulation and expansion of stem cells also contribute to this widened access for patients who need HSCT.

The early transplants involved the principle of myelo-ablation of the bone marrow to eradicate haematological disease but this resulted in significant complications.The introduction of non-myeloablative preparative regimes with greater reliance on immunotherapy meant a reduction in regimen-related toxicities and allowed more patients to be eligible for HSCT particularly, the elderly or those with co-morbidities.

Increased acceptance and application of HSCT are also due to the improved supportive care which incorporates a wider range of immunosuppressive agents, better anti-microbials and infection control.

What childhood malignancies then would benefit from HSCT?

If we consider the most common childhood cancer acute lymphoblastic leukaemia (ALL), patients with good or standard risk disease may expect 80% event free survival while those with high risk may achieve leukaemia free survival of 60% with chemotherapy. With these high cure rates, HSCT is only reserved for ALL patients with bad prognostic factors like Philadelphia chromosome positivity. These patients should be transplanted in first remission. For ALL patients who relapse, generally HSCT with matched sibling donors would give better outcomes compared with chemotherapy particularly if the relapse occurred early. For patients who do not have matched sibling donors, there is some evidence that unrelated donor transplants give results close to matched sibling transplants.

For childhood acute myeloid leukaemia (AML) the current good risk factors include t(8,21), t(15,17) and inversion 16. Patients without these factors would generally benefit and be offerred HSCT if a matched sibling donor is available. For those without a matched sibling donor, some centres may offer autologous transplantation but the benefit of this is unclear. For AML patients who relapse, HSCT is probably the only mode of treatment which may provide a cure.

Children with myelodysplastic syndromes and juvenile myelo-monocytic leukaemias are recommended to undergo HSCT as chemotherapy is not curative. Use of matched sibling or alternative donor transplantation may offer disease free survival of 38-87%.

Although chronic myeloid leukaemia (CML) is rare in childhood, the best modality for cure is still HSCT. The role of the tyrosine kinase inhibitor imatinib mesylate is currently being explored.

Among the non-haematological cancers encountered in children, medulloblastoma, neuroblastoma, Ewing sarcoma, nephroblastoma and germ cell tumour are the few cancers which have shown some response to high-dose chemotherapy followed by HSCT. As these cancers primarily affect non-haematological tissues, autologous transplantation using peripheral blood stem cells, is now the preferred mode of therapy. Indications for HSCT would include high risk, refractory or relapsed disease where the tumour remains chemo-sensitive and a state of minimal residual disease is achieved.

In medulloblastoma where surgery and radiotherapy are the mainstay of treatment, HSCT is useful for the very young patient as it allows avoidance or dose reduction in radiotherapy which is detrimental to the developing brain.

The protean complications pursuant to HSCT may be acute events like bacterial and fungal infections, veno-occlusive disease, bleeding, acute graft-versus-host disease or graft failure. Alternatively, they may be delayed events related to infections, chronic graft-versus-host disease, graft rejection and relapse of the primary disease all of which may result in mortality.

In the University of Malaya Medical Centre, the HSCT programme began in March 1987. From then till March 2005, a total of 290 HSCT were performed for which 150 (51.7%) were for malignant diseases. Most of these transplants were performed with bone marrow.

Disease	Number transplanted	Stem Cell Source			Dead	Alive	% Survive
		BM	PBSC	Cord			
ALL	47	32	7	8	32	15	32
AML	42	31	7	4	17	25	60
CML	22	18	3	1	7	15	68
Other Leukaemia	8	1	4	3	5	3	38
MDS	3	2	1	0	2	1	33
NHL	3	1	2	0	1	2	67
HD	1	0	1	0	0	1	100
Neuroblastoma	13	6	7	0	9	4	31
Brain tumours	6	0	6	0	3	3	50
Retinoblastoma	3	0	3	0	0	3	100
Ewing Sarcoma	1	0	1	0	0	1	100
Germ Cell tumour	1	1	0	0	1	0	0

Conclusion

HSCT has contributed to improved survival for many types of childhood cancers. There is a need to better identify the patients who would benefit from this procedure by increasing our knowledge of the biology of the different types of cancers and ways to achieve minimal residual disease. Preparative regimens need to be tailored to the patients' co-morbidities with consideration for long term sequelae. With an enlarging unrelated donor pool and improved immunosuppression, it is envisaged that practically every patient who needs a HSCT will be able to get one to secure a good chance of survival in their fight against cancer.

RECENT ADVANCES IN NEUROTOLOGY

John R
Department of Otolaryngology, University Health Network, University of Toronto, Canada

Introduction

The past decade has seen numerous advances in our understanding, diagnosis and management, both medical and surgical, of patients with inner ear dysfunction and disorders of the cerebellopontine angle and brainstem.

Benign positional vertigo (BPV) remains the most common inner ear disorder seen in neurotology. In this condition patients experience recurrent attacks of episodic vertigo lasting seconds when the head reaches the provocative position (eg looking up, bending over or moving from a sitting to a lying position). BPV usually occurs spontaneously but may also result from head injury. BPV following head injury is more likely to be persistent and bilateral, and less likely to respond to physical therapy (ie Brant-Daroff exercises, Semont's and Epley's manoeuvres).

The discovery of free-floating particles in the posterior semicircular canal (PSCC) of the inner ear at surgery provides the rationale for particle (or canalolith) repositioning in the treatment of BPV. This simple procedure has proven extremely effective in providing patients with relief. However, when BPV does not respond to particle repositioning and proves incapacitating non-ampullary posterior semicircular canal occlusion surgery is usually recommended, providing there is no contraindication to surgery. At the University Health Network this procedure has been universally curative in 32 consecutive patients with incapacitating BPV over the last 15 years with no deterioration in their sensorineural reserve. Autogenous periosteum is typically used to occlude a fenestration made into the posterior canal at surgery in part to prevent movement of the free-floating particles causing BPV. Unlike singular neurectomy (perhaps the most difficult of all procedures in neurotology) the advantage of non-ampullary PSCC occlusion is that it defunctions rather than deafferentates the posterior canal.

The discovery that PSCC occlusion surgery could selectively defunction this canal without ill effect to the rest of the inner ear has led to new surgical approaches through the inner ear that maintain function but allow access to the antero-medial brainstem and cerebellopontine angle (CPA) for treatment of brainstem vascular lesions such as cavernomas or basilar aneurysms that hitherto had been considered untreatable. With this approach, both the posterior and superior semicircular canals are occluded and then resected providing the surgeon direct access to the internal auditory canal and the anterior aspect of the CPA. In nine patients operated on at the University Health Network the sensorineural reserve for hearing was maintained at its preoperative level in seven of nine (77%) patients. Preservation of partial vestibular function (i.e., the lateral semicircular canal and the utricle and saccule) also appears possible.

Other advances have occurred in the systematic analysis of eye movements their interaction with the inner ear. For example, our knowledge of how the vestibulo-ocular reflex (VOR) works in the real world has been significantly enhanced by the introduction of magnetic scleral coil eye movement studies. The subject wears a contact lens with an embedded wire and a similar coil attached to their head, and is placed inside a magnetic frame. Movements of the eyes or head relative to the magnetic field induce a current within the coils that can be measured precisely. This new technology has allowed us to accurately record even the most minute movements of the eyes as they respond to head movements overcoming previous technical problems such as electrode slippage and electrical interference.

Using scleral coil technology we have found that the vestibular portion of the inner ear now appears to have a frequency specific function (ie high frequency vs low frequency) in a fashion somewhat analogous to hearing. This explains the phenomenon of oscillopsia (visual blurring with head movement) in patients with normal conventional balance tests and explains why certain individuals cannot adequately compensate following a unilateral vestibular loss despite active vestibular rehabilitation therapy. For the most part caloric testing has been found to be a test of low frequency vestibular function. Although this has not lead to any formal treatment of patients with a high frequency vestibular

loss, the knowledge gained from this test is often invaluable in medicolegal and forensic cases involving workplace and disablility issues.

Over the last decade we have witnessed advances in the basic molecular science of how ototoxic agents affect the inner ear. Our increased knowledge of the mechanisms for ototoxicity, both systemic and topical, has tremendous implications for future patient care, prevention of complications and possible treatment of disorders such as Meniere's disease. Intratympanic gentamicin therapy for incapacitating Meniere's disease has successfully relieved vertigo in 80% to 100% of series to date and as a result has replaced the major neurosurgical procedure of vestibular neurectomy as the initial treatment of choice in patients with serviceable hearing.

Somewhat humbling has been the realization that whatever enters the middle ear can ultimately reach the inner ear. Topical aminoglycoside containing drops have now been irrefutably demonstrated to cause clinical ototoxicity in humans. Surgical preparation solutions, especially those that contain alcohol and chlorhexidene, that reach the middle ear and then the inner ear through the round window membrane may also be ototoxic. We have discovered the genetic basis for the increasingly frequent clinical phenomenon of aminoglycoside antibiotic induced deafness (AAID) and now have a better understanding of cellular injury and apoptosis in individuals exposed to prolonged or toxic doses of aminoglycosides and platinum based chemotherapeutic agents.

Basic research into AAID has demonstrated a mitochondrial pattern of inheritance. There is a mitochondrial DNA 1555 A to G mutation in the 12s ribosomal RNA making it resemble a bacterial 12s ribosome. This increases aminoglycoside binding in the ribosome, which alters protein synthesis leading to the formation of iron binding complexes and free radical formation ultimately resulting in cell death.

Conclusion

The phenomenon of AAID is especially important in Southeast Asia. For example, populations in China appear to have an extraordinary propensity for severe deafness following a single exposure to the aminoglycoside kanamycin. In Shanghai, it has been estimated that over 22% of deaf mutes could attribute their hearing loss to short term aminoglycoside use (often only one dose). Exposure to aminoglycosides (including drops reaching the middle ear) may also be responsible for premature progressive sensorineural hearing loss. We hope that with further advances in molecular biology and genetics we may soon have a way of preventing this type of hearing loss in susceptible individuals and better understand the mechanisms that cause age related changes in hearing and vestibular function.

THE ROLE OF THE MAXILLOFACIAL SURGEON IN THE MANAGEMENT OF TRAUMA PATIENTS

Zainal Ariff AR
Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, University of Malaya, 50603 Kuala Lumpur, Malaysia

Introduction

Trauma has been among the leading causes of death in this country. The main aetiology has been road traffic accidents. The increasing number of patients turning up at the trauma centre throughout the country had demand a greater role and attention of maxillofacial surgeons in management of such patients. Currently, the maxillofacial surgeons are involved in early, definitive and later management of patients with maxillofacial injuries.

Airway problems in patients during the early phase of injuries may be due to distortion of anatomical structures at maxillofacial regions. Simple manoevres like reduction and temporary immobilization of fracture may help to save lives. The high level midface fracture tends to displace backwards and downwards along the incline plane of skull base. This movement may result in impingement of soft palate against the tongue and posterior wall of the pharynx hence causing blockage of upper airway. Reduction of this fracture by pulling the midface forward may help to keep the airway patent. Bilateral fracture of parasymphysis area of edentulous mandible may allow the fracture fragment to flip backward causing posterior displacement of tongue thus blocking the upper airway.

Haemorrhage into the potential facial tissue spaces may be another possible threat to the airway. Bleeding into the sublingual space can be very dramatic sometimes. The blood may keep filling up the loose space and finally the floor of the may protrude out and at the same time push the tongue backwards to occlude the airway.

Torrential bleeding from maxillofacial region may also cause by base of skull, midface or mandible fracture. Reduction of fractures with temporary immobilization with pressure pack may help to control the hemorrhage.

Soft tissue injuries of the maxillofacial region need to be repaired within 24 hours to minimize scarring and risk of infection. Proper wound toilet and debridement required to facilitate healing. Tissue loss may be replaced at later date. It is important to ensure that all wounds are closed primarily.

Management of hard tissue injuries is similar to management fractures of other bones. They are control of pain, infection and hemorrhage followed by reduction and immobilization. The reduction can be done by open or closed technique. The fixation can be either rigid or non-rigid. Rigid fixation can be achieved by various osteosynthesis material comprising titanium plates and screws. The stainless steel wire, various form of external fixators and archbars are used for non-rigid fixation of fractures. The choice of treatment may depend on factors as describe below:

1. the severity of the fracture,
2. site of injury,
3. general health status of the patient,
4. socio-economic status of patient,
5. associated soft tissue injuries, and the
6. availability of facilities and expertise.

The aims of treatment are to restore bony continuity, occlusion, function and facial aesthetic. The sound knowledge of occlusion is required in management of maxillofacial fractures. The occlusion is the most important and reliable guide for maxillofacial fractures. Discrepancy or derangement of occlusion may lead disturbances in speech and mastication.

Close reduction can be achieved by various technique as mentioned below:-

1. Using intermaxillary fixation
   The archbars are placed on the upper and the lower dentition. The upper and lower teeth are then dragged by elastic band tied to both arch into correct occlusion. This technique is valuable for simple non-displace fracture of mandible.

2. Using disimpaction forceps
   Various disimpaction forceps available for reduction of impacted fracture of midface.

3. By Gillis's approach
   The malar elevator forcep are used to reduced the zygomatic complex fracture. The access is gain through temporalis fascia from incision made at the temporal region.

4. Poswillo hook
   This hook can also be used to reduced malar fractures via a stab incision at the base of temporal process of zygomatic bone.

In open reduction, the bone can be directly manipulated by using various instruments or by using intra-osseous wiring to bring the two fracture piece together.

In case of close reduction, the fracture is usually immobilized by external fixation. Most popular and widely use is the intermaxillary fixation (IMF). The upper and lower dentitions are tied together in correct occlusion to immobilize the mandible. The IMF will stay for about five weeks.

Various internal fixation are available to immobilize maxillofacial fractures. These include craniomandibular suspensions, osteosyntheses, intra-osseous wire, bone pin and kirshner wire. Osteosyntheses is widely used nowadays. However, there is still a role for other fixation in management of fractures especially in patient with low socio-economic status.

When applying bone plate and screws for fixation of maxillofacial fractures, the surgeon should consider the distribution of forces within the bones. To ensure the strength and stability of the fixation, the long axis of the plate should be place parallel to direction of the forces.

For the mandible there is pre-existing tension forces over the upper border and compression force over the lower border. A single plate at the lower border may not be sufficient to stabilize the fracture.

The facial harmony should also be given due attention in fracture management. The displaced bone need to reposition back to their original place. Discrepancy of more than 2 mm will be visible on the face.

The difficulties of reduction and fixation may be encountered in the following situations:-
1. Loss of facial height
2. Gross bone comminution
3. Pan facial fractures
4. Extensive bone loss
5. Impacted fractures
6. Delayed treatment
7. Atrophic edentulous mandible
8. Children

There is always problem in achieving optimum aesthetic results in management of maxillofacial fractures especially in case of gross displacement and extensive bone. It is almost impossible to reposition the fracture piece to an accurate three dimensional coordinates manually. The computer technology had much to offer to improve the treatment outcomes. We had use the computer cad software to produce the three dimensional view of the facial skeleton. With the help of this software we could visualized the extend of the problems and plan for definitive correction. The computer software also able to virtually corrected the damage and from this a life-size model can be produce by stereo lithography (STL). The model can be use to fabricate the bone plates and also to construct a template as a guide during actual surgery. Our experiences with the usage of computers in correction of maxillofacial injuries are described in the case reports below.

Case reports

Case 1

A 28-year old Chinese male came with the parent to see us in the clinic two years after a bad RTA. The patients had multiple injuries (including head injuries) during the accident and remain in ICU for a very long period. No definitive treatment given to the maxillofacial injuries at that time.

The patient had a CT scan done and the digital image was translated into a three dimensional facial skeleton using CAD software. Virtual correction of the deformity was done by mirroring the normal side to the damage side. The life size model of normal and damage facial bone were produced by STL.

From the model, the following deformities were noted:-
1. Lateral displacement of frontal process of zygomatic bone

2. Inward and downward displacement of body of zygoma, and

3. Downward and lateral displacement of the zygomatic arch.

The bone plate was fabricated using the STL model prior to surgery. The surgical access gain via coronal flap. The displaced bones were refractured and repositioned. The fabricated bone plates were use as guidance for bone repositioning. Bone deficiency was replaced by outer calvarium graft. The healing was uneventful and the outcome was satisfactory.

Case 2

A 38-year-old Malay male motorcyclist hit by a lorry on the way to work. He had comminuted fracture of right frontal, orbital and zygomatic bone. The area was debrided by a neurosurgeon. A year later the patient was referred to maxillofacial clinic for reconstruction of the residual defect.

A CT scan was taken to acquire imaging data and then process into three dimensional images. The life size model of the facial skeleton was produced. The model showed extensive bone loss over frontal, orbital and zeugmatic area causing severe depression over the region. Virtual reconstruction of the defect was attempted by mirroring the normal side to the damage side however there was a problem as the defect extended across the midline. The virtually reconstructed 3D image had a defect at the front nasal suture area. A prototype to cover defect was produce in acrylic and place over the model. The hole over the front nasal area was patch manually. The model was then scan to produce a virtually reconstructed STL model. A second prototype to cover the defect was made in acrylic and was place on the actual 3D model to match. A few minor adjustments required before the acrylic piece able to fit into defect satisfactorily. A mould was made based on the acrylic piece for fabrication of 1mm thick titanium mesh. The mesh was placed onto the defect in the actual surgery. The mesh fit well with the defect and the titanium screws were use to fix it in place. The recovery of patient was uneventful and the patient was discharged three days after the surgery. The post-operative 3D image showed almost symmetrical facial bony contour. However, there is some minor soft tissue adjustment required.

Conclusion

Maxillofacial surgeons involved in early, definitive and delayed management of patients with maxillofacial trauma. The maxillofacial surgeons must work hand in hand with other trauma teams to provide input especially during early part of the injuries. A sound knowledge of the occlusion and distribution of the forces over facial skeleton is required to manage the facial fractures effectively. The main problem in correction of facial fractures is to reposition the grossly displaced bone into the original position with accuracy in all the 3D coordinates. Computer technology help to solve this problem thus facilitate to ease the surgical correction and improve treatment outcome.

HANDLING SEXUAL ISSUES IN THE PRIMARY CARE CONSULTATION

Nik-Sherina H
Department of Primary Care Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Introduction

There are abundant sexual issues in primary care consultations. This presentation discusses some points to practice in handling patients with various sexual issues.

Main messages

Sexual issues are those which are related to sexual health, which can be defined as 'the integration of the somatic, emotional, intellectual and social aspects of sexual being, in ways that are positively informative and that enhance personality, communication, and love'. One way of dividing sexual issues is to divide them into related clinical syndromes such as impairment of sexual functioning, emotional attachment, compulsive sexual behaviour, gender identity conflict, violence and victimization, reproduction, sexually transmitted infections and other conditions.

The comprehensive care provided in primary care practices allows for opportunities to discuss the matter with the various age groups, ranging from adolescents, women of reproductive age group, postmenopausal women, men and the elderly. This presentation discussed some studies which have shown that sexual issues are common in such a setting.

In considering the reasons why sexual issues are considered taboo by most, one has to consider the various physician, patient and practice factors. Some of these physician factors are the feeling of embarrassment and ill-prepared, believing that sexual history is not relevant to the chief complaint as well as having time constraints. Similarly, patient barriers to discussing sexual health are sensing physician discomfort and anticipating non-empathetic response to sexual problems.

In taking history, one can take steps to reduce the barriers that may exist. Such steps include asking questions in a matter-of-fact yet sensitive manner, providing an initial explanation on the need for asking such questions. It is also essential that doctors assure patients that such information will be kept confidential. Practitioners must also avoid moral or religious judgments to allow for more effective consultations.

A detailed sexual history should not be confined to frequencies and types of sexual relationship. Other issues that should be covered are the social and medical history such as the presence of diabetes, heart diseases or previous operations. Questions about medication, whether for medical or recreational use, must be asked. It is also important to get the patients' and their partners' views on the issue being discussed. Finally, both parties should agree to the management plan.

While sex can be a natural process, one cannot run away from the possibility of sexual abuse. The Malaysian Child Act 2001 law has clearly defined a child as being a person under the age of eighteen years. A child is considered to have been sexually abused if he has taken part, whether as a participant or an observer, in any activity which is sexual in nature for the purposes of:-

1. Any pornographic, obscene or indecent material, photograph, recording, film, videotape or performance; or

2. Sexual exploitation by any person for that person's or another person's sexual gratification.

When confronted with the possible situation of child sexual abuse, the practitioner would need to take certain actions in order to protect the child.

Finally, effective communication skills will help to bring out sexual issues in the consultation. The language used need to be easily understood by patients according to their cultural, socioeconomic and language backgrounds.

Conclusion

In conclusion, it is important for the practitioner to handle sexual issues with confidence, to be well-informed about human sexuality, to know how to deal with sexuality problems and when, as well as to whom, to refer. In short, there is a big need for one to be proactive in taking sexual health history.

References

1. Pan American Health Organization (PAHO), World Health Organization(WHO).
2. Nusbaum MRH, Hamilton CD.The proactive sexual health history. Am Fam Physician 2002; 66(9):1705-12.
3. Annon JS. The behavioral treatment of sexual problems. 1st ed. Honolulu: Enabling Systems, 1974-1975.
4. Mace DR, Bannerman RHO, Burton J. Geneva: World Health Organization, 1974.
5. Marwick C. Survey says patients expect little physician help on sex. JAMA 1999; 281:2173-4.
6. Malaysian Law, Child Act 2001. Section 17, subsection Section 2(1), Act 611.

HOW TO COMMUNICATE WITH PATIENTS ABOUT RISKS AND BENEFITS?

Ng CJ
Department of Primary Care Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

Introduction

Have you been asked by a 50-year-old lady about her risk of developing breast cancer? Has a 65 year-old man asked you whether you should do a prostatic specific antigen (PSA) to screen for prostatic cancer? Or have you tried to explain to an elderly patient with atrial fibrillation about the risks and benefits of starting warfarin? There is a common issue in all these scenarios: the doctors have to explain statistical concepts to the patients in order to help them make informed decisions about their medical problems. This happens almost everyday in a doctor's life and it involves communicating risks and benefits of a diagnostic test or a treatment option to the patient.

However, studies have shown that doctors are not well trained to handle such situations (1). To make things worse, the patients are not good at processing the information given by doctors. They tend to extract the gist, rather than the details, of the information received to make decisions about their health care (2). Most of the patients assess the risks based on emotions, rather than by facts (3)! With these problems in mind, it is thus crucial for doctors to acquire some basic communication skills when communicating with patients about risks and benefits. This paper aims to cover some commonly encountered clinical scenarios where doctors need to discuss these issues.

Single Event Risk

When prescribing fluoxetine to a patient with depression, a doctor explains, '*You have a 30% chance of developing sexual problem with the drug*.' To the doctor, he means that this patient, if taking fluoxetine, has about 1 in 3 chance of getting sexual problems, like loss of libido or erectile dysfunction. However, the patient may interpret it differently. The patient may think, '*Oh no, 30% of my sexual encounters will fail*!'

To avoid this confusion, it is thus important to explain the risks in terms of numbers rather than percentages. For example,
'Out of 10 people who take fluoxetine, three will develop sexual problems such as impotence or loss of interest in sex, while the other seven will not.'

Sensitivity, Specificity, Positive Predictive Value

When explaining to a lady who is going for mammography, we may need to address the following questions:

1. *'What is my chance of getting breast cancer?' (Probability)*
2. *'How accurate is mammography?' (Sensitivity and specificity)*
3. *'If the test is positive, does it definitely mean that I have breast cancer?' (Positive Predictive Value)*

	Breast Cancer +	**Breast Cancer –**	
Mammography +	7	70	77
Mammography –	1	922	923
	8	992	1000

Probability
Assuming that the probability of the lady developing breast cancer is 0.8%, we can answer the first question by saying,
'Out of 1000 women, 8 have breast cancer.'

Sensitivity and Specificity
If the sensitivity is 90% and specificity is 93%, we can explain the accuracy of mammography to the patient by saying,
'Out of these 8 women who have breast cancer, mammography will pick up 7 of them. However, one will be missed.'

'As for the rest of those who do not have cancer (922), 70 of them will still have positive mammography. They will need to undergo further tests.'

Positive Predictive Value

If the positive predictive value is 9% (7/77), we can explain the implication of a positive mammography test to the woman by saying,

'Out of 100 women who are tested positive, 9 have breast cancer and 91 do not have breast cancer.'

Relative Risk versus Absolute Risk

It is confusing when we try to explain relative risk reduction and absolute risk reduction to the patients, depending on which 'risk' we choose.

For example, *'For women above 50 years of age, mammography screening reduces your risk of dying from breast cancer by 25%.'*

Relative risk reduction

$$= \frac{(4/1000 - 3/1000)}{(4/1000)} \times 100\% = 25\%$$

Similarly, we can also substitute the '25%' with '0.1%' if we intend to explain absolute risk reduction. Generally, absolute risk reduction gives a more accurate picture as it takes the probability of breast cancer into consideration.

Absolute risk reduction

$= (4/1000 - 3/1000) \times 100\% = 0.1\%$

	Breast cancer Alive at 10 years	**Breast cancer Dead at 10 years**	**Total**
Underwent mammography	997	3	1000
Did not undergo mammography	996	4	1000
	1993	7	2000

We can explain to the woman in a simpler manner using numbers instead of percentages:

'Out of 1000 women who do not go for mammography, 4 will die from breast cancer within 10 years; Out of 1000 women who go for mammography, 3 will die. Therefore, with 1000 women going for mammography, we can avoid one woman dying from breast cancer.'

However, not all patients will understand numbers and figures. There are other decision aids which can help the patients to understand these statistical concepts better. Examples include visual aids such as Paling Perspective Scale and Paling palette (4). A useful website for both doctors and public is the BestTreatments, which 'helps patients and doctors work together by providing them both with the best research evidence about the treatments for many medical conditions'. (www.besttreatments.org/risk) Through innovative decision support tools such as these, the patients will be in a better position to make decisions about their own health.

When it comes to effective risk communication, being competent in explaining the risk is not enough. The doctors have to adopt a caring attitude, and win the trust of the patient during the consultation. It is also essential to involve allied health professionals such as nurses and pharmacists, as well as patient support groups in developing a standardized way of risk communication.

Conclusion

In conclusion, it is prudent for doctors to explain to patients about risks and benefits in a manner that is easily understood by them. In order to do this, the doctors have to master some of the basic risk communication skills discussed above, mainly to use numbers rather than percentages, to highlight both positive and negative outcomes, to use absolute numbers rather than relative risk. Use of supporting decision aids also facilitates the explanation of risks and benefits. Finally, we should create a trusting environment and adopt a patient-centred approach during the consultation, and respect patients' final decisions no matter what they are.

References

1. Alaszewski A, Horlick-Jones T. How can doctors communicate information about risk more effectively? Br Med J 2003; 327: 728-31.
2. Lloyd A, Hayes P, Bell RF, Naylor AR. The role of risk and benefit perception in informed consent for surgery. Med Decis Making 2001; 21:141-9.
3. Ropeik D, Clay G. Risk! A practical guide for deciding what's really safe and what's really dangerous in the world around you. New York: Houghton Mifflin, 2002.
4. Paling J. Strategies to help patients understand risks. Br Med J 2003; 327:745-8.

VALUES-BASED PRACTICE : A NEW APPROACH TO UNDERSTANDING CLINICAL INTERACTIONS

Jeremy DMP, Bill F
Centre for Primary Health Care Studies, Warwick Medical School, University of Warwick, Coventry CV4 7AL, United Kingdom

Introduction

This paper describes the basic principles of the Values-based Practice (VBP) framework and its application to overweight and obesity. VBP is a theoretical system in which the pre-eminence of values is recognised as integral to all clinical practice. The concept was first developed in the book Moral Theory and Medical Practice (1) with a focus on mental health. The theory and skills underpinning VBP are being taken up in the UK through a number of service development and training initiatives in mental health. Research has also been initiated on the application of the framework to other areas of health care.

VBP has common grounds with bioethics and patient-centred philosophies, yet starts from a broader understanding of 'value' than the former and attends to the values of a wider range of stakeholders than the latter. It is concerned with ways in which evidence-based medicine can be made relevant to the individual patient and specific patient groups, and in which multidisciplinary team-working can become more than a coordinated distribution of tasks and competences. It is about valuing differing beliefs, perceptions, points of view, and basic assumptions.

A central concept of the VBP-framework is that all decisions are informed by both facts and values (2); decisions cannot be made from facts alone. Within contexts in which similar sets of values tend to be shared, values may become a constant and ignorable parameter (3). However, scientific advances have created greater choices, with different options accommodating different values (3). Patients have changed — society has become both more heterogeneous and more open to different forms of living with the diverse values they embody. In addition, the new patient-consumer is more knowledgeable, powerful, and explicit about his or her values. Clinical focus has also changed - there has been a shift of emphasis from treatment to prevention, from hospital to community healthcare, from the intensity of the in-patient ward to the iterativity of our lifestyle and everyday practices.

VBP offers a less prescriptive and more local approach than traditional bioethics. Bioethics aims to define courses of action that are as morally acceptable and uncontroversial as possible, and is committed to eliciting maximally shared values and to disentangling their interactions in complex health-related situations. Values-based practice, on the other hand, is interested in those differences of values to which the moral qualification does not apply or is only marginal. These differences can be thought of as permissible variations within a widely accepted moral code or as differences for which the good-bad distinction is superfluous.

In this paper, the basic principles of VBP are introduced, and their application to the problem of overweight-obesity considered. Overweight-obesity is chosen for its topicality, its public health importance, its value-ladenness, and for the unchallenged 'rightness' of certain values associated with it.

Main messages

The problem of excess weight is an arena of a complex interplay of values: the discriminatory-accusatory attitudes of a pro-thin culture; the personal perceptions of what makes an excess of weight, a desired level of weight reduction, or an acceptable sacrifice in its name; the ethnic and cultural differences in the preferences for and the symbolism of certain body shapes; the fluctuations of self-esteem as a function of what the scales are showing; and so on. Such parameters are tacit modifiers of traditional weight reduction plans and obesity prevention strategies focussing on diet and exercise with no adjustments for cultural and individual variables. Significant practical implications follow from exploring the values that underlie models of overweight and obesity, from becoming more aware of our values, and from accounting for the perspectives, beliefs, priorities, etc., of the overweight and obese person.

Scientific progress creates choices. The advancement and commercial exploitation of science has created a huge variety of weight-loss options. They offer different

balances of convenience, stringency, rapidity of results, affordability, etc. for patients and clinicians to choose from. In the majority of cases weight loss is short-lived.

Identifying overweight or obesity correlates imperfectly with objective weight indices. For example, 40% of overweight mothers and 45% of overweight fathers judged their own weight 'about right' and only a quarter of parents recognized overweight in their child. The opposite tendency of perceiving one's normal weight as overweight, is also common, especially among women. Healthcare professionals themselves are liable to perception biases. Women as well as older men tend to be evaluated as obese by their doctors more often than anthropometric measures would justify.

Awareness of the values associated with overweight and obesity may lead to more effective and rewarding practice. There are vast cultural, ethnic, social class, group, etc., differences in what is recognised as normal weight and overweight. The types of questions VBP asks about overweight and obesity are: What cultural, ethnic, class, age, professional, etc., values influence the perception of oneself or others as overweight or obese? What scientific assumptions underlie current research on overweight and obesity? How does the importance of the goal of weight loss/ maintaining healthy weight vary among individuals? How does the healthy weight goal rank among an individual's life priorities? What values determine people's preferences for certain methods of weight loss? How does the negative and sceptical societal attitude affect the ability of the overweight and obese persons to achieve and maintain weight loss? What overt and covert values govern the current anti-obesity campaign?

Values tend to be noticed when they are diverse or conflicting. A major obstacle to tackling overweight lies in the values that affect the identification of oneself as overweight or obese. There are four distinctive ways of relating to one's weight. Overweight as the state of things, value-neutral; overweight as a non-important problem; overweight as a problem central to one's well-being and self-esteem; overweight as an asset. However, the norms for low, normal, and over-weight are extremely varied. Cross-cultural and cross-chronological comparisons bring out vast differences in perceptions of normal weight and desirable body shape. Those preoccupied with thinness to health-damaging proportions contrast starkly with those appearing to be genuinely comfortable with their overweight. Although recognition of one's overweight as a problem is a clear prerequisite for attempting weight reduction, it is less clear how and to what extent this recognition can be facilitated.

Careful attention to language use can raise awareness of values. Everyday language and the language of the media reveal pervasive discriminatory attitudes towards overweight and obese persons. Scientific and official publications are not exempt: for example, the latest UK House of Commons Health Committee Report on Obesity, for instance, describes children with sleep apnoea as 'choking on their own fat'. The stigma of obesity and the emotional over-investment in weight loss may act as a primary failure factor - the principle of counter-productivity of excessive motivation.

Instituting change rests with the overweight person. Good clinical guidance and systematic reviews support decision making, but uncovering values, bridging perceptions, and improving communication between clinicians and their overweight and obese patients is as important as enhancing the knowledge base about the condition and its management. Many factors threaten the co-operation between clinicians and their overweight and obese patients. These include the different attributions of the problem; the incongruence of expectations regarding contributions to its resolution; the ambiguous attitude on behalf of patients as to whether their doctors should give unsolicited advice on weight loss; the clinicians' perception that weight management makes inappropriate demands on their time.

Conclusion

Values-based Practice is a framework in which the pre-eminence of values is recognised as integral to all clinical practice. People relate to their weight differently, and the recognition of one's overweight or obesity as a problem is not a simple reflection of what weight indices show. Weight loss is desired not only for health reasons, but also for its appearance and social benefits. Directly targeting overweight and obesity may strengthen psychological defences and trigger self-defeating motivations. Understanding values and beliefs is paramount to the provision of appropriate care. The VBP-framework provides tools for opening up discussion issues that have appeared self-evident or purely evidence-based. It increases sensitivity to the values of one's particular standing in the healthcare field, such as the values of one's background discipline, professional roles, and personal style of practice - and an awareness of one's own values is a fundamental prerequisite for a capacity to notice and communicate about the patients' values and to engage in productive multidisciplinary work. It provides a common ground and language for bringing together diverse approaches without a need to establish an ultimate priority of one over another. Strengthening and reorganizing diverse

values-sensitive strands of knowledge and practice along simple and manageable lines and raising awareness of the values and contingencies on which these strands are based, could make a significant practical difference.

References

1. Fulford KWM. Moral theory and medical practice: Cambridge: Cambridge University Press, 1989.
2. Fulford KWM. Ten principles of values-based medicine. In: Radden J, eds. The Philosophy of Psychiatry: A Companion. New York: Oxford University Press, 2004; Ch.14: 205-234.
3. Fulford KWM, Dickenson D, Murray TH. Introduction. Many voices: human values in healthcare ethics. In: Fulford KWM, Dickenson D, Murray TH, eds. Healthcare Ethics and Human Values: An Introductory Text with Readings and Case Studies. Blackwell, 2002.

Journal of the University of Malaya Medical Centre
JUMMEC
Supplement 1 2006

CONTENTS