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Systolic heart failure: dilated cardiomyopathy
(Courtesy of Professor C C Lang, Department of Medicine, Faculty of Medicine, University of Malaya)

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Title page: The title page should contain a concise title of the article. It should identify all the authors, the name(s) of the institution(s) and their full addresses where the work was carried out. The initial and address of the corresponding author should also be indicated.

Abstract and Keywords: The second page should contain an abstract of about 150-200 words. It should state the purpose of the study, a brief description of the procedures employed, main findings and principal conclusions. Three to ten key words should also be listed below the Abstract.

Text: Wherever possible, the text should consist of an introduction, materials and method, results, discussion and references.

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IN MEMORIAM

PROFESSOR JOHN JOSEPH BOSCO
31.1.1945 - 24.4. 1999

On April 24, 1999 Malaysian Medicine lost a valued friend and contributor, including the JUMMEC, for which he served as a member of the editorial board since 1997.

Prof. John J Bosco was born in Seremban on January 31st, 1945. He graduated from the University of New South Wales in 1970. He had advanced training in Medicine/Hematology and Oncology from 1970 to 1979 in Malaysia and Australia. He joined the Faculty of Medicine, University of Malaya in 1979 and greatly contributed to the development of the Adult Hematology and Oncology Unit at the University Hospital. John Bosco's accomplishments in the field of Medicine are enormous. At the time of his death, he was at the height of his career, recognized as a leading Oncologist in our country. A man of superior intellect, he had creative and conceptual talents. He used these talents well and shared them unselfishly with others. John was an extraordinary human being and a dedicated physician, good researcher and a great teacher. Prof. Bosco was a legend among students, an extraordinary teacher who loved his students and his students loved him. He taught his students how to think clinically. Those who were lucky to be taught by him will always remember his passion for his profession, his love of life, his friendly disposition and seemingly limitless energy.

Prof. Bosco's achievements are numerous. He will always be remembered for having started the first adult leukaemic centre and BMT unit in the country. He will also be remembered as our head of medicine who blazed the trail of our achievements. He was greatly instrumental for starting the Part II MRCP examination, U.K. in Malaysia. He has won numerous awards, including the coveted Tun Razak award in 1987, but the one that was closest to him was the one awarded by his almamater, The University of New South Wales Alumni award. Before his death he was appointed as the first Dean of the International Medical University.

The personal side of John and his loyalty to friends were his best assets. He was devoted to his wife and children. The memorial service held in his honor was attended by people from all walks of life and from all over Malaysia,

reflecting love, admiration and affection for a very special person capable of pioneering and organizing an entire field of Medicine in Malaysia. We give thanks for the life of a man we are all proud to call our friend. The unique compassionate, sincere and the courageous Prof. John Bosco's love will never be extinguished from our minds and his legacy will continue in everything we do. We unite in sorrow with his wife Gracie, his children, Anne, Marie, Julian and Joanna for whom he cared so deeply. We will not forget this man whom we were so fortunate to know and to work with for his life was not just a passing light.

Editorial Board
JUMMEC

POSTGRADUATE EDUCATION IN MALAYSIA

Postgraduate medical education in Malaysia received a shot in the arm with the introduction of the "open concept" for the local postgraduate Masters programme in 1996. Numerous applications are received each year from spirited young doctors who wish to take full advantage of the new system which allows doctors in the Ministry of Health (MOH) hospitals to pursue their postgraduate training in MOH hospitals, under the direct supervision of MOH specialists and with the blessing of the 3 participating local Universities, namely Universiti Malaya (UM), Universtiti Kebangsaan Malaysia (UKM) and Universiti Sains Malaysia (USM). Such a system has minimised the disruption of services in MOH hospitals, which would have otherwise occurred if doctors in MOH were compelled to pursue the 4-year Masters programme entirely at the universities. The other advantage of this system is of course the greater volume of specialists trained each year using existing training facilities in MOH hospitals. Also, senior and experienced MOH specialists will now have the opportunity to prove their mettle in postgraduate training, something they have always been doing, albeit in an ad-hoc and unstructured manner.

Since the implementation of the Masters Programme, under the "open system" in 1996, 2,502 applications have been received for the 16 courses offered by the 3 local universities. Of these, 1,800 (72%) have been accepted for training. At the time of writing, 1399 (78%) are still in the Programme. The other 22% have left the course, either because of failure or other reasons. Only doctors who have completed 2 years of service after their housemanship are eligible to apply. Selection of candidates will be made by the local universities based on set criteria and methods which are different for each university. The 16 courses offered are *Internal Medicine, General Surgery, Pediatrics, Anesthesiology, Obstetrics & Gynecology, Orthopedics, Ophthalmology, Otorhinolaryngology, Pathology, Radiology, Psychiatry, Family Medicine, Sports and Rehabilitative Medicine (UM only), Public Health, Emergency Medicine (USM only) and Rehabilitative Medicine (UM only).*

The placement of trainees placed in MOH hospitals and the Universities is decided by the National Co-ordinating Committee, comprising representatives from the relevant sections of the MOH and the 3 Universities, based on a 60:40 ratio in favour of MOH training centres. Training places are limited by the number of trainers available at accredited training centres. Despite initial hiccups, the local Masters programme under the "open concept" has taken off very well. All parties involved in the programme appreciate the importance of effective communication using existing mechanisms to ensure the success of the programme.

It has been estimated that the country requires more than 6,000 specialists by year 2020. This number represents approximately 15% of 42,319 doctors needed for that year (using the norm of 1:800, which some may consider outdated!). However, if we use the projected population of 23 million in the year 2000, we will need at least 6,786 specialists for the country, using varying specialist:population ratios for the various disciplines as the basis. The local universities have successfully produced approximately 700 specialists since 1986 and 1,399 more are presently being trained, of whom 288 are expected to graduate next year. Although the number of doctors trained in postgraduate medical education has doubled since the introduction of the local postgraduate programme under the open system in 1996, it can be appreciated that we will still be short of our target.

Overseas postgraduate courses

The other alternative of course is for our doctors to sit for the overseas postgraduate examinations. The exact number of doctors pursuing postgraduate education at overseas centres is not known as almost all of them do so quietly at their own expense and without declaring their intentions to the authorities. Although the Public Services Department (PSD) no longer offers scholarships to those pursuing basic postgraduate degree overseas, it allows doctors to do so on fully-paid leave. The Part I and II of The MRCP (UK) for both adult and pediatric medicine can now be taken once a year in

Malaysia. Most overseas professional colleges, however, have made or will make significant changes in the structure and conduct of the postgraduate examinations. Doctors wishing to take up surgery, for instance, have to sit for the MRCS or the AFRCS (entry qualifications) before being permitted to undergo a formal 4-year surgical training programme leading to the FRCS (exit qualification). Places for the latter programme are limited and there is no guarantee that our doctors will be offered places. Not many of our doctors wishing to do surgery, therefore, relish the thought of going overseas to fulfill their aspirations in surgery. The local Masters programme is probably the best option for them. Those interested in Internal Medicine, Pediatrics and O&G can still sit for the MRCP and the MRCOG examinations in Malaysia and at overseas centres and the degrees obtained are still accepted as "exit" qualifications in Malaysia. They will then have to undergo 18 months of supervised training at accredited training units in Malaysian hospitals before being gazetted as specialists. Those who qualify from the local Masters programme require only 6 months for gazettement.

Number and type of specialists produced

Although the number of specialists trained locally and abroad in Malaysia has increased, it falls short of the required projection for the year 2000, even if we take into consideration the numbers presently available at the Universities and the private sector. Also there is some disparity in the distribution of specialty services within the MOH. As of 1.4.99, the MOH has 156 general physicians, 131 pediatricians, 130 surgeons, 80 obstetrician & gynaecologists, 55 psychiatrists, 60 radiologists, 70 pathologists, 62 orthopaedic surgeons, 86 anaesthetists, 57 ophthalmologists and only 27 otorhinolaryngologists. Doctors applying for the "less popular" disciplines will be given special consideration in order to correct the imbalance.

Subspecialty training

Malaysia has yet to offer a certified subspecialty postgraduate course. I believe UKM will be offering such a course in Cardiology soon. There are however accredited subspecialty training centres in Malaysia and these include cardiology, cardio-thoracic surgery, nephrology, urology, neurology, neurosurgery, gastroenterology, hepatology, respiratory medicine, rheumatology, endocrinology, dermatology, infectious disease, hematology, plastic surgery and hand and microsurgery.

In the MOH, doctors wishing to subspecialize after procuring the basic specialist degree will have to undergo a 3-year formal training programme locally, with the option of completing the third year at overseas centres to learn procedural skills and upgrade knowledge in very specialized areas that are not freely available in this country. The PSD provide scholarships for this purpose. As it stands, the MOH has under its wings 14 dermatologists, 5 neurologists, 9 nephrologists, 8 respiratory physicians, 7 forensic pathologists, 7 cardiologists, 13 urologists, 10 neurosurgeons, 5 plastic surgeons, 9 pediatric surgeons, 7 cardiothoracic surgeons, 1 hand and microsurgeon, 5 radiotherapists and 3 specialists in rehabilitation medicine. The total number of specialists, including 58 doctors who are presently undergoing subspecialty training, in MOH hospitals is 1,003 at present. The lack of accredited subspecialty training centres in some disciplines in MOH hospitals makes it necessary for some of our doctors to be posted to the universities and even private hospitals for such training.

In the pursuance of specialization, we must not forsake our unique training system which teaches us to be competent in common medical emergencies, for example, and yet retain the right to provide highly specialized services whenever the need arises. The concept of a generalist physician with special interest in a specific clinical area is probably the best model to follow and is being strongly advocated by professional colleges abroad. However we still need a pool of doctors to undergo advanced subspecialty training to provide the best possible service to the community. While we welcome specialists to subspecialize after procuring their basic specialist qualification, we are concerned about the increasing trend towards greater subspecialisation to a degree that makes them terribly dependent on others when confronted with patients with multiple problems. In other words, there is a trend towards *learning more and*

more about less and less.

Generalists

Concerns have been expressed in western counties regarding the dwindling number and role of specialists with general interest (the so-called generalists). The trend towards more specialization is inevitable of course if one wishes to achieve excellence in a particular field. Also with greater specialization, we will be in a better position to attract patients from the region in the spirit of medical tourism. Notwithstanding this, generalists with special interest in certain areas still play a very important role in the total management of patients and will be in a very good position to provide initial treatment and advice to patients with acute illnesses and multiple medical problems, something the highly specialized subspecialists find difficult to do. There needs to be a balance between the two. The Malaysian postgraduate training programme is unique as it adopts a holistic approach to postgraduate training. In the UK, professional colleges are structuring their training programmes for the benefit of general physicians including those with special interests in a specific clinical areas. This holistic approach is chosen to provide a "seamless" service to patients.

Development of a subspecialty service

The development of specialist services should be well co-ordinated and well-planned. Specialists can be rendered helpless without a supportive specialist team. Their ability to function efficiently and effectively depends to a large extent on a supportive skilled workforce eg. skilled nurses. They need to also establish inter-disciplinary and inter-institutional linkages to provide the best possible care for their patients. A hepatologist for example will require the expertise of pathologists, radiologists, virologists, hepatobiliary surgeons in order to execute quality treatment. If possible the whole team should be trained at the same centre.

In the planning of our subspecialty services, we must put the interest of the nation first before that of the doctor. Doctors tend to aspire for disciplines that will allow them to be more "marketable". Being able to perform procedures eg. interventional cardiology and endoscopy is one way of achieving this status. Unfortunately after having mastered these skills, they begin to get restless and give any number of reasons to leave for the private sector. It is most important for the MOH to allocate places for all subspecialties and attract doctors to take up "less popular" disciplines. Otherwise we may end up training more of the same and after some years when they leave the service, we churn out even more of the same as well. Doctors have 2 choices when they wish to take up postgraduate training. Either they choose one that is readily available (probably because it is still new or is not "popular") or one that they have to wait for (because of too many applications as they are considered "popular"). A bit of "policing" may be necessary to ensure greater accessibility and equity of highly specialized care for our patients. Otherwise, we will continue to lag behind the rest of the world in the various fields of medicine and be forever dependent on other countries whenever we are faced with a problem or a crisis, wasting precious ringgits along the way.

Clinical governance

Clinical governance is the acceptance of the responsibility by individual physicians to work in a way which is consistent with the values and strategic objectives of the organization which employs them. Within this, there is a responsibility to maintain good medical practice and achieve high standards. The responsibility of the organization to provide appropriate facilities for medical work and to support the professional development of physicians and clinical teams on a continuing basis. We must be accountable for clinical performance of our doctors. We must examine new ways to deliver clinical excellence

A high standard of medial practice is prerequisite of good medical care and clinical governance is the means for ensuring maintenance of high standards. The Academy of Medicine of Malaysia and other professional bodies must be involved with the development of standards in the clinical specialties.

Specialists of the future

Quantity is of no use without quality. We all know that. We must ensure that the specialists we produce can and will improve the quality of care of our patients. They should practise evidence-based medicine and work towards improving

medical and health outcomes. Healthcare costs must always be considered before making management decisions. They must be prepared for the numerous challenges in the next millenium, be prepared to accept the public as healthcare advocates, be mature enough to accept constructive criticisms regarding their clinical competence, engage actively in continuing professional development (CPD) and self regulation and be prepared to learn management skills. In addition, specialists of the future must be proficient in information and communications technology. These are some of the factors we need to consider as we plan our postgraduate education for the future.

Good medical practice requires putting patients first. Doctors must have the commitment to sustain and improve the quality of care through greater professionalism and teamwork. Postgraduate education of the future is not just about the acquisition of core knowledge. It needs to incorporate the learning of newer disciplines such as the cell biology, molecular biology, genetics, behavioural and social science, ethics and law, management skills, public health medicine, epidemiology, health economics and health informatics. Specialists of the future must know the difference between efficacy, effectiveness, efficiency, equity and economy.in the management of their patients and still be able to care for their patients through improvement in their communications skills.

Challenges for the future

Dramatic changes in healthcare are expected in the 21st century as a result of changes in the practice of medicine and in society. These include changing demographics and the pattern of disease, new technologies, changes in healthcare delivery, increasing consumerism, patient empowerment and autonomy, changing professional roles and emphasis on effectiveness and efficiency. These represent challenges facing the medical profession in the next millenium. Our postgraduate programmes must be tailored to address these challenges. Initiatives such as distance learning under the Telemedicine Flagship Application of the Multimedia Super Corridor should be maximally exploited to facilitate all levels of training and promote personal empowerment and responsibility of health. Patients should be provided with all levels of care wherever they are.

The most important consideration in the development of future postgraduate training programmes is whether such an effort will indeed improve the quality of care of the community and improve health outcomes. If specialization is to be developed, it has to be for the benefit of patients, the community and the nation as a whole and not health professionals alone.

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Dato' Dr. Mohd. Ismail Merican, FRCP

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PHYSICIAN TRAINING -TOWARDS THE NEW MILLENNIUM

Donald Cameron
President, Royal Australasian College of Physicians

Let me tell you how honoured I am in my own right and on behalf of the College to have been asked to give this oration. I am certainly unaccustomed to speak on such a topic.

I wish to begin by telling you a short story. The famous English detective Sherlock Holmes and his trusty companion Dr.Watson left their lodgings in Baker Street to go camping. They set up their tent and, after a good dinner, went to bed. In the early morning hours Holmes nudged Watson and woke him up. "Tell me, Watson," he said, "What do you see?" "Ah" replied Watson. "I see millions and millions of stars." "Yes", said Holmes, " but what does it mean to you?"

"Well," said Watson after some thought, "Emotionally it indicates to me the endless beauty of nature. Astronomically it indicates that there are millions of galaxies and probably billions of planets out there, theologically it confirms my belief that there must be a god to have created all of this, meteorologically it tells me we will have a fine day tomorrow. Now tell me Holmes what does it tell you."

"Elementary, my dear Watson", replied Holmes, "some scoundrel has stolen our tent."

In some ways this exemplifies the problem confronting us as medical educators - a need to produce doctors with the social and cultural perspective of Watson but also the pragmatic analytical capacities of Holmes.

As we approach the end of this millennium and contemplate the next, it is appropriate to think about where postgraduate medical education should be heading. It is important that you realise what I am. I am not a professional educator, I am a physician and a subspecialty one at that. I have, however, had opportunities in my professional life to teach undergraduates and postgraduates and for a time had the privilege to participate in and subsequently Chair at various times the Written Exams Committee, the Committee for Exams and the Board of Censors of the Royal Australasian College of Physicians. In my present role as President of the College I have an overall responsibility for our educational activities. We have recently started an overall review of our education and assessment procedures leading to Fellowship to run alongside our review of our MOPS program which had previously been put in place. Although various modifications to our procedures had been put in place over the years no comprehensive review had been undertaken since Bryan Hudson had introduced his radical reforms in the early 1970s.

When I try to think of what characterises the system of medicine we espouse and sets it apart from others, I conclude it is that it is based in empirical science. Of course we continue to value a range of humanistic qualities but these are valued equally in other systems. Thus, whatever else we do with postgraduate education in the next millennium we must ensure that young physicians are well grounded in science and that ageing physicians continue to understand the science in which their craft is embedded. This is not just an option but a necessity. As has been pointed out by Holly Smith practising physicians must continue to understand the language of their profession. When we turn to read the Lancet or the New England Journal not just Nature or Cell, we are confronted with the language of molecular genetics or cell biology or with the language of the social sciences. Not to understand is to cut ourselves off from the knowledge we need to practice at the highest level. I wonder what will be the new dialects in 50 or 100 years time?

Before considering some of the factors impacting on postgraduate education I think it is important to suggest that it is desirable if not essential that we set ourselves a philosophical framework with which we pursue our educational objectives.

The Royal College of Physicians and Surgeons of Canada has been undertaking an extensive review of its training with a view to the new millennium. One of its working parties has addressed the issue of the essential roles and key competencies of specialist physicians. It has defined these, outlined the competencies and defined the specific objectives of training.

The essential roles they have defined are:

- Medical Expert
- Communicator
- Scholar
- Collaborator
- Manager
- Health advocate
- Professional

I do not intend to go through these in detail but I believe anyone with a serious interest in postgraduate medical education would find a careful consideration of the Canadian documents useful. Since, as I have mentioned, we are currently undertaking a detailed review of our education and assessment procedures and also of our maintenance of professional standards program, we have included them in our review.

Let me however refer to three of the roles I mentioned, to give you the flavour.

Medical Expert and Clinical Decision-Maker. The Canadian document (1) offers the following definition and list of desirable competencies from which I qoute:

Definition

Experts possess a defined body of knowledge and procedural skills, which is used to collect and interpret data, make suitable clinical decisions, and perform diagnostic and therapeutic procedures within the boundaries of their expertise. Their contribution is characterised by up-to-date, ethical, and cost effective clinical practice and effective communication, in partnership with patients, health professionals, and the community. The role of a medical expert and clinical decision maker is central to the function of specialist physicians, and draws on the competencies included in the roles of scholar, communicator health advocate, manager, collaborator and professional.

Competencies

The expert is able to:

- Demonstrate diagnostic and therapeutic skills to effectively and ethically manage a spectrum of patient care problems within the boundaries of his or her specialty.
- Demonstrate medical expertise in situations other than in direct patient care. Recognise personal limits of expertise.
- Demonstrate effective consultation skills. This includes presenting well documented assessments and recommendations in both written and oral form, in response to a request from another health professional.

Manager

Definition

Specialists function as managers when they make daily practice decisions involving resources, co-workers, tasks, policies and their personal lives. They do this in the setting of individual patient-care, practice organisations, and in the broader context of the health-care system.

Competencies

The specialist is able to:

- Use time and resources to balance patient care, learning needs, outside activities and lifestyle.
- Allocate finite health care resources effectively. This implies the ability to make sound judgements on resource allocation based on the evidence of benefit to patients and the population served:
- Work effectively and efficiently in a health care Organisation.
- Use information technology to optimise patient care, continued selflearning and other activities. This implies the ability to use patient-related databases, access computer-based information, and understand the basics of medical informatics.

Professional

Definition

Specialists have a unique societal role as professionals with a distinct body of knowledge, skills and attitudes dedicated to improving the health and well being of others. Specialists are committed to the highest standards of excellence in clinical care and ethical conduct, and to continually perfecting mastery of their discipline.

Competencies

The specialist is able to:

- Deliver the highest quality care with integrity, honesty and compassion. This implies an awareness of racial, cultural, and societal issues that have an impact on the delivery of care, and an ability to maintain and enhance knowledge, skills and professional behaviours.
- Exhibit proper personal and interpersonal professional behaviours.
- Practice medicine in an ethically responsible manner that respects the medical, legal, and professional obligations of one who belongs to a selfregulating body.

I will not list the specific objectives which are really meant to set the educational agenda. While we may all have some quibbles with the detail of the Canadian document I think the clear definitions which they have arrived at are enormously helpful in allowing one to set a framework around which one can define educational objectives, educational methodologies and appropriate assessment procedures. You may say that the Canadians are defining supermen and women but I believe we should make no bones about the fact that what organisations such as ours are about is excellence and standards.

There is now a clear recognition that postgraduate training must be seen as part of the continuum starting at entry into Medical School and ending with retirement from practice. It is also becoming clear that this must apply to all doctors not just those who have undertaken traditional vocational training. Undergraduate education in general, and in the postgraduate schools in particular, is intended to prepare students for continuing self education placing emphasis on developing the abilities to define problems, obtain information and draw conclusions - skills that will be needed lifelong. It is also recognised that young doctors emerging from medical school are not equipped, after a further year or two of unstructured apprenticeship, to undertake unsupervised practice.

In Australia, the immediate postgraduate years are now being specifically integrated into the education continuum. Under the auspices of Postgraduate Committees in all States, objectives for training in PGY1 have been established, educational activities put in place and assessment of outcome established. A similar process to cover PGY2 is in process of development. The underlying philosophy is that these should be years providing a wide general experience although it is recognised that some vocational streaming would be appropriate in the 2nd year. For those individuals who do not wish to undertake one of the College based training programs, there are plans to develop training programs for PGY3 and beyond. Due to the peculiarities of our health system, as well as for sound educational reasons, there are now very considerable pressures for all medical graduates to undertake formal vocational training. If we are to insist that all doctors need to undertake further formal training after they leave medical school, regardless of which branch of medicine they will practice in, it clearly has enormous resource implications. It is equally clear that the knowledge acquired by the end of vocational training will not sustain a lifetime of practice and thus there is a need for continuing education to ensure the maintenance of professional standards. In Australia particularly through the auspices of the Committee of Presidents of Medical Colleges, we are examining the possibility of different Colleges developing educational activities in common. It is apparent that many (perhaps all) Colleges have, in common, certain core learning objectives for their trainees, e.g. a knowledge of ethics, of epidemiology and statistics and perhaps even basic sciences. Thus it is seen to be sensible both in terms of pooling expertise and maximising resources to develop educational modules which can be shared. The development of shared modules also allows trainees to retain credits if they wish to change direction after some time in a particular training program.

Some particular issues are impacting on our educational activities in Australia and give force to efforts to provide efficient and flexible vocational training emphasising educational content rather than mere time serving. These include

1) the move to an increased age of medical graduates brought about by the emergence of Graduate Schools of Medicine and a more liberal late age entry policy in the traditional straight from school program. For example, in Queensland in the first year of the Graduate Medical Course the mean age at entry was 27 although this fell in the next year, and
2) the increased percentage of women in Medicine and the increased percentage of those women who are undertaking further postgraduate training. These two factors will mean that we have to evaluate such things as the optimal length of postgraduate training, the place of part time training etc.

A matter of ongoing debate is what is the correct balance between general and subspecialty training for future physicians and paediatricians? Our approach has been to have three years of broadly based training followed by a further three years of specialised training. This general approach is widely used although in some countries specialisation can begin immediately after graduation or even as an undergraduate. What should our future direction be? Given the ever-increasing information load, how realistic is it that specialists can maintain even rudimentary general skills? Given the nature of physician practice, based on the central role of the consultation, I would hold that a strong general basis can only enhance the standard of subsequent specialist practice. However, if we are honest, there are already those in the physicianly ranks for whom the traditional consultation is no longer the central event in their practice. For instance, does the procedural cardiologist need to have a broad range of physicianly skills or should he go from medical school to a technical training course so he can carry out these procedures at a time in his life when his hand is steadiest, his vision most acute and his stamina greatest. Should he be considered a physician or an interventional radiologist practising in a very limited area? I conclude that we need to keep our minds open and not be mesmerised either by tradition or by a belief that one model fits all. If we can define the roles of the particular doctor, clearly we can develop educational objectives and develop appropriate educational methodologies. We train surgeons differently from physicians and cardiologists differently from endocrinologists. I believe we need to give very much more thought, even within internal medicine, as to what are the common needs and what is discipline specific. In addition we should question whether it is appropriate to define adequate training in terms of time rather than content and particularly whether all disciplines or even all individuals within a discipline require the same length of time to, be adjudged competent to practice as consultants.

What principles should we be applying to education in the future? The Canadians are at pains to point out that the educational methods should be tailored to the particular objective. In our own review which is still at an early stage, two principles already appear to be emerging. One is that training should continue to be on an apprenticeship model and the other is that education should be based on the principles of adult learning.

It is our hope, and indeed our expectation, that tomorrow's graduates will be better versed in the principles and practice of self directed learning than those of our generation. In the undergraduate courses they will already have had to cope with an information overload far greater than that which confronted us. They will

have been expected to set learning objectives, seek information and decide what is important and above all, to use the incredible resources available to obtain factual knowledge. It will be our duty to foster and expand these skills. However, it will also be our duty by precept and example to help develop the clinical and humanistic skills that surround the scientific basis of our profession.

Part of our contract with our young colleagues will be to show that our own practices are based on evidence. Our authority as teachers will be vulnerable as never before because of the ready access to information. The old tension between "it is not known" and "I don't know" will be starkly evident. The very presence of this easy access to factual knowledge can bring with it a difficulty in dealing with uncertainty. Teaching how to cope with this uncertainty in the many circumstances when adequate information is not available and we are forced back on a combination of first principles and experience will be an important role.

If I can just pursue the issue of evidence based medicine a little further. I have already stated my belief in the centrality of science to our craft. I am a strong believer in using the best available evidence for all our activities. However, what we should also be encouraging our young people to do is to question the fundamental basis on which that evidence is constructed. They should consider whether our basic constructs are not the newest version of the miasmic theory of disease.

This leads me on to the place of research in the training of future physicians. There are two aspects. First, it would be my contention that the best education for future physicians takes place in institutions and by people active in research. The chance to be exposed to the enquiring mind of the true researcher is invaluable. Second, undertaking research as part of training is potentially valuable. I personally do not believe making a period of research mandatory is appropriate, particularly if it is coupled to a requirement to publish at least one paper before being granted certification. While this may encourage a few to take on a serious research commitment in the long term, it may well give rise to a lot of superficial research which will add to the glut of lower quality publications. What I believe we should do is be careful in designing our education and training programs to foster significant research experience without imposing a crippling burden either financially or in time in the overall training program. We have addressed this with partial success by allowing MD or PhD programs to overlap the time usually devoted to clinical training and thus not lengthening the time taken to obtain our diploma. There is still, however, the risk that the seriously research oriented physicians by the time they have finished professional training, a PhD and one or more post docs, will be approaching the retirement age by the time they are in a position to obtain a substantive post. The capacity to develop true clinician scientists will be one of the most significant challenges we will have to face in the coming years in postgraduate medical education.

Let me now turn to one of the most vexatious issues in postgraduate education, that of assessment. I will confine myself to some remarks about assessment of physician vocational training. I would contend that most assessments should be formative although of course summative assessments are necessary. Again the Canadian framework makes apparent what is well known to all of us - that the methods of assessment need to match what it is one is trying to assess. Among our responsibilities we must assure that the type of assessment is appropriate and of a very high technical standard. This requires a high commitment of resources. It is still our view that direct assessment of clinical competence is important for physicians and paediatricians. We persist with a national clinical examination at the end of the basic training program. In the last few years we have modified the clinical exam to enhance its psychometric properties. The Director of Education, Neil Paget, assures me it is now a robust examination for this type of exam. However, the downside is that the logistics of providing this exam with its increased number of observations have become horrendous. We have explored other formats e.g OSCE. We have discussed the role of standardised patients and a range of other issues and decided for various reasons not to adopt them. One thing we have done in order to improve the reliability of the exam is to run regular training and calibration sessions for our examiners.

As you are probably aware, after our trainees have passed the examination at the end of basic training, we do not have an exit exam. For this we are often criticised. However, I am a stout defender of our system. During advanced training our trainees can expand their horizons, develop particular interests and further their abilities to set their own objectives. Most will need some guidance and all will need a stimulating environment in which to develop. In my opinion it is far more important for the trainees to develop a sense of excitement and enquiry, and decent critical skills than to try to see 100 examples of every condition known to their specialty. In the more technical areas a sufficient experience is clearly necessary. What is of particular concern to me is that as mentors we should not be trying to clone ourselves. Our skills are becoming dated. There is a new world awaiting the young. This of course is not to decry the importance of role models which remains as crucial as ever.

In keeping faith with the community it is, of course, crucial that we ensure those completing our programs are well qualified. Since in our system we rely on supervisors' reports for this assurance, we must ensure that

these supervisors are well trained and competent. We are developing a system of training and certification of our supervisors. Chairmanship of a department does not guarantee one has the necessary skills to be a good supervisor.

Before turning to consider, briefly, some issue to do with MOPS I would like to mention some of the principles and directions coming out of our review of education and training. The first is the need to broaden our curricula to encompass a public health perspective as well as illness models of care. The second is to reconsider the setting for training moving much of our education from tertiary level teaching hospitals to ambulatory and community settings.

Points that have been raised some of which I have already mentioned are:

- There must be clear objectives and guidelines for training. Clearly, examinations drive curricula or at least the activities of trainees. However, most would now agree that there is a need to define a curriculum and training objectives and that the assessment procedures should subserve that curriculum. The problem in medicine is to strike the balance between a series of motherhood statements and a proscriptive list that looks like the index to Harrison's textbook. While I have previously been opposed to the definition of competencies for a complex profession like medicine, I have become more attracted to the Canadian approach of defining roles and competencies since they can be framed in a way which still allows a broad approach and not be proscriptive. We are currently trying to produce a satisfactory statement on curriculum and it is proving very difficult.
- Training and assessment should include humanistic skills and attributes, including ethics, self-management, self-appraisal, communication skills, an understanding of the health care system and critical appraisal. The real difficulty in many of these areas is developing valid assessment tools.
- The educational principles and methods of undergraduate and early postgraduate learning need to be continued
- Training should continue to be apprenticeship based
- Training should be patient-oriented, learner driven, should encompass health needs as well as illness models of care, and should have a significant focus on ambulatory and community needs
- Training should provide a foundation for lifelong learning and self-appraisal after qualification as a consultant
- Supervision must be of the highest standard, with supervisors trained and accredited
- Assessment should be predominantly formative

May I turn briefly to CME, or as we term it, MOPS. If the issues surrounding vocational training are significant, these are formidable. Here we must have strategies which will sustain learning over 30 - 40 years. These strategies must allow for an infinite range of individual practice but must address areas of need as well as areas of interest for the individual and ultimately must reassure the community of their efficacy in maintaining a high quality workforce. The use of the principles of adult learning with self directed learning and the use of a variety of technologies will be prominent. In general the group is highly motivated but one has to develop mechanisms to ensure participation of the whole group. Perhaps the greatest challenge however is to develop methods that can attest to the standards of performance of all physicians, not just their knowledge or competence as judged by some exam process.

Finally, if I could again state the obvious. The group of people we are asked to educate are highly intelligent and highly motivated. Our duty is to fuel their enthusiasm and facilitate their journey of discovery. However, we have to answer to the community for our efforts and therefore must have an appropriate means to ensure we have been successful. It is worth reflecting on the fact that failure of our trainees to reach the goals we set, probably reflects more on us as educators that the trainees as scholars. I believe that the products from our own College system practice high quality medicine as I am sure those who emerge from your system do as well. However, Physicians are by nature conservative and the institutions we inhabit are conservative and difficult to change. We must remember that we are not in the business of training young doctors for yesterday or even for today but for the future. So, we should be prepared to question all the old dogmas, all the things we hold most dear to our hearts and, after careful consideration as befits good physicians, change those things that will benefit from change.

(1) Societal Needs Working Group, CanMEDS 2000 Project, "Skills for the New Millennium". Annals RCPSC, 1996:29,206-216.

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MAGICAL MOMENTS IN MEDICINE
Part 6: Renaissance Medicine

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Prologue

The period between the last breath of the medieval night and the first glimpse of dawn of the next era is a dreary 75 years, during which we see no spectacular happenings. After the devastating medieval Black Death in 1347 AD, the process of medical evolution appears to have taken a long sabbatical. Demoralised physicians and barber surgeons, who could offer no cure for the plague epidemic, lost their credibility with the public and therefore, lapsed into oblivion. Shakespeare's comment "trust not the physician; his antidotes are poison" in *Timon of Athens* (1607) therefore, does not strike us as bizarre.

However, in the middle of the fifteenth century, there was a discernible pattern of change occurring in the minds of men. This new mind-set pushed them away from traditional beliefs towards independent thinking and created eagerness within them to consider aspects of the world and human life. This movement was, naturally, away from spiritual realms and quite innocuous at the start and I dare say the church saw this change as one that might eventually undermine its authority. But later, when the church tried to defend its authority, it realised it was fighting a losing battle, since Universities were now forging ahead with studies totally independent of the church and clergy. Thoughts, observations and experiments were unconstrained by theological doctrines. Interpretations of phenomena were made without consideration of religious implications. Political independence from the church coupled with a renewed interest in ancient classics, fostered a flowering of scientific, medical and cultural accomplishment that is almost unparalleled in human history. This welcome and worthy transformation warranted an appropriate name and was christened Renaissance. The term originates from *rinascita* (meaning rebirth or revival), a word first used by a Florentine artist named Giorgio Vasari to describe the period where evolution looks back to ancient Greek and Roman culture to rediscover their truth and glory. Officially, it extended between 1451 and 1600 AD.

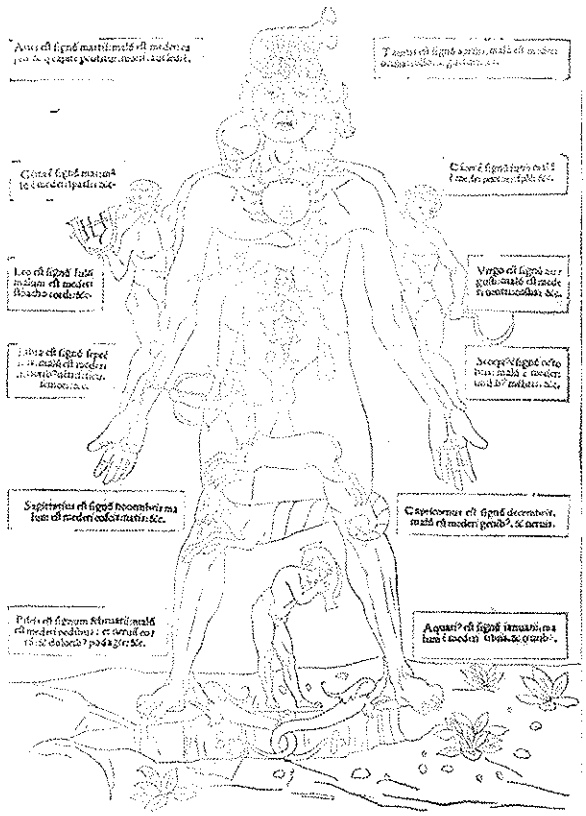
The first nation to recover from late medieval inactivity was Italy, which realised it was time to patch wounds, tighten belts and move on. The Italian Renaissance stimulated medical practice, just as it did all other intellectual pursuits. Physicians and scholars began to scientifically study medicine with renewed zeal and vigour. Nobody knows where all this creative energy came from, but the boot-shaped Mediterranean peninsula was surfeiting with new ideas and artistic thinking. The fine "art' of medicine was literally made artistic, thanks to the gifted artists of this period.

The landmark breakthrough of this age, however, came from an obscure goldsmith in Germany named Johanes Gutenberg, who invented printing with mobile type in 1454. This one technique itself may be said to have changed the nature of the human world. Knowledge, which was hitherto the prerogative of the elite rich, became gradually available to the masses.

Art and Astronomy

It may seem strange (and even inappropriate) to include descriptions about the evolution of natural sciences apparently remote and unrelated to the practice of medicine. But in the final analysis, it would be clear that the advancement of medicine is very much dependent on the technology gained from basic natural sciences. The laser, the ultrasound, gamma radiation and the like were contributions to medicine from physics, while antiseptics and antibiotics were nothing but chemicals with pharmacological value. Therefore, it is evident that ideas and the discoveries that arise from hypotheses of natural knowledge have significance to other fields as well.

Vast knowledge was gained in astronomy, thanks to the work of Copernicus and his contemporaries. Its progression was scientific, rational and methodical. However, Renaissance astrology was just an extension of popular ancestral doctrines and although it was taught as a subject in the Universities, many Renaissance treatises explicitly condemn it. Certain astrological concepts eventually got entangled with medicine, resulting in a hybrid product called astrological medicine. This assumed that the motions of the heavenly bodies influenced all human affairs and health. In practice, astrological medicine required knowing the exact time at which the patient became ill. With that information and the study of the heavens, the physician was able to predict the gravity of the condition, the prognosis of the disease and even foresee critical periods, where the patient's condition is likely to get worse. Jerome Cardan was a mathematician cum doctor, who firmly believed in astrological medicine. In his book *De Vita Propria* (Book of my Life) he states that specific points on the patient's head can represent astral influences (Picture A). Cardan invented a system called *metocoscopy*, which was a kind of astrological divinatory technique to diagnose diseases. Horoscopes



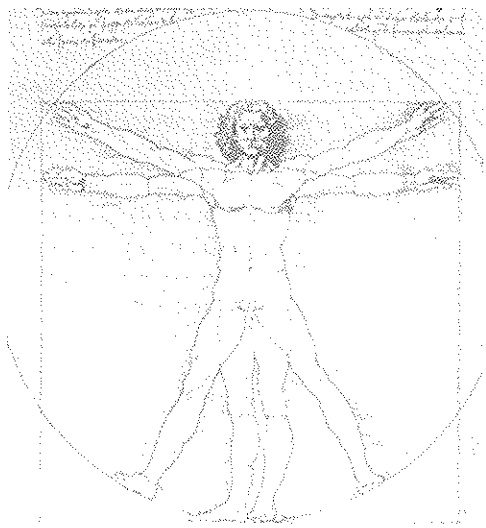
Picture A. Astrology and Medicine: Picture from Johanes de Kelham's Fasciculus Medicinae (1522) which is a zodiac illustration relating the astrological ties of Renaissance Medicine.

soon came into vogue and astrologers started writing them as soon as babies were delivered.

Professional artists and sculptors played a vital role in the early development of anatomy. Apart from familiar names like Leonardo da Vinci, Michelangelo and Raphael, there were others like Durer, Titian, Donatello, Verrocchio and Tintoretto who were no less accomplished. However, Leonardo da Vinci deserves mention since apart from being an extraordinary artist, he was also an anatomist, an inventor, alchemist, engineer and architect.

Leonardo da Vinci

Leonardo da Vinci (1452 - 1519) is perhaps the ideal "Renaissance Man" who studied almost everything that existed. Although he focused on the practical workings of nature, he also had an idealised sense of humanity that was the hallmark of the Renaissance era. We see this left-handed artist as a genius with great intellectual hunger. He hypothesised on human beings, animals, light, mechanics and had numerous futuristic projects on the anvil. However, none of them took off, including the aeroplane and helicopter that he designed. (I would recommend the movie 'The Hudson Hawk' to those who would like to see a very realistic Leonardo and his laboratory, complete with alchemy cauldrons, aeronautical models and other gadgets). He might have been a wee bit paranoid about people stealing his ideas, since he kept all his notebooks in a code. He had made thousands of pages of scientific and other observations, but since most of them remained undiscovered or unpublished, no major scientific breakthroughs resulted from



Picture B. Mathematics and Medicine: The Vitruvian Man of Leonardo da Vinci, illustrating the geometric symmetry, proportion and relations of the human body.

his work. Therefore Leonardo's legacy has been described as "the epitome of greatness in failure."

Leonardo's interest in anatomy started when he joined Andrea del Verrachio as an apprentice. Verrachio insisted that all his pupils learn anatomy and hence, to make realistic drawings and to further his knowledge of anatomy, Leonardo dissected human bodies at a hospital in Florence to see how the structures were put together. He is said to have spent countless nights dissecting and apparently he enjoyed "cadavers by candlelight". He also dissected pigs, oxen, horses and monkeys. He was convinced that all problems could be reduced to mathematics and mechanics. In his famous "Proportional Study of Man in the Manner of Vitruvius" (drawn in 1487) Leonardo saw a kind of mathematical perfection in the human form. It depicts the human body within the ideal form of the circle and within the perfect proportions of the square. (Picture B). More than 750 anatomical diagrams of Leonardo are in existence today and most of them show amazing accuracy and detail. They represent the skeletal, muscular, nervous and vascular systems and many of them also have annotations of a physiological nature. His correct assessment of the curvatures of the vertebral column and exact depiction of the foetus *in utero* were examples of his meticulous work.

Medicine

Renaissance medicine was a bit slower to develop than other subjects like astronomy and physics mainly since medicine did not have suitable technologies available as

they were to others. Moreover, medicine was a discipline having not only physical and biological dimensions, but also another abstract dimension of psychological, social, philosophical and religious overtones. This made understanding of the human body much more difficult than the stars and the sky.

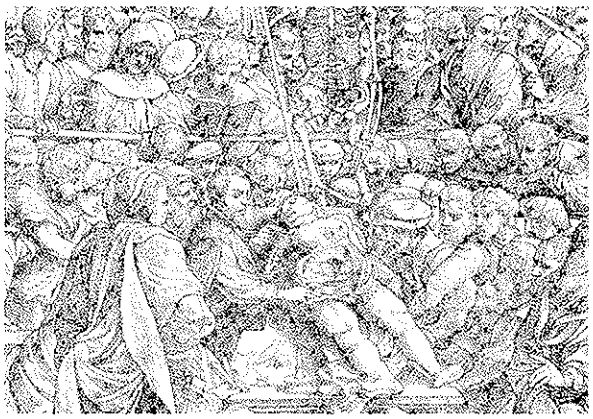
Pharmaceutical practices established by Arabic physicians were studied and refined. Pain was identified as one of the key elements causing emotional and physical distress to mankind and new medicines (like laudanum) that helped to stop or reduce pain were introduced. Some Renaissance physicians investigated the spread of infectious diseases. Human anatomy was one area where a great deal of attention was paid. This led to the detection and correction of many of the errors that had gone undetected for centuries and were rapidly disseminated through the new invention of printing. One man – an anatomist – considered the greatest of his time (and perhaps of all times) who played a key role in this process was Andreas Vesalius.

Andreas Vesalius

Born in Brussels on New Year's Eve, 1514, Andreas Vesalius came from a long line of physicians who were in royal service. His father was an apothecary to Emperor Maximillian and later, to his son Charles V. Vesalius matriculated at the University of Louvain in 1530 to pursue an arts curriculum and studied ancient languages. It is unknown when or why he decided to study medicine, but he enrolled for a medical degree from the University of Paris. He was, however, forced to discontinue in 1536, when he fled Paris because of the war between France and the Holy Roman Empire. He returned later to continue his studies and received his bachelor's degree in medicine the following year. In the same year, he enrolled in the medical school of the University of Padua. With his previous clinical experience and knowledge at Louvain and Paris, it was only months before Vesalius passed his exams and received his second doctorate in medicine.

Picture C. Andreas Vesalius. *Anatomist Extraordinaire.*

His primary interest was in anatomy, but medicine, physiology and pharmacology also intrigued him. He acquired great skill in dissection, but for a period, remained under the influence of the Galenic concepts of anatomy. Immediately after his graduation from Padua, Vesalius accepted a position there as an *explicator chirurgiae* or a surgical demonstrator and began lecturing on surgery and anatomy. Very soon, he established a style of his own and rose to the professorial cadre. In his time, there was a definite hierarchical system, at least as far as anatomy teaching was concerned. The professor, draped in long robes, sat in a great chair reading the lecture, with a cadaver on a table down below. A junior colleague – the *ostensor* – pointed out the line of incision, while the third – the *demonstrator* – did the actual cutting. But Prof. Vesalius broke protocol and shifted paradigms by carrying out his own dissections for his classes. In his audience were medical students, physicians, interested civic officials, sculptors and artists (Picture D). He first produced, as teaching aids, four large anatomical charts. As one would expect, one of his charts was plagiarised and published. As copyright violation acts hadn't yet been enacted, Vesalius painfully soon realised that there were unscrupulous businessmen around and printed the remaining three charts with three views of the skeleton. This work appeared in 1538 as *Tabulae Anatomicae Sex*. The following year, he produced an anatomical manual for his students called the *Institutiones Anatomicae*. Vesalius's anatomical researches began to reveal findings contradictory to that of those recorded by Galen in his works. By 1540, Vesalius was convinced that Galen's research did not reflect human anatomy, but was rather the anatomy of animals, which wasn't quite the same as humans. Thereafter, his aspiration in life was to revolutionise the teaching of the anatomy of the human body and to overthrow the then prevailing teachings of Galen,



Picture D. Vesalius performing a public dissection. The audience consisted of people from all walks of life.

the medieval hero, who had drawn his conclusions from dissections on apes and pigs. It took him only five years to shake the hitherto infallible Galenic foundations and convince the people of the truth.

As a student of anatomy in Paris, Vesalius did not mind fighting savage dogs to collect bones from the Cemetery of Innocents. In Louvain, he supposedly stole the remains of a robber chained to the gallows and smuggled the bones back home hidden under his coat. In fact, incidents of grave-robbery were reported wherever Vesalius conducted his lecture – demonstrations. His students were no less enthusiastic in collecting corpses. One ingenious group is reported to have obtained a cadaver, dressed it and "walked" it into the dissecting room as an inebriated student!

In 1543 Vesalius published two works on anatomy directed to two separate audiences. The *De humani corporis fabrica libri septum* or simply the *Fabrica,* was his masterpiece. It was essentially a classical anatomical text and the longer of the two. Apart from being a magnificent volume in the history of medicine, it revealed the courage and independence of thought in line with the resurgent spirit of the Renaissance. It was aimed to persuade the established medical world to appreciate anatomy as the foundation of all other medical research. Vesalius pointed out the glaring errors of Galen and his followers and said that only active dissection and observation of the structure of the human body could correct these misconceptions. It is noteworthy that this great work - considered the foundation of modern medicine - was published when the author was only twenty-nine. The *Fabrica* is a exquisite book, complete with 23 full-page woodcuts, about 180 illustrations in the text, and dozens of charming historiated initials. A second edition was published in 1555, which scholars consider the more interesting of the two, because it contains important corrections and additions. One such revision is the denial of the permeability of the septum of the heart, which contributed very substantially to the ultimate discovery of the circulation of the blood. It met with a great deal of opposition initially, especially from diehard Galenists who reviled and ridiculed the work. Even his teacher Jacobus Sylvius (who perhaps, couldn't stand being overshadowed by his own student) dubbed his once favourite pupil "Vesanius" which meant 'madman'. However, the validity of Vesalius' work soon overcame detractors and *Fabrica* became a classic, which Sir William Osler would later hail as 'the greatest medical book ever written.' The *Epitome*, was for students, and emphasised the importance of dissection and anatomical knowledge in general, in relation to the practice of medicine. It was written in simpler style and was intended to help orient students and other readers before attempting the more formal and advanced *Fabrica.* It is described as "a pathway beside the highway" of the major work. Both works had ample illustrations by Jan Stephan van Calcar, a pupil of Titian, who was a contemporary artist. His ancillary interest in Pharmacology encouraged Vesalius to write the *Epistola* in 1546, in which he mentions the discovery and therapeutic use of chinaroot in the treatment of syphilis, which was terrifying the public during that time. He was also the first to introduce a new surgical procedure for the drainage of empyema. He studied human bones extensively and could identify carpal bones (and their side) blindfolded. The skeleton he articulated remains in Basel till this day.

The publication of the *Fabrica*, saw Vesalius being offered a royal appointment and keeping up with family traditions, Vesalius left academic research in 1543 to become chief physician to the imperial household. He held this position for twenty years under Charles V until his abdication and later under his son Philip II, whom Vesalius served until his own death. While in royal service, Vesalius was the King's chief military surgeon and an esteemed consultant to the various members of the court. An interesting tale is mentioned about King Philip's son, who fell down a flight of stairs, while in amorous pursuit of a pretty servant maid. He developed a haematoma in the forehead, which later got infected, resulting in high physical fever, in addition to that of love. Vesalius incised the abscess, which led to the dramatic recovery of the prince and perhaps, further passionate advances.

With honourable rank attained and ambitions fulfilled, a satiated Vesalius lost steam and abandoned any further research in medicine. He made no subsequent contributions to the cause of medicine. It is not known whether this was a result of the storm of vilification and abuse hurled at him by his contemporaries, following the publication and success of *Fabrica.* Robinson says "His numerous enemies did not silence him, the Inquisition did not smite him in his prime, but the siren of aristocracy seduced him from science." Some historians even insinuate that his early work was almost a sideline to impress the Emperor enough to gain royal commission. Whatever the motives for his initial enthusiasm, he, however, started new approaches to anatomy and physiology. Seldom has any man single-handedly produced a work so phenomenal, at such young an age. Dissection, description and depiction seemed to be the watchwords for Vesalius. Vesalius drowned on 15 October, 1564, in a shipwreck in the Ionian Sea (near the Greek island of Zakynthos) while returning from a pilgrimage to Jerusalem. However, other anatomists carried on the good work in the decades that followed, proving that an innovative motivator can assuredly inspire followers to exploit his methods and gain additional knowledge. Science has always progressed thus and continues to do so until this day.

Anatomical nomenclature

When knowledge began to be shared among the masses, there rose a need for standard nomenclature and thus began the naming of anatomical parts. Jacques Dubois, Vesalius' teacher in Paris, named many blood vessels and muscles, but was lethargic in the publication of his nomenclature work until 1556. His complacency was taken advantage of by Vesalius, who, in a bid to outshine his master, hurriedly published his *Fabrica* and went down in history as the pioneer.

Vesalius took a holistic approach to the body and regarded it as a fabric of numerous inter-related parts. His contemporaries and successors, however, chose to be more regional and piece-meal in their approach. Gabriele Fallopio, who succeeded Vesalius as Professor of Anatomy at Padua is remembered for discovering the uterine tube, later named after him. He also described several cranial nerves, the canal for facial nerve, facial palsy, the inguinal ligament, the vagina and the placenta. Giralamo Fabricius

Picture E. Urethral catheterisation for retention of urine. Whether the obstruction was due to an enlarged prostate or a gonococcal stricture is anybody's guess.

explored venous valves and described the cloacal bursa of birds, which formed the basis for the discovery of B-lymphocytes and allied immunological principals. In Rome, Bartolommeo Eustachio discovered the auditory tube (also later named after him), a catheter, (Picture E) and the valve of the inferior vena cava in the heart. He also produced a superb atlas of anatomy, probably the first of its kind. This was lost for 138 years until 1714, when it was finally discovered and published. Jacobus Sylvius described the flexor digitorum accessorius and the auditory ossicles (the lenticular process of the incus is named after him). He is frequently confused with, Franciscus de la Boe Sylvius, a Dutchman, who discovered and named several arteries and fissures of the brain, much later in the 17th century. The lateral (Sylvian) fissure and the cerebral aqueduct (of Sylvius) are named after the Dutchman. However, Renaissance scientists remained clueless as to the principles of the true circulation of blood. They came close, though. Galen had mentioned that blood from the right ventricle passed into the left ventricle through 'invisible' pores in the septum. Vesalius, strangely, perpetuated this preposterous theory, in the first edition of *Fabrica*. But in 1546, Miguel Servede Servetus, a former Professor of Anatomy at Paris, completed a theological work entitled *The Restoration of Christianity,* which, rather surprisingly, included a theory on digestion and the first ever description of the pulmonary circulation. In page 171, he stated that "the blood from the heart moved through the lungs, where it is made red. Then after a long detour it returns to the left ventricle." However, this was a revolutionary statement, which was not in conformity to classical teachings and hence met with hostility. He was burned at the stake in Geneva for the controversial religious opinions voiced in the book. All traceable copies of his book were also fed to the fire together with him. Subsequently, an Italian botanist named Andrea Cesalpino is said to have stumbled upon the systemic circulation, but apparently he never realised the significance of his discovery or his finding met with lukewarm response. These two scientists changed the direction of anatomical research by focussing on the function and not merely the structure of the human body. Their findings paved the way for the research of William Harvey, who eventually discovered the mechanics of circulation of blood.

Nostradamus

One among the many fascinating personalities of 16th century France was Michel de Nostradame, (1503 - 1566) better known to the world by his pseudonym, Nostradamus. By virtue of his profession as a doctor, Nostradamus finds a spot in our narrative. However, he is renowned not for his healing skills, but for his prophesies. His mystical work, *The Centuries*, contained more than one thousand such predictions and ran into ten volumes. His ardent modern day devotees staunchly believe that

Picture F. Nostradamus - Dr. Doom of Medicine.

Nostradamus correctly predicted such events as the French Revolution[1] advent of Hitler (whom he calls Hister) and the Second World War[2], Napoleon[3], the assassination of President Kennedy[4], the end of the Cold War[5] and even the stock market crash of 1929! (Did stock markets exist then?)

From an early age, the boy showed a talent for prophecy and as a student he was skilled in mathematics and astrology and learned Greek, Latin and Hebrew. His grandfathers were instrumental in Michel's medical education, which included herbal folk medicine as well as the forbidden arts of *Kabbalah* (a mystical, occult science) and alchemy. Michel entered the University of Montpellier as a medical student in 1522, but was annoyed with the ignorance of his teachers about such matters as personal hygiene and the dangers of bleeding and catharsis. After receiving his degree, he held a place on the medical faculty for three years before moving on to practice in Toulouse. A master astrologer, Nostradamus was sought out by wealthy citizens to prepare their horoscopes. He travelled widely, practising medical arts by day while at night participating in an underground network of alchemists and Kabbalists.

He then took to the countryside with his medical and astrological books and bravely assisted in the care of victims of the Bubonic Plague. His prescribed fresh unpolluted air and water and clean bedding for the patients. He had all the corpses removed immediately and the streets cleaned frequently. Each morning before sunrise, Nostradamus would go into the fields to harvest rose petals, which he then would dry and crush into fine powder. From this he made "rose pills", which patients were advised to keep under their tongues at all times, without swallowing them. He is reputed to have saved thousands from plague in Narbonne, Carcassone, Toulouse and Bordeaux.

In 1537, the plague struck again, but this time Nostradamus wasn't so lucky. He confidently applied his methods, but when his own family was fatally afflicted, his medical reputation was ruined. He fled and spent a nomadic life for the next six years wandering all over Europe. It was during this period that he began prophesying in earnest. In 1554, he began writing the first of his books of prophecy. His fame spread throughout Europe and he became a favourite of Queen Catherine de Medici. Nostradamus is said to have died at the age of 66 of renal complications following gout (which apparently he didn't or couldn't prophesy), but his name lives, as believers look forward to the fulfilment of his prophecies.

Before I wrap up the lowdown on Nostradamus, I have some good news and bad news. Actually, I had saved one of Nostradamus' most terrifying and disheartening prophecies for the end. It says,

In the year 1999 and seven months,
From the sky will come the great King of Terror.
He will bring back to life the great king of the Mongols.
Before and after war rules happily.
(Century 10, Quatrain 72)

Interpreted it means that a great catastrophe would happen in July, 1999, which could well be the Third World War, with total annihilation. This is indeed bad news since it means that neither will I be around to write the next episode of this chronicle nor you to read it. However, the good news is that it would not be the end of the world, since according to Nostradamus the world would be ending only in 3797 AD. That leaves mankind with more than a millennium and half to continue walking its wicked ways.

[1] *From the enslaved people, songs, chants and demands,*
The princes and lords are held captive in prisons:
In the future by such headless idiots
These will be taken as divine utterances.
(Century 1, Quatrain 14)

(The French Revolution, which began when the Bastille was attacked on July 14, 1789. Members of the aristocracy were imprisoned and some lost their heads — as did the mob, metaphorically, while engaging in violent actions.)

[2] *Beasts ferocious with hunger will cross the rivers,*
The greater part of the battlefield will be against Hister.
Into a cage of iron will the great one be drawn,
When the child of Germany observes nothing.
(Century 2, Quatrain 24)

(Hitler and the Second World War.)

[3] *The captive prince, conquered, is sent to Elba;*
He will sail across the Gulf of Genoa to Marseilles.
By a great effort of the foreign forces he is overcome,
Though he escaped the fire, his bees yield blood by the barrel.
(Ward 311)

(Napoleon was exiled to the small island of Elba but escaped for 100 days. After a defeat at Waterloo he relinquished all power for exile on tiny St. Helena)

[4] *The ancient work will be accomplished,*
And from the roof evil ruin will fall on the great man:
They will accuse an innocent, being dead, of the deed:
The guilty one is hidden in the misty copse.
(Century 6, Quatrain 37)
The great man will be struck down in the day by a thunderbolt,
The evil deed predicted by the bearer of a petition:
According to the prediction another falls at night,
Conflict in Reims, London, and pestilence in Tuscany.
(Century 1, Quatrain 27)

(US President Kennedy assassinated by a bullet fired from the roof top. Oswald shot and assigned guilt; grassy knoll; Jean Dixon's warning; Robert Kennedy shot at night time; students' riots in France and England; flood in Florence.)

[5] *One day the two great leaders will become friends,*
Their great power will be seen to increase:
The new land will be at the height of its power,
To the bloody one the number [is] reported.
(Century 2, Quatrain 89)

(Predictions regarding the end of the Cold War between Russia and the US.)

Paracelsus

Another of the key figures during the Renaissance is Paracelsus. Born in Einsiedeln, Switzerland in 1493 (a year after Christopher Columbus set foot in America) and christened Theophrastus Philippus Aureolus Bombastus von Hohenheim, he rejoiced in his third name. His father – an illegitimate offspring - practised medicine; his mother – suffering from manic depression - committed suicide when he was nine years old. While still a youth Paracelsus became aware of many of the conflicting currents of his age. History suggests that his childhood wasn't exactly enjoyable.

Picture G. Paracelsus. Bombastic Bombastus.

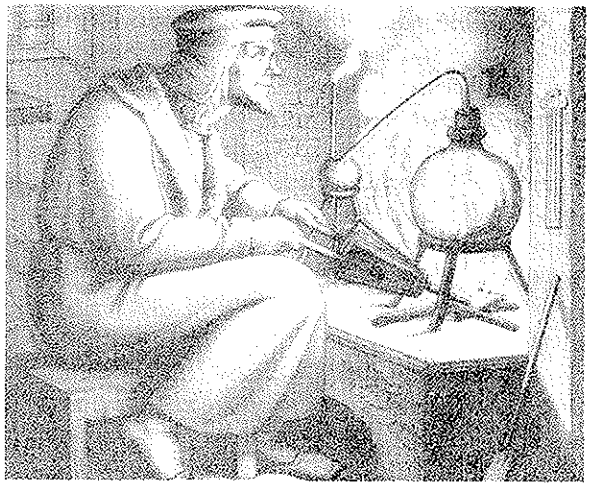
At the age of fourteen the boy left home to begin a long period of wandering. Reports of his education are contradictory. Some state that he had University education, while others state that there is no proof that he ever took a medical degree. Most books, however, agree that he was city physician, permitted to lecture at the University of Basel, although he had no official appointment with the medical faculty there. He is reported to have picked up enormous practical medical knowledge by working as a surgeon in a number of the mercenary armies that ravaged Europe in the seemingly endless wars of the period.

Almost immediately after he assumed his position, Paracelsus became a figure of contention. He heaped scorn on the conservative physicians of the University remarking that "even flies would disdain to sit on them except to make their dirt". During the St. John's Day bonfire, he pitched Galen's works and Avicenna's *Canon* to the blaze, while upholding the works of Hippocrates and no doubt, those of himself. This was followed by a disastrous lawsuit and he left Basel in haste, even leaving behind his manuscripts. The final years of his life found Paracelsus leading a nomadic existence, moving from town to town. As in Basel, he often he had to leave his manuscripts behind as he fled to escape the wrath of his irate contemporaries. He wrote that he visited most of the countries of Central, Northern, and Eastern Europe.

From a positive viewpoint however, it must be conceded that Paracelsus had brilliant insights and comprehension in the treatment of mental disorders. He concluded that man had equal measure of animal instincts and godly spirits and that the former had to be suppressed in order to attain fulfilment. This is remarkably similar to the description of the *Id* and *Ego* in modern psychoanalytical systems. Freud and later psychoanalysts state that *Id* is the unconscious part of the mind that consists of natural instincts, urges and drives that are repressed. It includes "internal events" which stem from the influence of heredity. *Ego* is a defence mechanism that is partly conscious and contains the capacities to calculate, reason and plan. In contrast to the *Id*, which relates to internal events, the *Ego* is occupied with the external world and it regulates and controls the instincts provided by the *Id*. *Super-ego* is the connection between the *Id* and *Ego*. It is the mind's link to reality and society and contains the influence of what is learned from other people. The *Super-ego*, unlike the *Id*, is not intuitive from birth, but acquired from childhood. Feelings of guilt are said to be one of its manifestations. Paracelsus was convinced that several diseases were only manifestations of underlying mental illness and advised treatment of the soul rather than the body. He maintained that human intelligence and reasoning power remained lucid in insane individuals. To elucidate his hypothesis, he pointed out the keen logic seen in the rantings of the paranoid, although they are always based on imaginary or false premises. This reminds me of a joke that exactly proves Paracelsus' point. A man driving a car suddenly loses control of his car as one of his wheels flies off. He manages to get back the wheel, but all the four retaining nuts are lost. As he sits by his car wondering what to do, he sees a man standing in the gate of a lunatic asylum nearby, motioning him to come over. The man walks over and the inmate of the asylum advises him to remove one nut each from the remaining three wheels and use them for the fourth. Thoroughly mortified, the man feels like kicking himself for not having thought this himself and says to the inmate "You are so normal, you shouldn't actually be in there!" For which the inmate replies, "I am here for being crazy, not stupid, man!"

In his unrelenting quest for knowledge, Paracelsus hacked out new paths through thick scholastic underbrush. In an era governed by herbal remedies, Paracelsus applied alchemy to transform raw metals into new remedies. Tin, silver and sulphur were all experimented upon. Paracelsus appears to be the first man to conceive the idea of test tube babies. He claimed that a homunculus could be created by placing human sperm and horse dung into a retort and baking it for 40 days. (Picture H). Though ridiculous in materials and methods, he had, nevertheless, envisaged the concept.

No figure in the noble history of medicine has been more controversial than this man, who is conjectured to have



Picture H. Paracelsus incubating a homunculus. It is unlikely that he successfully *conceived a baby* in the flesh this way, but was the first to *conceive the concept* of test tube (retort?) babies.

given the word 'bombastic' to literature. This is erroneous, but nevertheless, appropriate. His assumed name Paracelsus meant "better than Celsus," (who was a great Roman encyclopaedist) and I guess no further explanation is required of his pretentious and conceited nature. He also went to the extent of modestly ranking himself the Saviour of the 16th century. None of the books I consulted for this manuscript had a kind word for him as an individual. He was contemptuous, cantankerous and caustic in his attitude towards his peers. In his lectures, he ignored Latin (the language of the learned) and used vernacular German, which at that time was 'a language purportedly fit only to address horses'. He comes across as an angry man who antagonised many of those he met - even those who tried to be helpful. However, as a contemporary of Nicholas Copernicus, Martin Luther, Leonardo da Vinci (and a host of other Renaissance heroes), Paracelsus did play a part in shattering medieval thought, inspiring revolutionary thinking and being instrumental in the birth of the modern world. During his lifetime he was called by some the "Luther of Medicine" and it is reported that the scientific debates of the late sixteenth century were centred more frequently on the innovations of Paracelsus than they were on the heliocentric astronomy of Copernicus. His interest in alchemy earned him the title 'father of pharmacology' in spite of his limited contributions to pharmaceutical science. We need therefore, to acknowledge his contributions and give the iconoclast a decent (if not dignified) place in Medicine's Hall of Fame. Paracelsus not only lived a life true to his reputation, but also perished infamously in a drunken tavern brawl. Paracelsus is surely a character whom I would have loved to have met, but hated to have messed with.

Renaissance Humanism

Renaissance was a period where scientists strove for perfection. Over a period of time, the ancient languages had become corrupted and many translations were in crude language and did not convey the original meaning. Renaissance authors desired to replace the barbarous Latin of the Middle Ages with Latin that was stylistically pure. For this purpose, they travelled in search of old manuscripts that might have survived in isolated monasteries. They also studied Greek so that they might make pristine translations of the ancient literary treasures. This search for the work of ancient authors was felt first in literature, rhetoric and history, but by the late fifteenth century there was an increasing interest in the sciences and medicine. Astronomers and mathematicians sought an accurate text of Ptolemy's *Almagest* and both the observations and the mathematics of this text were to form the foundation for Copernicus' *De revolutionibus orbium* published in 1543. In medicine, the works of Hipprocates, Galen and Dioscorides were newly translated from Greek. The recovery of the medical writings presented medical terminology in the elegant Latin of the first century AD. To the Renaissance humanists, the discovery of new texts seemed as exciting as the discovery of the new lands being made by contemporary explorers. However, the recovery of ancient classics and their translation was not limited to the works of Aristotle, Galen, Ptolemy, and Dioscorides. In addition to the works of many lesser figures there were new areas of study made available to Renaissance scholars. Important among them was the recovery of the *Corpus Hermeticum*, a group of treatises supposedly written in Egypt by Hermes Trismegistus. Hermes was one of the great figures of alchemy and even today we speak of a hermetic seal in chemistry.

In short, by 1500 the impact of the newly recovered texts was leading in two directions. On the one hand the natural philosophers and physicians of the schools had developed an increased respect for Aristotle, Galen and other ancient authorities. On the other hand, the recovery of the Corpus Hermeticum and other more mystical texts placed an emphasis on natural magic, the relationship of man to the macrocosm, and sought divine truths in the study of nature. The first path led to truth through traditional medicine and a reliance on mathematics and the physics of motion for our understanding of nature: the second led to a more mystical and religious basis of knowledge and turned to chemistry as a key to man and nature alike.

Renaissance Herbs

During the Renaissance, many of the great herbals were written, compiled and for the first time in history, printed. *Bancke's Herbal* was the first printed herbal published in 1525. A year later, the *Grete Herball* was printed by Peter Treveris and had a high reputation among the earlier English herbals. William Turner (1510-1568) became the first Englishman to study plants scientifically and came to be regarded as "the father of British Botany".

He produced *Turner's Herbs* in 1550. The *Aztec Herbal*, published in 1552 is the earliest treatise on Aztec pharmacology. Its authorship is attributed to Martin de la Cruz, an Aztec doctor. It was discovered in the Vatican library in 1919 and has become known as the *Baliano Codex*..

The *Pemptades* written by Rembert Dodoens, a Belgian botanist, in 1554 (1517-1585) became the basis of the English herbal known as *Gerard's Herbal*, written by John Gerard (1545-1612) of greatest English herbalist trio, Turner, Gerard and Parkinson. Gerard was a well-travelled surgeon with a passion for gardening. His garden supposedly had over a thousand plants. His herbal is largely based on the early *Pemptades* by Dodoens, but Gerard added a great deal from his personal observations and altered the classification of plants. He believed firmly in the efficacy of herbs to treat not only physical diseases but also those of the mind and spirit. This belief, incidentally, is shared by the world's greatest and ancient civilisations. Gerard also describes methods of 'aromatherapy' involving the inhalation of volatile oils, the absorption of these through the skin into the circulatory system. Even to this day, amateurs calling themselves "herbalists" are reportedly plagiarising material from Gerard's *Herbal*.

A distinguished Spanish physician, Nicholas Monardes, published a book on drugs, in which he included those which were now being brought from America and the Far East. Wealthy Italian importers brought in cinnamon bark from India, resinous balsam from Peru and the most exciting tobacco from America. Jean Nicot considered this a miracle herb and brought seeds from Portugal. It was named *nicotina* after him. Its leaf was applied over cancerous ulcers; its powder was snuffed to cure headaches; it was also smoked to cure asthma.

Syphilis

Close on the heels of plague and leprosy, the malevolent medieval epidemics, came a disease which earned itself the name the "Scourge of the Renaissance" - syphilis. With an unworthy mode of transmission, it is still worthy of a full biography. No one really knows where it came from, but being a sexually transmitted disease, it serves as a sensitive tracer of human contacts, relationships and morality throughout the world.

In 1530 there was a nobleman from Verona called Hieronymus Fracastorius. He was a man of many talents and was a poet, astronomer and a doctor with a passion for pathology. He also features among the world's pioneers in epidemiology, since he was the first to recognise typhus fever. In his book *De Contagione* published in 1546, Fracastorius mentions the possible existence of invisible "seeds of disease which multiply rapidly" which proves that he had some inkling about bacteria long before researchers proved their existence. He published a medical poem called *Syphilis, sive Morbus Gallicus*. According to his poem, a shepherd boy Syphilus (*susphilein* means swineherd) offended Apollo and was punished by the affliction which was named Syphilis. This mythical attribution created some diversion since until then, it was strongly believed that it was America's gift to Europe. But it is a fact that the disease spread in epidemic proportions only after Columbus' return in 1493. Some of his sailors reportedly passed it on to the 'liberated' ladies of Naples and this resulted in an outbreak in Naples in 1494. Later, when the French soldiers captured the city, the ladies faithfully transferred it to them to take back to Paris. In three years' time, syphilis had spread to Germany, Russia, Holland, Switzerland, Hungary and Scotland. Sea voyagers carried it to India, China and Japan and left it as their calling card at every port they berthed.

Soon the disease was so widespread that no one could trace its aetiology. The English blamed it on the French. The French blamed Naples and the Italians (calling it the Neapolitan disease). The Russians accused the Poles. Indians and Japanese knew for sure that the culprits were the Portuguese voyagers. There was generous mudslinging from all quarters and I suppose they all had some justification each in their accusations.

During that time, people described syphilis as a 'gentleman's disease' and discussed it proudly among peers (considering it a prized souvenir of their lecherous conquests). This is evident by the fact that a man named Ulrich von Hutten, a syphilitic patient himself, jotted down his observations on the manifestations of the disease and published it dedicating it to the Archbishop of Mayence. However, on the sly, people were seeking cures, which were not quite available. Physicians and pharmacists were experimenting on various drugs and chemicals. Guaiacum was the first drug offered for syphilis and was considered the miracle drug of the Renaissance. Guaiac wood, like the disease itself, was imported from America, which tallied well with the public belief that the Almighty provides the cure of an ailment at its place of origin itself. But its popularity was short-lived, as soon people were quick to realise its ineffectiveness in curing syphilis.

Picture 1. The stove-house and its syphilitic tenant. One of the caretakers prepares hot towels, while the other brings in glowing coals.

Where guaiacum left, mercury took over. Syphilitic pustules were smeared with mercuric ointment. In severe cases, the patients were asked to live inside a stove-house for a month without food (Picture I). The stove was kept hot by glowing coals and as if that was not warm enough weather, the occupants were constantly covered with freshly warmed towels. Most of them suffocated, had a heart attack, starved to death or died of heat exhaustion. Which makes one wonder whether this was a clever ruse to get rid of syphilitic patients!

During the syphilis epidemic, since traditional medicine did not have a sure-fire cure, Renaissance quacks saw an opportunity and were quick to take advantage of the situation. They played on human psychology to attract patients. They assured them that there was still hope for all those forsaken by qualified physicians and hopeful patients flocked to them by the dozen. The quacks were true to their word and often it was only hope that they received and nothing else! Particularly gullible were the syphilitic patients who eagerly bought quicksilver (mercury) ointments and medications. Quacksalver became the name for these peddlers of quicksilver, which has now been abbreviated as 'quack' to denote any unqualified medical practitioner who deals in wondrous cures.

Renaissance quacks were ready to perform everything from dental extractions to cataract removals, but moving bowels with potent laxatives seemed to be their forté. The quack's flag clearly sends across the message to the educated and illiterate alike. (Picture J)

Picture J. A Renaissance quack performing a dental extraction. Observe his flag and guess what his speciality was!

Ambroise Paré

Ambroise Paré (1510-1590) was of French descent, but nothing certain is known of his geneology. His father is believed to have been either a cabinet-maker or a barber-surgeon and valet to the Duke of Laval. He is reported to have had school education, but never went to University. After apprenticeship with Vialot, Master Barber-Surgeon of Vitre in 1523, and later to another barber-surgeon in Paris, he became house surgical student at the Hotel-Dieu in 1533, studying anatomy by dissection until 1535. He was licensed as Master Barber-Surgeon in 1541. In 1554, he passed an examination by the College of Surgeons as Bachelor of Surgeon and licensed as sworn surgeon. His deep knowledge of anatomy stood him in good stead in all these endeavours.

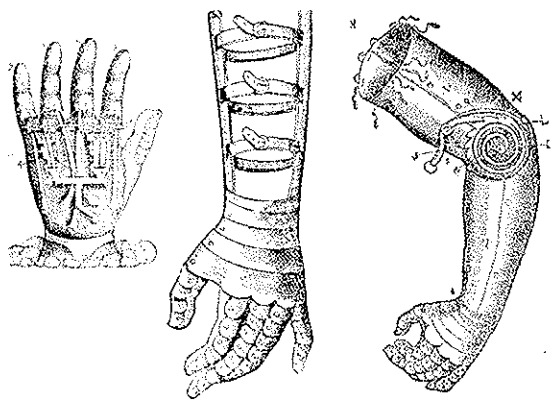
Picture K. Ambroise Paré. Father of Modern Surgery.

Soon, Paré realised that surgery had been inert for the past two centuries. Stooping down to pick up the knife from where Guy de Chauliac had dropped it, Paré started salvage efforts of his profession. As an army surgeon, he was touched by the misery undergone by wounded soldiers. In one moving incident, it is said that he watched three wounded warriors being slit at their throats, in an act of euthanasia. Although, he consoled himself that in a similar position, he would also pray for such a merciful end, he resolved to do his best to mitigate the misery, by curing the wounded and comforting the dying soldiers. Paré took into his personal custody the next severely wounded man who came his way and served him as physician, surgeon, pharmacist and cook. The man, given up for dead, recovered and the whole camp rejoiced. Jubilant fellow warriors collected a purse for Paré and presented it to him. A modest Paré then declared his historic maxim, " *Je le pansait; Dieu le guarit* " which translates as " I dressed him; God healed him."

However, for Paré, God's services were easier to obtain than fresh bandages to dress war wounds. During the war at Hesdin, Paré is said to have deployed the serv-

ices of four fat prostitutes to wash the soiled bandages for re-use. Allegiance to their profession, however, must have kept them distracted as Paré, in despair, records that "they had to be kept at the job with the stick". Insufficient water and soap added to his woes.

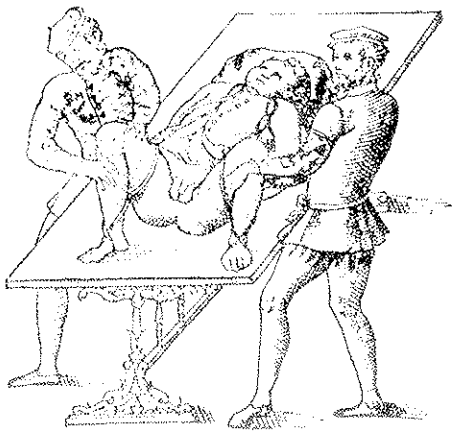
In those days, doctors routinely cauterised gunshot wounds, which were considered poisoned by powder burns. Cautery was done by pouring a boiling mixture of oil and treacle into the wounds or scalding with a red-hot iron. Most soldiers died due to the horrors of cautery rather than the gunshot itself. Paré discovered that gunshot wounds were not in themselves poisonous and did not require cautery. This observation was accidental, since one day the oil supply ran out and he was forced to extemporise. He fashioned a 'digestive' (which was a concoction of egg yolks, rose oil and turpentine) and experimentally applied it to the wounds. The experimental 'guinea pigs' recovered comfortably while the cauterised unfortunates were in great pain and feverish. He published his observations and impressions in his first treatise, *La methode de traicter les playes faites par les arquebuses et aultres bastons a feu* in 1545. The treatise brought him immediate fame. After leaving army service in 1552, Paré went into private practice and practised surgery for a while. In 1562, he happened to treat the Duke de Vendome successfully, who strongly recommended Paré to the King, commending highly on his surgical skills. The King ordered his premier physician to record him as a Surgeon in Ordinary to the King. He held his position at court under the next three monarchs right until his death in 1590.



Picture L. Artificial limbs designed by Paré.

Paré had a reputation for kindness, but his consuming curiosity never allowed him to pass up any opportunity to use human subjects for his scientific tests. He once challenged King Charles IX that the bezoar stone (hairball found in the intestinal tract of animals) was not an effective antidote for poisons as popularly believed. The King's cook had recently been caught red-handed for stealing two silver plates and was awaiting the gallows. The condemned man was recruited 'volunteer' for the experiment and given the bezoar stone and a poison. Unfortunately for the cook, Paré was right.

Paré made several other useful contributions. He re-introduced the internal podalic version in cases where labour was difficult in order to avoid a Caesarian section. Although risky, it gave a better chance of life for the mother and child, especially in obstructed labour with no chance of delivery by any other means.



Picture M. The lithotomy position first described by Paré.

Paré left a powerfully reactivated surgical tradition at his death at a ripe old age of 80. By that time, apart from having served four French kings, he had won recognition from the College of St. Come and discovered new methods of treating wounds. He had described sound methods for setting fractures and draining wounds. He had designed artificial limbs (Picture L), surgical instruments and lightweight leather trusses for hernia, which replaced cumbersome iron models. He was the first to link aneurysms to syphilitic aetiology and painful micturition to prostatic pathology. He was also, perhaps, the first to describe the classical lithotomy position for the removal of bladder stones. (Picture M) The humble barber's apprentice who worked his way from the bottom up to become the greatest surgeon of the 16th century (and later elevated to the position of "Father of Surgery") had many publications, which were circulated throughout Europe. They were to have considerable influence during his life and well into the following century.

The Royal Colleges

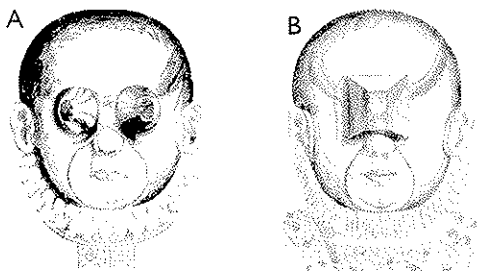
It didn't take long for the intellectual blizzards sweeping Europe to hit England. Dedicated scholars of high calibre went back to study ancient literature, in order to revive the healing arts. A doctor named Thomas Linacre was quick to gain fame with his immaculate translations of Hippocratic works, which included the first English version of the Hippocratic Oath. The medical profession gained prestige and Linacre felt

that this respect needed to be safeguarded. His apprehensions were well founded, as there were many masquerading mountebanks in the medical ranks. He obtained permission from King Henry VIII to form a body of physicians to supervise the practice of medicine in London. All doctors were examined for their competence before they were admitted to the society and allowed to practice. Graduates from Oxford and Cambridge were, however, exempted. This supervisory body, formed in 1518, soon emerged as the Royal College of Physicians in 1551. It represents, till this day, excellence, dignity and professionalism in medicine.

Not to be outdone, the barber-surgeons made a pact in 1540 with the King's sanction. The surgeons had formed a small exclusive guild much earlier than the physicians, but soon realised that they were too small in terms of numbers to make an impact on society. The barber's guild was politically strong and so they joined forces with them to gain strength. The United Company of Barber-Surgeons was thus born with Thomas Vicary as its first president.

Renaissance Ophthalmology

Ophthalmology was surprisingly, one discipline which never caught on in the West and Bettmann states that a 600 BC Hindu in India with a cataract was better off than an European of 1500 AD with the same affliction. Susruta, affectionately called the 'Hippocrates of India' had perfected the technique of couching a cataract in the sixth century BC. Twelve centuries later, technology transfer occurred when a Persian physician took the technique to the Middle East. Although the Arabs adapted it around 7 AD, it remained degenerate in medieval Europe, where nomadic peddlers and tooth drawers operated on cataracts in public market places for a meagre fee of seven cents. Usually the veil of blindness was lifted



Picture N. Strabismus masks for squint correction: A - For convergent squint. B - For divergent squint.

for the patient for a period, before he went blind following postoperative complications. The itinerant mountebanks however, went on unchallenged practising quack ophthalmology, until a man called Georg Bartisch brought about its renaissance. He was a court oculist and had gained considerable experience in eye care. He knew his ocular anatomy well, thanks to Vesalius' textbooks. In his treatise *Augendienst* published in 1583, he comprehensively described care and cure of several eye problems. It can be considered the first step towards rational ophthalmology. He constructed special masks for convergent and divergent squints. (Picture N). The book, however, had one critical blind spot. By this time, spectacles had been invented, but Bartisch had scant regard for them and dismissed them as completely useless, emphatically declaring that "man needs two, not four eyes".

Spectacular Spectacles

While we are in the topic of eyes and vision, it might be a good idea to consider the evolution of reading glasses. Recently, in a survey conducted by Edge (www.edge.org) scientists and other thinkers were asked to nominate the most important invention of the last 2000 years. Featuring among the offerings (alongside computers, clocks, numerals, erasers and delete keys) are the simple pairs of spectacles. According to psychologist Nicholas Humphrey of the New York School for Social Research, spectacles "have effectively doubled the active life of everyone who reads or does fine work – and prevented the world from being ruled by people under 40". By this invention, man has proved that people need not accept the body nature gave them and that physical limitations can be overcome with ingenuity.

Picture O. A Renaissance scholar using spectacles.

From Pliny's records we are led to believe that Emperor Nero was one of the earliest users and he reportedly watched the Roman circus through an eyeglass. However, there is no mention about eyeglasses until the 13th century when Roger Bacon recommended reading lenses for the old. Renaissance scholars used spectacles extensively (Picture O). Johannes Kepler, (the man who enunciated laws of planetary motion) did a study of optics and was the first to realise that light passes into the eye through the lens converging in the form of a cone. He then understood that if the focal point fell behind or in front of the retina vision would be blurred. The mystery of how spectacles improved eyesight was hence solved, but the terms myopia and hypermetropia were subsequent and more recent designations.

Renaissance attitude

In spite of the great advances in Medicine during the Renaissance, it was a paradox that people, being people, still regarded the doctor with an emotional attitude rather than an rational attitude. The drawings of Dutch artist Hendrik Goltzius (based on couplets by Euricius Cordus*) declare the eternal truth that the doctor is loved or hated depending upon the patient's condition. In sickness, the patient exalts his doctor as God (Picture P). Once healed, the doctor is demoted to the status of mere man. When it is time for payment of fees, the doctor is equated to a diabolical devil.

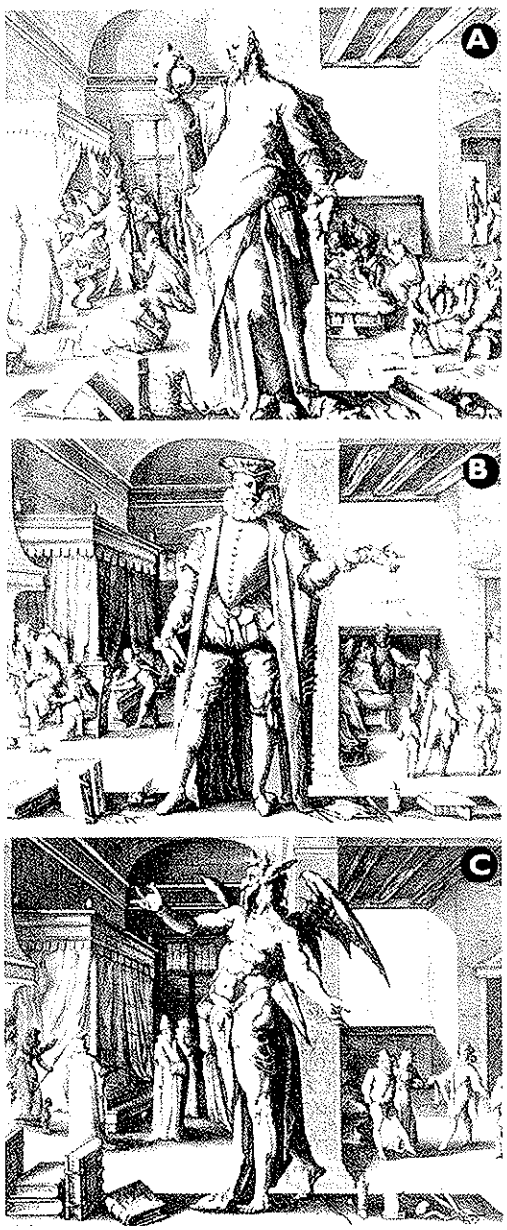
> * *God and Doctor we alike adore*
> *When on the brink of danger, not before.*
> *The danger past, both are alike requited*
> *God is forgotten and the doctor slighted.*
>
> *- Euricius Cordus*

And speaking of the devil, during the 16th century, it was widely believed that madness was created by the devil himself and mental disease was considered an outgrowth of witchcraft. Insanity was one disease for which Renaissance physicians had no answer and they prudently excluded it from medical domain. This left the deranged in the hands of exorcists and witch burners. People kept their eyes peeled for demonic manifestations in others, which could be something as innocuous as a bad dream. So severe was this drive of rounding up demented people (mostly women) that at one point even those who related their nightmares were condemned to death. It is said that even fathers did not hesitate to squeal on their own daughters, should they act strangely. The smart ones, perhaps, kept their bad dreams to themselves.

Epilogue

By the end of the sixteenth century, medieval thoughts and philosophy had almost entirely been discarded. In a sharp contrast to the medieval period that was static and practically brain dead, the Renaissance era was dynamic and versatile. The development of a special relationship among the sciences, especially anatomy, optics and mathematics gave Renaissance much of its unique character. None of the scientific theories – existing or new - was taken for granted. Even the writings of ancient authorities and the translations were subjected to independent verification to prove the validity of assumed truth. Ancient languages were learnt in order to appreciate the true meaning conveyed in ancient texts. Experiments became an integral part of scientific research whereby hypotheses were either proved or disproved.

The Renaissance era also saw many great feats being achieved. Gutenberg's movable metal type printing flagged off the season by permitting dissemination of



Picture P. The vacillating viewpoint of the patient regarding his physician. A - A God during sickness B. Mere mortal when cured C. A diabolical devil during payment time

knowledge at drastically reduced costs. In 1492, Columbus discovered America. The Royal College of Surgeons, Edinburgh was chartered in 1505, followed by the Royal College of Physicians, England in 1518. In Sep 6, 1522, Ferdinand Magellan's ship *Victoria* completed its epic voyage around the world, which remains the millennium's first and greatest sailing adventure till date. (However, protracted sea voyages of the Renaissance era left sailors without the benefit of Vitamin C in fresh fruits and vegetables and this saw the emergence of scurvy). The discovery of sea routes to India and America created new potentials for exploration and exploitation. Establishment of trade

routes to distant lands and local industries saw the formation of money economy. Population statistics and demographic studies became organised when in 1538, King Henry VIII directed that government authorities maintain records of marriages, christenings and deaths. Copernicus described the revolution of planets around the sun in 1543. In the same year, apothecaries were legalised by an Act. Physicians and barber-surgeons formed regulatory bodies. Renaissance was a time where maintenance of standards for the health care professions was given great consideration. In 1593, there was even an Act against overcrowding in dwellings in London. Lenses were known for a long time, but Renaissance inventors reassembled them to produce the telescope and the microscope. In Netherlands, Hans Jansen and his son Zacharias combined several lenses and designed the first compound microscope in 1590. These preparatory works were the prelude to several remarkable discoveries by Harvey, Descartes, Bacon, Boyle and Newton in the seventeenth century.

(Next: Seventeenth Century Medicine)

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β-BLOCKERS IN CONGESTIVE HEART FAILURE

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ABSTRACT: Activation of the sympathetic nervous system (SNS) and renin-angiotensin system (RAS) plays a pivotal role in the pathophysiology and progression of the disease in chronic heart failure (CHF). Blocking the activation of the RAS with angiotensin converting enzyme inhibitors not only improves symptoms but also prolongs life in symptomatic CHF. Does a similar analogy hold true for the use of β-blockers in CHF? Evidence from a number of small trials and several recent large prospective trials show that b-blockers may improve ventricular function and symptoms in CHF. In a combination of trials investigating the use of carvedilol (an α_1 and β–blocker) in congestive heart failure a mortality benefit appears to be evident. There are still a number of key questions that remain unanswered regarding the tolerability, patient type and stage of CHF in which β-blockers should be advocated. Several large-scale trials are in progress to answer some of these questions and also to add further information regarding its efficacy and impact on survival. *(JUMMEC 1999; 1:26-33)*

KEYWORDS: Beta-adrenoreceptor antagonist, congestive heart failure.

Introduction

In clinical practice, the idea of giving a negative inotropic agent to patients with congestive heart failure (CHF) would be considered counter intuitive. Therefore, it may seem paradoxical to learn that β–blockers, long recognised as "negative inotropes", are seriously being considered as a new approach in the treatment of CHF. However, any new approach or treatment of CHF must address two fundamental issues, namely the ability to improve the patient's quality of life and the ability to prolong survival. Previous experience tells us that these two closely related but distinct parameters may be influenced in different ways by different agents. By the same token, CHF is not a single entity, and therapy that is effective for CHF with one cause may not be effective for CHF with other causes. Moreover, treatment that is useful at one stage in the natural history of CHF may not be beneficial at another stage. Finally, some CHF therapies may have beneficial short-term effects but over a period of time may lose these effects and may even adversely affect mortality. All these issues are relevant to the use of β–blockers in CHF. This review will discuss in turn the following questions: Do β–blockers improve symptoms and functional capacity? Do β–blockers prolong survival? What are the likely mechanism(s) for these beneficial effects? Are β–blockers useful in all types of CHF? How safe are β– blockers and should they be used routinely?

Do β–blockers improve symptoms and functional capacity?

β–blocker as a treatment for CHF was first described in 1975 by Waagstein and colleagues (1). Their report was based on clinical experience in 7 patients with idiopathic dilated cardiomyopathy and with resting tachycardia who were treated with alprenolol or practolol for approximately 5 months. All the patients showed haemodynamic improvement, and no adverse effects were reported. The rationale for this novel therapy was based on the investigators' experience with β–blockade in patients with acute myocardial infarction (2). The same Swedish investigators published additional data on long term benefits with β–blockade (3) and reported deterioration after withdrawal of β–blockers in patients who had "improved conspicuously" (4). It is important to note that none of these studies were randomized. Since β–blockers could aggravate CHF (5), the use of β–blockers was initially greeted with skepticism, which was reinforced by 2 small short-term controlled trials which failed to show any benefit (6,7). It has since been argued that both these 2 trials might have been too small and too brief (<4weeks) to define the potential benefits of these drugs. Furthermore, both these studies were crossover studies which may have

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permitted any favourable effects of the β–blocker to have crossed over into the placebo treatment period and thus limited the ability to detect any difference between active and placebo therapy.

In the 1980s, experimental findings led to a resurgence of interest in the clinical use of β–blockers as treatment for CHF. Experiments in ventricles from explanted failing human hearts exposed to prolong adrenergic activity show progressive desensitization of cardiac β_1-adrenergic receptors which desensitize the heart to sympathetic stimulation (8,9). This desensitization is due to β–receptor downregulation and also changes in the regulating G proteins that couple the receptors to adenylate cyclase (10). At the same time, studies in animal models using intact hearts and cell cultures as well as clinical observations in patients with cardiomyopathy due to pheochromocytoma suggest that prolonged activation of the sympathetic nervous system may exert a direct sustained deleterious effect on myocardial function and contribute to progressive myocardial damage (11-13). Such deleterious long term effects of excessive sympathetic stimulation on cardiac mechanical performance may outweigh any immediate benefits of inotropic support to the failing myocardium, thus providing a rationale for the use of β–blockers in CHF.

In the last decade, there have been at least 17 trials of β–blockers in CHF (4 open and 11 randomized controlled) involving a total of 2985 patients (14-30). Table 1 summarizes the results of these studies. The possibility of publication bias leading to selective reporting of favourable results needs to be considered as does the widespread use of pragmatic (rather than intention to treat) analysis. Even allowing for these confounding influences and that the studies differed in design, duration of treatment, choice of β–blocker and patient characteristics, the findings were fairly consistent with improvements in symptoms, exercise capacity, left ventricular function and haemodynamic and neurohormonal indices. Of the few large-scale placebo controlled trials, the Metoprolol in Dilated Cardiomyopathy trial was the first and was published in 1993 (25). Three hundred and eighty-three patients with mild to moderate CHF (NYHA functional class II-III) caused by idiopathic dilated cardiomyopathy and not associated with significant ischaemic heart disease were randomized to receive either metoprolol or placebo in addition to other standard therapy for CHF including diuretics, digoxin and angiotensin converting enzyme inhibitors. Over the 12 to 18 months assessment period, metoprolol significantly improved haemodynamic status (ejection fraction and pulmonary capillary wedge pressure) and treadmill exercise times. In addition, the rate of deterioration of the patients who received metoprolol was slowed as judged by the clinical end point of "being assessed as requiring cardiac transplantation" during the study period (2 vs 19 patients; metoprolol vs placebo respectively). There was also a reduction in the hospitalization/emergency room visits for decompensation in the metoprolol-treated group. Quality of life, assessed

Table 1. Summary of 14 major trials of β-blockers in congestive heart failure.

	Design	No.	Type of CHF	Drug	Length (mths)	Symptoms	Ex Cap	LVEF	Survival
Engelmeier *et al.* (14)	DB	25	DCM	Metoprolol	12	+	+	+	na
Anderson *et al.* (15)	DB	50	DCM	Metoprolol	19	+	±	na	na
Waagstein *et al.* (16)	O	33	DCM	Metoprolol	16	+	+	+	na
Eichhorn *et al.* (17)	O	15	DCM/IHD	Bucindolol	3	na	na	+	na
Das Gupta *et al.* (18)	O	17	IHD	Carvedilol	2	+	+	+	na
Pollock *et al.* (19)	DB	19	DCM/IHD	Bucindolol	3	+	+	+	na
Leung *et al.* (20)	DB	12	DCM	Labetolol	2	+	+	na	na
Nemanich *et al.* (21)	O	10	DCM/IHD	Metoprolol	2	+	+	+	na
Woodley *et al.* (22)	DB	50	DCM/IHD	Bucindolol	3	+	±	+	
Paolisso *et al.* (23)	DB	10	DMC	Metoprolol	3	+	+	na	
Gilbert *et al.* (24)	DB	30	DMC	Carvedilol	4	+	±	+	
Waagstein *et al.* (16)	DB	383	DMC	Metoprolol	18	+	+	+	not significant
Fisher *et al.* (27)	DB	50	IHD	Metoprolol	6	+	+	+	na
CIBIS (28)	DB	641	DCM/IHD	Bisoprolol	23	+	na	na	not significant
Aust/NZ Carvedilol Study (29)	DB	415	IHD	Carvedilol	19	=	=		not significant
US Carvedilol Study (30)	DB	1094	DCM/IHD	Carvedilol	6-12	na	na	na	65% decrease risk (P<0.001)

Keynotes: DB = double blind; O = Open; DCM = idiopathic dilated cardiomyopathy; IHD = ischemic heart disease; + = improvement; = no change; na = not available

at the end of follow-up or the latest assessment before an endpoint was reached, improved significantly more in the metoprolol group than the placebo group. These results are supported by the recently published Cardiac Insufficiency Bisoprolol Study (CIBIS) which randomized 641 patients with CHF of various etiologies to receive either bisoprolol or placebo and were followed for almost 2 years (28). There was significant improvement in functional status in the bisoprolol treated group; fewer patients in the bisoprolol group required hospitalization for cardiac decompensation and more patients improved by at least one New York Heart Association functional class by the end of the treatment.

An assessment of the data from these trials show that the improvement in left ventricular function associated with the use of β–blockers have been impressive, with improvements in left ventricular ejection fractions greater than any form of CHF therapy (31). For example, vasodilators, angiotensin converting enzyme inhibitors or inotropic treatment does not typically increase left ventricular ejection fraction by more than 5% relative to change in a placebo group, whereas it is common for B blockers to increase left ventricular ejection fraction by 6-15% in idiopathic dilated cardiomyopathy (22,24) and 4-8% in ischaemic cardiomyopathy (27). These findings have justifiably been questioned because none of the other agents slow the heart rate to the same extent as β–blockers and it could be argued that the decrease in heart rate could have contributed to an improvement in ejection fraction by allowing more ventricular filling. Both left ventricular ejection fraction and the plot of stroke volume versus pulmonary capillary wedge pressure are a load-dependent measures of cardiac function and it is possible that some of these effects of β–blockers might be load mediated. To address these issues, Eichhorn and colleagues recently conducted a study of the haemodynamic effects of bucindolol, a new generation B blocker with some vasodilatory properties, in CHF patients (32). Confounding influences of changes in heart rate and loading conditions were avoided by performing all measurements at matched atrial pacing rates and measurements of interest were of indices of cardiac performance that were relatively load independent. Bucindolol augmented contractility as assessed from the end systolic pressure volume relation and the peak positive dP/dt end diastolic volume relation and also improved myocardial relaxation as shown by a reduction in the time constant of left ventricular isovolumic relaxation. These changes in systolic and diastolic function were achieved without any rise in myocardial oxygen consumption, indicating an improvement in the efficiency of myocardial energetic

The findings related to exercise capacity in the trials conducted to date have been somewhat conflicting. Although most studies have reported statistically significant improvement in total exercise duration with β–blockade (14,16,18-21,23,25-27), others have not (15,22,24). Long term β–blockade can attenuate maximal oxygen consumption; consequently, maximal exercise testing may not be the most appropriate method for assessing improvement in functional capacity. In a recent randomized trial of the effects of carvedilol, a combined a- and β–blocker, submaximal exercise time (determined by stressing patients at a workload fixed at 85% of their baseline maximal oxygen consumption) was significantly increased in the carvedilol group compared with the placebo group whereas maximal exercise time was not changed (33). This method of assessing submaximal performance is often preferred by patients and may better reflect limitability of their regular daily physical activity than does maximal exercise testing.

Do β–blockers prolong survival?

In addition to quality of life, patient survival is another consideration in the treatment of CHF. Trials of β–blockers have not been shown to decrease mortality in any appropriately designed study. Although, Swedberg et al. reported in 1979 that patients with CHF treated with β–blockers had a significantly better survival experience, this data was compared with retrospectively selected controls (34). Sacks et al. (35) have highlighted the problems related to historical, rather than concurrent randomised controls, stating that studies using historical controls are prone to producing false positive conclusions.

Until recently, most of the studies have been small and lack the statistical power to define an effect on mortality. The Metoprolol in Dilated Cardiomyopathy Trial was the first large scale placebo controlled trial that tested the effects of β–blockade on mortality although it should be noted that it had a predefined combined endpoint with fatal (all-cause mortality) and non-fatal components (clinical deterioration to a point at which cardiac transplantation would normally be offered as a treatment option). The study showed no difference in all-cause mortality between the groups (23 vs 19, metoprolol vs placebo treated groups respectively). The authors argued that because the patients were on optimum therapy (including angiotensin converting enzyme inhibitors) on entry into the trial, there had been too few deaths for the trial to detect an effect. They also argued that because the trial design was such that patients with the highest risk of death were placed on a waiting list for heart transplantation and therefore patients who were transplanted would otherwise have died. This latter possibility is supported by the finding of a significant difference in favour of metoprolol in the combined overall endpoint of death or transplantation (25 vs 38, metoprolol vs placebo respectively, p=0.06, Fig 1). In the recently published CIBIS trial (28), the main endpoint was mortality and the results showed a 20% risk reduction with bisoprolol (67 patients died on placebo, 53 on bisoprolol; relative risk, 0.80) but this observed reduction did not reach statistical significance (p=0.22) (Fig 2). No

significant difference was also observed in sudden death rate (17 on placebo, 15 on bisoprolol) or death related to documented ventricular tachycardia or fibrillation (7 on placebo, 4 on bisoprolol).

Despite the absence of significant benefit in mortality for the entire population in the CIBIS trial, subgroup analysis according to the etiology of CHF was of interest. Among 303 patients with a history of myocardial infarction, 19% died on placebo compared with 21% on bisoprolol (p=0.55). However, among 338 patients without a history of myocardial infarction, 22.5% died on placebo and 12% died on bisoprolol (p=0.01). There is no clear explanation for this differential effect since it might be anticipated that β–blockade would confer cardiac protection in ischaemic patients. After myocardial infarction, β–blockade therapy has largely proven to be beneficial with a 20% to 25% reduction in 1-year mortality and in nonfatal myocardial reinfarction rate (36,37). In addition, benefit appears to be greater in high risk patients with a history of compensated or mild congestive heart failure before randomization (38,39). However, it must be emphasized that this subgroup analysis of the CIBIS trial should be interpreted with some caution as no stratification based on etiology of CHF was performed at randomization which would exclude valid separate analysis according to these subgroupings. Therefore these results of subgroup analysis can be considered only suggestive, and differential results of bisoprolol efficacy according to etiology must await formal studies.

Four moderately large randomized, placebo-controlled, US trials (29) with carvedilol, designed to look at symptomatic and other non-fatal endpoints, also prospectively reported mortality, for safety reasons, to a common Data and Safety Monitoring Boad (DSMB). The DSMB recommended early termination of this programme of carvedilol trials (after a median follow-up of only 6.5 months) based on the finding of a significant 65% relative reduction in death in the active therapy group compared to the placebo group - placebo group mortality 7.8% and carvedilol group mortality 3.2% after a median follow-up of 6.5 months (P<0.001) (30). Four meta-analyses, (40,43) published before these results became available supported a benefit of bete blockers on left-ventricular function, symptoms and hospitalization but not total mortality (unless cardiac transplantat was equated with death). An updated metaanalyses (44), following the publication of the US trials and a less favourable Australian-New Zealand study, supports a reduction in total mortality, although this new overview is necessarily biased by the relatively large size of the carvedilol trials compared to previous bete-blocker trials. Three further large, placebo-controlled mortality trials with beta-blockers (bucindilol, bisoprolol and metaprolol) are still underway, as is a trial comparing cantedilol to metoprolol.

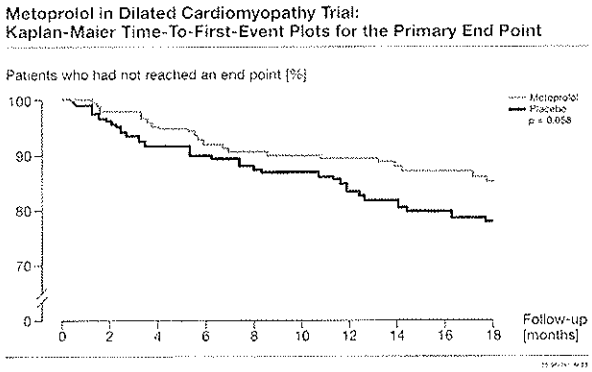

Figure 1. Metoprolol in Dilated Cardiomyopathy Trial. Likelihood of reaching the primary endpoint of death or need for heart transplantation. 211 patients were followed for 12 months and 178 for 18 months. 38 patients in the placedbo group reached a primary endpoint compared with 25 in the metoprolol, representing a risk reduction of 34% (p=0.058).
With permission from Waagstein et al. (25)

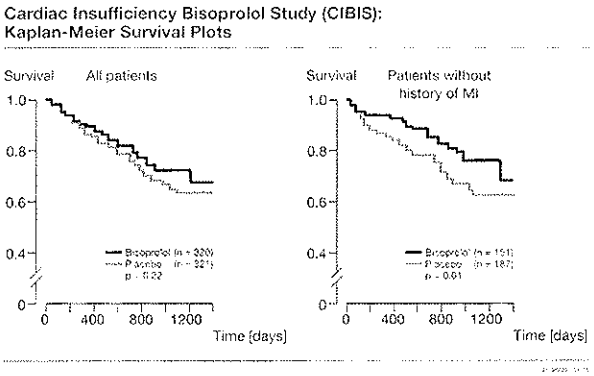

Figure 2. CIBIS Trial. Survival curves (Kaplan-Meier) in 641 CIBIS patients: 67 patients died receiving placebo, and 53 died receiving bisoprolol. Risk reduction on bisoprolol: 0.80 (95% confidence interval + 0.65 - 1.15).
With permission from the CIBIS Investigators (28)

What are the likely mechanisms for the beneficial effects of β–blockers in CHF?

The mechanisms for the positive impact of β–blockers in CHF are not clear and a number of hypotheses have been proposed. Some investigators have proposed that protection from catecholamine toxicity may be one mechanism for the improvement in left ventricular function. As alluded to earlier, studies in animal models using intact hearts and cell cultures, as well as clinical observations in patients with cardiomyopathy due to pheochromocytoma have confirmed the adverse impact of high levels of catecholamines on the heart (11-13). Several mechanisms could be involved in catecholamine mediated cardiotoxicity including intracellular calcium accumulation (45) and generation of free radicals by catecholamine metabolites such as adrenchrome (46). In CHF, catecholamines may also mediate their adverse effects by increasing metabolic demand on an already energy

starved myocardium. Catecholamines may also compromise coronary blood flow by shortening diastole and by causing vasoconstriction. With respect to the latter, it is now recognised that successful revascularisation is capable of causing marked improvement in some patients with depressed ventricular function due to stunned or hibernating myocardium. It is possible that β–blocker induced alteration of supply/demand imbalance can mediate similar recovery in patients with CHF. β–blockers might also improve contractility in patients with abnormally prolonged mechanical restitution by slowing heart rate and thereby allowing systole to occur in the more advantageous plateau portion of the restitution curve (47). The observation that only prolonged therapy (>4weeks) with β–blockers can produce haemodynamic and clinical improvement suggests that the deleterious effect of catecholamines is reversible and that long periods of protection from the actions of endogenous catecholamines are required for the recovery of cardiac function.

Because the defect in contractile function seen in CHF may be caused, in part, by a deficiency of intracellular cyclic AMP which is related to a loss of myocardial B-receptors, some workers have suggested that β–blockers might be effective in CHF because they increase the density (upregulate) of B-receptors and thus sensitize the heart to the positive inotropic and lusitropic (relaxant) actions of endogenous catecholamines (48). This hypothesis, however, fails to explain a number of observations. Firstly, although β–blockers increase the density of B-receptors, they would at the same time block these receptors from the effects of endogenous catecholamines, and thus prevent any favourable haemodynamic effect of endogenous sympathetic stimuli might exert on the upregulated receptors. Second, B-receptor upregulation occurs rapidly (within hours or days) after the institution of treatment with β–blockers, but the beneficial haemodynamic effect of β–blockers are delayed (for several months). Thirdly, in patients with idiopathic dilated cardiomyopathy, there is no correlation between the degree of improvement in ejection fraction and the changes in receptors (49). Finally an anti-ischaemic and anti-arrhythmic effect of β–blocker might be important in the prevention of sudden death in CHF. However, no effect on sudden death has so far been observed in all the trials of β–blockers in CHF except in subgroup analysis of the post-infarction trials of the BHAT trial and the Norwegian Timolol study when the greatest reduction in cardiac mortality was among patients with evidence of CHF. In particular, in the BHAT study, there was a striking 47% reduction in the incidence of sudden death in this high-risk cohort compared with only a 13% reduction in patients without a history of CHF.

Are β–blockers useful in all types of CHF?

Most of the early trials were confined to the relatively uncommon condition of idiopathic dilated cardiomyopathy but more recently β–blockers have been evaluated in patients with CHF secondary to other causes including coronary artery disease. It has been suggested that β–blockers may be less beneficial in CHF associated with coronary artery disease than in patients with idiopathic cardiomyopathy (18,22,28). Several reasons have been proposed. Firstly, it has been argued that the chronicity of coronary artery disease and the relatively large areas of fibrosis that may be associated with previous myocardial infarction may prevent any marked increases in ejection fraction. Biopsy data from studies of idiopathic cardiomyopathy suggest that the extent and type of fibrosis predicts the "likelihood of increased ejection fraction with β–blocker therapy" (50). Some data (51) suggest that alteration of the inhibitory G proteins may differ in failing hearts with ischaemia versus idiopathic dilated cardiomyopathy. This difference has some functional relevance to inotropic responsiveness to endogenous catecholamines. Conceivably, it may influence the response to B-adrenergic blockade as well. There is some support for this from the subgroup analysis in the CIBIS trial which suggest an enhanced action on bisoprolol in patients without ischaemia, in the absence of a history of myocardial infarction or in patients with an idiopathic dilated cardiomyopathy (28). However, as discussed earlier, caution should be exercised when interpreting this data from the CIBIS trial since no stratification based on etiology was performed at randomization. Besides, Fisher et al. (27) recently reported a definite symptomatic and functional improvement in patients with CHF secondary to coronary artery disease with a mean increase in ejection fraction of 4% and 10 (20%) of 38 patients had improvement in ejection fraction of greater than 8%.

It is also not clear what stage of CHF β–blockers should be used in. Since CHF show different pathophysiologic changes at various stages in its evolution, it could be unrealistic to accept a single agent or class of agents as effective throughout the natural history of the disorder. It could be argued that β–blockade may be unnecessary in early CHF where there is no or minimal activation of the sympathetic nervous system. There have been no trials of β–blockers in early CHF. Most of the trials have been in symptomatic patients. In the Metoprolol in Dilated Cardiomyopathy Trial, eligible patients had symptomatic CHF with ejection fractions less than 40%. Another requirement was that patients had achieved a state of compensated CHF by means of conventional CHF treatment which included digitalis, diuretics, angiotensin converting enzyme inhibitors and nitrates. Eighty two percent of the placebo and 78% of the metoprolol treated pa-

tients were on an angiotensin converting enzyme inhibitor and improvement in myocardial function was not affected by concomitant treatment with an angiotensin converting enzyme inhibitor and the authors suggested that the 2 types of drugs produced improvement by different mechanisms.

How safe are β–blockers and should β–blockers be recommended for routine use?

There is no doubt that some patients remain very intolerant to these drugs. Even with cautious dosing, some patients who had participated in these trials have to be withdrawn because of worsening CHF, bradycardia or hypotension. It is difficult to glean from the published results the incidence of acute intolerance, it may range from 0%-30%. Intolerance may occur even with small initial doses in approximately 10% to 15% of patients (29). Das Gupta et al. (18) reported a 29% incidence of intolerance to a single 12.5 mg dose of carvedilol. In the Metoprolol in Dilated Cardiomyopathy Trial, about 5% of the original eligible patient group were intolerant of the smallest dose and had to be excluded. It is also unclear whether patients with decompensated or severe CHF are liable to be intolerant since some of these seem to tolerate β–blockade without problems and one group has even reported the successful use of low-dose metoprolol on patients with end stage CHF requiring inotropic support (52). In the US carvedilol trial, 7.8% of the placebo group and 5.7% of the carvedilol group discontinued the study medication because of adverse reactions. Since there is some difficulty in identifying patients that may become intolerant to β–blockers and the evidence to date have yet to show an impact on mortality, it could be argued that the available data does not justify the widespread use of β–blockers in all patients with CHF. The experience with other agents in CHF, such as xamoterol (53) and milirinone (54) which produce favorable short-term haemodynamic and clinical effects but actually increase mortality in the long termindicates the importance of mortality data in the consideration of general treatment recommendation. But are there any CHF patients which might be considered suitable for a therapeutic trial of β–blockade. It could be argued that a carefully selected group of patients who remain symptomatic despite being on maximal therapy may benefit from this novel approach. Clearly, treatment must be started at an extremely low dose. A useful description of how to use beta-blockers in heart failure is given in the recent European Society Guidelines on the treatment of heart failure (55) as shown in Table 2.

Conclusion

Thus, the role for modulation of B-adrenergic nervous system in CHF has been encouraging with reports of improvements in symptoms, left ventricular function and functional capacity. To date, trials of β–blockers in CHF have yet to show an effect on mortality, although in an analyses of a combination of trials of carvidelol suggest that it may have a benefit. The exact mechanisms by which benefit may be mediated are still to be determined. Besides this, there are still a number of unanswered questions. Exactly which patient population may derive the most benefit remains unclear. What stage of CHF may benefit from β–blockers? How long should we treat these patients with a β–blocker? Which β–blocker should we use? Most of the early studies have used metoprolol. More recently, attention has switched to the newer generation of β–blockers with vasodilating properties such as bucindolol. These agents have been developed in the hope that they might be less likely to precipitate acute haemodynamic deterioration than conventional β–blockers. It has also been argued that since β_1 selective blockers, such as metoprolol, do not block the β_2 receptor there is still the potential for catecholamine stimulated myocardial β_2 receptors to result in arrhythmias and sudden death. Furthermore, metoprolol does not block presynaptic β_2 receptors and therefore does not reduce plasma norepinephrine (56) which is an important prognostic marker in CHF. The β_1 β_2 receptor antagonist bucindolol has been shown to reduce plasma norepinephrine (26) and it has mild vasodilator properties which may be the reason why this drug appears to be better tolerated than propanolol in CHF (17, 22). This is the rationale for

Table 2. Initiating dose, target dose and titration scheme of bet-blocking agents in placebo-controlled large trials

Beta-blocker	First Dose (mg)	Titration scheme total dose (mg)							Target total daily dose (mg)
Metoprolol (MCD trial) (25)	5	Wk1 10	Wk2 15	Wk3 30	Wk4 50	Wk5 75	Wk6 100	Wk7 150	100-150
Bisoprolol (CIBIS) (28)	1.25	Wk1 1.25	Wk2 2.5	Wk3 3.75	Wk4-7 5	Wk8-11 7.5		Wk12-5 10	10
Carvedilol (US trial) (30)	3.125	Wk1 6.26	Wk2	Wk3 12.5	Wk4	Wk5 25	Wk6	Wk7 50	50

selection of bucindolol in the NHLB/VA Cooperative study, Beta Blocker Evaluation of Survival Trial (BEST). This trial along with several large scale controlled trials are already in progress to assess the long term safety and efficacy of β–blockers in CHF and, most important of all, their impact on survival. Until these large trials are completed, the use of β–blockers remains a promising but as yet unestablished form of treatment for CHF.

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ANTIGEN SPECIFIC LYMPHOCYTE PROLIFERATIVE RESPONSE OF PATIENTS WITH ACUTE AND CHRONIC TOXOPLASMOSIS

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ABSTRACT: *In vitro* lymphocyte proliferative response of peripheral blood leucocytes (PBL) to purified *Toxoplasma gondii* antigen were evaluated by 3[H] methyl thymidine incorporation in patients acutely and chronically infected with *Toxoplasma gondii*. PBL from three patients with acute symptomatic toxoplasmosis showed no response to *T. gondii* antigen during the emergence of anti-*Toxoplasma* IgM antibodies and the response returned as the infection became chronic. Lymphocytes of twelve chronically-infected patients responded positively to the antigen. In all patients the lymphocyte proliferative response to the mitogen, Concanavalin A (Con A) was normal. Analysis of *Toxoplasma* proliferative response of PBL from a patient with acute toxoplasmosis showed that $CD8^+$ cells were responsible for induction of suppression while the response during the chronic infection was mediated by $CD4^+$ cells. In human toxoplasmosis there was antigen-specific lymphocyte unresponsiveness during the acute phase of the infection and it appears that the immunesuppression was mediated by $CD8^+$ cells. *(JUMMEC 1999; 1:34-38)*

KEYWORDS: Toxoplasmosis-lymphocyte blastogenesis-antigen specific-$CD4^+$, $CD8^+$

Introduction

Toxoplasma gondii, one of the most common parasites of man all over the world, is known to cause latent infection in man and produce a persistent antigenic stimulus. *T. gondii*, even in asymptomatic humans, is known to stimulate a humoral response (1). In addition, a well-developed cell-mediated immune response against the parasite is characteristic of toxoplasmosis and can be demonstrated by delayed type hypersensitive reactions to specific antigens (2,3). More recently *in vitro* studies of cell-mediated immunity in humans with toxoplasmosis showed that lymphocytes proliferate differentially in response to *T. gondii* during the acute and chronic phases of the disease (4,5,6,7). However due to the scarcity of the number of cases that could be followed-up from the time of initial infection to the latent stage of infection, the dynamic change or pattern in the lymphocyte responsiveness during the course of the disease is yet to be fully delineated.

In this study we analysed the responses of patients lymphocytes to specific *Toxoplasma gondii* antigen and to non-specific mitogen, Con A. We now report the results of lymphocyte transformation in healthy individuals, acute and chronic patients with toxoplasmosis and characterize the cells that may be responsible for the observed results.

Material and Methods

Patients and controls

This study was carried out according to the principles of the Declaration of Helsinki, with patients' consent and Universiti Sains Malaysia Human Experimental Committee approval.

A total of 20 subjects all female, ages ranging from 20 to 35 years were randomly selected through the antenatal clinic. They were divided into three groups; group I consisted of five subjects who were negative for both IgG and IgM *Toxoplasma* antibodies; group II comprised of twelve subjects who had *Toxoplasma*-specific IgG

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antibodies. The third group was three cases of acute infection, of which one was a laboratory acquired infection who presented with acute symptoms for three months. All three acutely infected patients were symptomatic and had high levels of *Toxoplasma*-specific IgM antibodies.

Preparation of Toxoplasma antigen

The RH strain of *Toxoplasma gondii* was collected from two sources, viz. peritoneal exudate of infected mice and *in vitro* cultures of infected nasopharyngeal carcinoma cells. The method of *Toxoplasma* antigen preparation is as described by Rahmah et al. (8). Briefly, the exudate was mixed with RPMI-1640 and fetal calf serum and incubated in plastic petri dishes for 45 minutes to remove macrophages. The suspension was centrifuged at 500 rpm for 5 minutes to remove cellular contaminants. The pellet was discarded and the supernatant recentrifuged at 3000 rpm for 20 minutes. The resulting supernatant was discarded and the pellet was washed with phosphate-buffered saline (PBS) twice by centrifugation at 3000 rpm for 10 min. The final pellet was stored at - 20°C until required.

Isolation of lymphocyte population

Twelve ml of blood was drawn into a venoject containing 100 U of heparin (Upjohn Co., Kalamazoo, Mich., USA) and mixed with an equal volume of sterile 0.15 M Na Cl_2. Twelve ml of diluted blood was carefully layered over 3ml of a mixture of Ficoll and sodium diatrizoate (Hypaque; Pharmacia, Sweden) in 15ml plastic centrifuge tubes (Costar, USA). The tubes were then centrifuged at 1300 rpm for 45 min at room temperature. The layer of mononuclear cells at the plasma Hypaque interface was removed and suspended in culture medium RPMI 1640 with 100U/ml penicillin, 50ug/ml streptomycin and 2mM fresh glutamine. The cell suspension was washed three times in serum free medium and resuspended at a concentration of 4×10^6 cells/ml in culture medium with 10% heat inactivated autologous plasma. Lymphocytes represented more than 90% of white cells recovered.

Lymphocyte Transformation Assay (LTT)

Mitogen-induced in vitro lymphocyte blastogenesis was performed in flat-bottomed microtiter plates (Nunc, USA) while antigen-induced lymphocyte blastogenesis was performed in round-bottomed microtier plates (Nunc, USA). Each well received 100 ml of 4×10^5 cells in RPMI-1640 supplemented with 3% penicillin-streptomycin and 10% autologous plasma. For smitogen-LTT, experimental wells were stimulated with 100 ml of optimal concentration of Con A, 64 ug/ml. For antigen-LTT, experimental wells received 100 ml of culture medium. The plates were incubated in a 5% CO_2-in air atmosphere for 72 hr for mitogen experiments and 120 hr for antigen experiments.

All cultures received a terminal 8-10hr pulse of 1C/well of tritiated thymidine (3H-TdR; Amersham, USA). Cultures were harvested on glass fiber filters using a Minimash 2000 cell harvester (Dynatech, England). To each filter paper disc, 3 ml of scintillation cocktail (Ready Protein, Beckman, USA) was added and the samples were then counted in an LS Counter 9800 (Beckman, USA). Results of triplicate cultures were expressed as mean counts per minute (CPM) ± standard error of the mean (SEM) or as a stimulation index (S.I.) which is the ratio of CPM of stimulated cultures to the CPM of unstimulated cultures.

Subpopulation of Peripheral Blood Lymphocytes

Monoclonal antibodies OKT against T cell subsets were purchased from Behringwerke, Germany. Lymphocyte suspension of 4×10^6 cells/ml was incubated with the appropriate monoclonal antibodies of the appropriate kind (OKT4 or OKT8) for 20 minutes at 4°C. The cells were then washed in RPMI 1640, followed by treatment with 100 ml of 1 : 50 diluted rabbit complement and incubated for one hour at 37°C. After three washings, the cells were resuspended in complete culture medium. Lymphocyte blastogenesis experiments were then performed as described above.

Serological techniques

IgG antibody titres were determined by the immunofluorescense antibody test and titres were expressed in two fold dilutions as previously described (9) using commercially available reagents (Behringwerke, Germany). IgM antibodies were determined by the specific and sensitive immunosorbent agglutination assay, ISAGA (Bio Merieux, France) which utilizes monoclonal antibodies as the solid phase.

Results

Lymphocyte proliferative response to Mitogen and Antigen

The individuals were divided into three groups on the basis of clinical and serological criteria. Individuals with negative serology for *T. gondii* antibody were treated as the control group (Group I), while individuals known to have positive serology for IgG were considered to have latent (chronic) infection (Group II). Group III consisted of acutely-infected patients.

The response of lymphocytes to the mitogen (Con A) and SA in the various groups is as shown in Table 1. Lymphocyte blastogenic response to the mitogen was present in all groups. The lymphocytes were capable of undergoing blast transformation at all times as indicated by their good response to the T-cell mitogen. PBL from

patients chronically-infected with *T. gondii* were found to be very responsive to *in-vitro* stimulation with *T. gondii*

antigen as shown by the high incorporation of tritiated thymidine. On the other hand, none of the control patients responded to *Toxoplasma* antigen. The patient who was accidentally infected with *T. gondii* presented with acute clinical symptoms of fever, lymphadenopathy, flu-like syndrome, abdominal discomfort, and a state of confusion. Prior to the infection, the patient was negative for toxoplasma serology and antigen-specific lymphocyte blastogenesis. After the infection her PBL were still capable of undergoing blast transformation to T-cell mitogen (Con A) at the time the lymphocytes were not responding to the specific *T. gondii* antigen. Thus unresponsiveness of antigen dependent (*T. gondii* specific) T-cell proliferation was observed in this patients. A time-course study of *Toxoplasma* - specific proliferative response of the accidentally-infected patient showed that her PBL failed to demonstrate lymphocyte proliferation to SA for as long as three months, which coincided with the period of her clinical symptoms. At four months after onset of the infection, her lymphocytes transformed to SA and the response continued to be positive thereafter. Therefore the positive cell-mediated immune response of this patient inversely correlated to the presence of her clinical symptoms. The time of onset of clinical

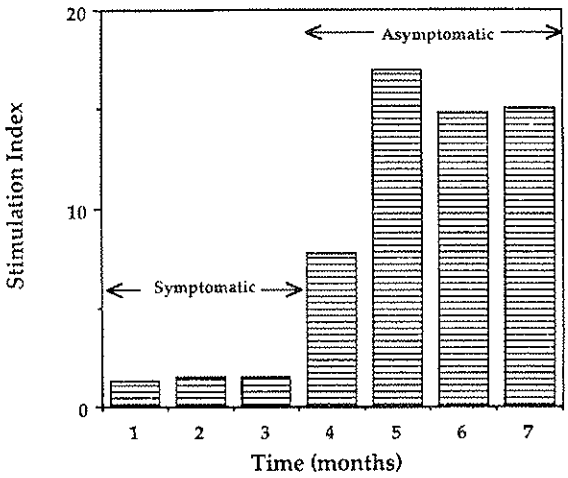

Figure 1. Longitudinal Studies of lymphocyte proliferative responsiveness to *Toxoplasma gondii* antigen of a patient with infection

symptoms of the other two acutely infected patients were not clearly defined.

Characterization of Toxoplasma induced suppressor and inducer T-cells

To characterise the cells responsible for suppression and responsiveness of proliferation of lymphocytes from

Table I. Serology and lymphocyte proliferate response of P BL to *Toxoplasma gondii* antigen from healthy controls, chronically and acutely infected subjects.

Group	Subject	Toxoplasma antigen (Stimulation index)	Concanavalin A (Stimulation Index)	Antibody titres IgG	IgM
Group I	1	0.96	43.8	Neg	Neg
Control	2	1.30	35.2	Neg	Neg
	3	1.90	28.6	Neg	Neg
	4	1.60	38.1	Neg	Neg
	5	1.25	40.9	Neg	Neg
Group II	1	10.1	46.7	1:1024	Neg
latent infection	2	15.8	39.6	1:1024	Neg
	3	11.7	40.1	1:2048	Borderline
	4	14.9	33.7	1:512	Borderline
	5	17.5	42.9	1:256	Neg
	6	26.1	28.4	1:128	Neg
	7	9.9	30.5	1:128	Neg
	8	18.6	41.3	1:128	Neg
	9	39.1	38.8	1:128	Neg
	10	9.8	34.6	1:128	Neg
	11	12.3	30.2	1:128	Neg
	12	14.6	45.2	1:128	Neg
Group III	1	0.9	32.6	<1:64	12+
acute infection	2	1.4	45.5	<1:64	12+
	3	1.3	40.3	<1:128	12+

Isaga results one read as follow :
0 - 5 = Negative, 6 - 8 = Border line (BL), 9 - 12 = Positive

patients with Toxoplasmosis, the cells were treated with monoclonal antibodies and complement. The monoclonal antibodies used were OKT4 (IgG2b) which characterizes CD4 antigen and defines the helper T lymphocytes, and OKT8 (IgG2a) which characterises CD8 antigen and defines the suppressor T lymphocytes. The effect of treatment with monoclonal antibody and complement on the ability of PBL to proliferate to *Toxoplasma* antigen was determined by the incorporation of ^{3}[H] TdR. The results of the experiments are shown in Table II. Treatment of cells from an acutely infected patient, with anti-CD4 and complement or complement alone did not alter the *Toxoplasma* specific unresponsiveness. However when the cells were treated with anti-CD8 plus complement the response returned, indicating that the CD8 positive cells were responsible for the induction of suppression during the acute phase of infection. In a separate experiment, the effect of monoclonal antibody against CD4 and CD8 was assesed on cells from a chronically infected patient. When the cells were treated with anti-CD8 plus complement or complement alone, the antigen specific response was not affected, but treatment with anti - CD4 eliminated *Toxoplasma* specific proliferative response. Thus these experiments show that *Toxoplasma* specific non-responsiveness during acute phase of infection was mediated by CD8 cells, namely the suppressor T cells, and the responder cells in both acute and chronic phase of the infection are the helper T cells.

Discussion

Lymphocyte transformation in *T. gondii* infection was first demonstrated histologically in sensitised rabbits by culturing lymphocytes *in vitro* in the presence of *Toxoplasma* antigen (10). Tremonti *et al.* (11) studied lymphocyte blastogenesis in humans with serological evidence of infection with *T. gondii*. They showed that *Toxoplasma* antigen stimulated blastogenesis in both seropositive and seronegative individuals, therefore demonstrating that antigen derived from *Toxoplasma* acted as a mitogen. Our study shows that asymptomatic patients with serological evidence of *Toxoplasma gondii* infection were positive for lymphocyte transformation to *Toxoplasma* antigen. On the other hand, individuals who were seronegative for *Toxoplasma* antibodies showed no such response of lymphocytes to the mitogen, Con A, thus indicating that the ablity of their lymphocytes to respond to non-specific antigen was intact.

The patient who was accidentally infected with tachyzoites from ascitic fluid of *T. gondii* infected mice showed acute symptoms for about twelve weeks post-infection. During this period, lymphocyte transformation to *Toxoplasma* antigen was not demonstrable. However during this period of depressed response to the specific antigen, her lymphocytes responded normally to Con A. Therefore this demonstrated that her general T-cell immunity was intact and that the unresponsiveness was antigen specific. The two other patients who were acutely infected showed similar findings expect that the lymphocyte responses to *Toxoplasma* antigen were positive much earlier. Yano *et al.* (12), Krahenbuhl *et al.* (13) and (14) also described similar lymphocyte unresponsiveness to specific *Toxoplasma* antigen, but not to T-cell mitogens, in patients with acute symptomatic toxoplasmosis. Other investigators have also documented that in some immunologically normal adults with acute acquired toxoplasmosis, positive lymphocyte blastogenesis to *T. gondii* antigen developed only after a lapse of several months post-infection (4,6).

Table 2. Analysis of Toxoplasma specific proliferative response in PBL of patients with Toxoplasmosis using monoclonal antibodies specific to human T-cell subsets.

		Antigen-Specific Proliferation Response of PBL[a]		
	Treatment of PBL	Medium	TOXO Extract (ΔCPM[b])	ConA (ΔCPM)
Acute	Normal	466±102	984	25,325
	Deplete MØ[c]		906	19,247
	C Alone		837	17,188
	OKT4 + C		972	5,421
	OKT8 + C		3,973	17,249
Chronic	Normal	391±96	5,032	ND
	C Alone		4,492	ND
	OKT4 + C[d]		546	ND
	OKT8 + C		4,113	ND

[a] peripheral blood lymphocytes
[b] counts per minute
[c] macrophage cells
[d] guinea pig complement

The mechanism of lymphocyte unresponsiveness to *Toxoplasma* antigen is unclear. An analysis of the T-cell subpopulations of the accidentally infected patient revealed that there was an absolute increase in the number of T 8 cells resulting in a depressed T4/T8 ratio (15). Luft *et al.* (14), Sklenar *et al.* (16) and De Waele *et al.* (17) also reported increase in absolute numbers of suppressor-cytotoxic T-cells in patients with symptomatic acute toxoplasmosis. On the other hand other investigators have reported that during acute infection of toxoplasmosis the T4/T8 ratio remains unchanged (18). Further analysis of her lymphocytes during the acute period of infection showed that the $CD8^{+}$ cells were responsible for the suppression and that the removal of $CD8^{+}$ cells reconstituted the blast transformation. Yano *et al.* (12) postulated that the mechanism of unresponsiveness could be operating through induction of suppression through suppressor

cells. In murine toxoplasmosis, immunosuppression has been postulated to be caused by T-cells (19); antigenic competition (20); activation of suppressor macrophages (21); and production of soluble factors (22, 23). These findings together with our finding further support the idea that transient immunosuppression during the acute phase of toxoplasma infection may be operating through interactions of multiple mechanisms.

This study concluded that in acute symptomatic phase of *Toxoplasma* infection, there was a delayed response to *Toxoplasma* antigen, whereas the response to mitogen was unaltered. Lymphocytes of patients who were not symptomatic but showed positive *Toxoplasma* serology responded to *Toxoplasma* antigen as well as to the mitogen. We also demonstrated that the suppression of response during acute symptomatic infection could be attributed to $CD8^+$ cytotoxic/suppressor cells; while the responder cells during the chronic phase of *Toxoplasma* infection were the $CD4^+$ cells.

Further studies on the unresponsiveness during the acute symptomatic phase with larger number of patients would cast more insights into the anergy of the subjects.

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WHY ARE NASOPHARYNGEAL CARCINOMA PATIENTS DIAGNOSED AT LATE STAGE ?

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ABSTRACT: 100 consecutive newly diagnosed patients with nasopharyngeal carcinoma (NPC) since January 1994 were the subjects for studying various factors related to the delay in the confirmation of the diagnosis. 79 of them were males and the peak age of incidence was the 5th decade. 92% were Chinese, 7% Malay and 1% Indian. 76% were agriculture worker or labourers with 66% having either no formal education (16%) or only primary level education (50%). For 50% of patients neck swelling was the first symptom, 26% had nasal symptoms, 12% ear symptoms and 11% had symptoms due to intracranial extension of tumour. As many as 80% were at UICC Stage IV at the time of diagnosis. While the median delay, on the part of patients, in consulting a doctor was 2.5 days, the median delay on the part of the doctors to confirm the diagnosis of NPC was as long as 127 days, which was particularly worse when the patients presented with ear symptoms (266 days) followed by those with neck swelling (94 days). For those patients who were required to undergo more than one nasopharyngoscopy and biopsy the median doctor's delay was 144 days. Since 82% of patients had consulted general practitioners who remained the first-line health-service provider, it is suggested that their level of awareness with regards to NPC be significantly raised so that the delay on their part be greatly minimized. *(JUMMEC 1999; 1:39-42)*

KEYWORDS: Nasopharyngeal carcinoma, delay in diagnosis, patient's delay, doctor's delay.

Introduction

Nasopharyngeal Carcinoma (NPC) ranks fourth among the most common cancers in Malaysia. It most commonly affects the ethnic Chinese in or originating from southern provinces of China, where the incidence(1) is as high as 30 per 100,000 per year. Natives (Malays, Kadazans, Ibans and Bidayuhs) in Malaysia and those in other Southern Asian countries as well as Maghrebian Arabs and Greenland Eskimos have an intermediate risk, while for the rest of the population in the world the incidence of NPC is as low as 1 per 100,000 per year. In Peninsular Malaysia it was noted(2) that the Chinese males, in the fifth decades of life, were at the highest risk (40.1 per 100, 000 per year). With almost 90% of population at either high or intermediate risk of developing NPC, it is a major health problem in Malaysia.

While the problem of establishing the diagnosis of NPC has been resolved(3), and there has been remarkable improvement in the survival of NPC patients at early stages(4), (UICC5 Stages I & II), for whom "cure" seems achievable, it is unfortunate that almost 80% of our patients are diagnosed at advanced stage6 (UICC Stages IV), for whom the survival rate is still far from satisfactory.

The present study was undertaken to investigate into the factors responsible for the delay in establishing the diagnosis of NPC.

Materials and Methods

One hundred consecutive newly diagnosed and histologically confirmed NPC patients seen at the University Hospital Kuala Lumpur from January 1994 onwards were the subjects for study. All the patients were interviewed by one of the authors (Pua Kin Choo). A properly designed pre-set questionnaire-form was filled up with relevant data obtained from the patients and their case folders.

The questions were set in order to obtain information concerning the patient's general characteristics (age, sex, race, education, occupation, personal habits), his state of awareness about NPC, first symptom noted by the patient, with its duration, first and subsequent doctors

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visited, difficulties encountered before confirming the diagnosis and date of final NPC diagnosis.

Data thus obtained were stored in a file under a programme "spread sheet" in Excel 7.0 of Windows 95, and analysed with a view:

1. to ascertain whether there was delay on the part of patient (Patients delay). This was noted as the time interval between the start of first symptom as observed by the patient and the date of first visit by the patients to see a doctor.

2. to ascertain whether there was delay on the part of the doctor (Doctor's delay). This was taken as the time interval between date of first visit by the patient to see a doctor (or the first doctor, if he had consulted more than one) and the date of confirmation of diagnosis.

3. to study the factors which could have caused the patient's and/or doctor's delay, if any, with special reference to patient's general characteristics as mentioned above, their awareness about NPC, the nature of first symptom noted by the patients, type of doctor first consulted and the kind of difficulties encountered by the doctor in confirming the diagnosis.

For both patient's delay and doctor's delay, the time interval was computed to denote "median" or the middle number, when the numbers were arranged in order or according to size. Median was chosen because the range of value was wide and the distribution was skewed to the left. Realizing the fact that several patients had problems recalling the date of first symptom or date of first visit to see a doctor most appropriate dates were selected based on patient's recollection.

Descriptive statistics was used in the presentation of the results.

Results

1. General characteristics:

a. Age and Sex (Table 1)

Largest number of patients (37) belonged to the age group 40 - 49. The overall median age of the patients was 49. There were 76 males and 24 females giving a male to female ratio of 3:1.

b. Ethnic and dialect distribution (Table 2)

92 patients were Chinese, with 37 (40.2%) belonging to the Cantonese dialect group (dialect of the patient's father was taken as patient's dialect even though mother spoke different dialect). 24 (26.1%) of them were Hokkien and 24 (26.1%) Hakka. There were 7 Malay patients and 1 Indian patient in this group.

c. Distribution according to occupation (Table 3) and education.

Based on the Dictionary of Occupational Classification of Malaysia(7), it was noted that as many as 73 (73%) belonged to workers or labourers class. Those female patients who were housewives were classified under their husband's occupational class.

As for education, majority (66%) of them had either primary education (50%) or no formal education (16%) at all. 31 (31%) had studied up to secondary level and only 3 (3%) had received tertiary education.

d. Awareness of NPC Before Diagnosis

34 (34%) patients had come to know about NPC before

Table 1. Distribution of 100 NPC patients according to age and gender.

Age Group Years	Female N	(%)	Male N	(%)	Total N	(%)
20 - 29	1	(4.2)	3	(3.9)	4	(4)
30 - 39	6	(25.0)	17	(22.4)	23	(23)
40 - 49	8	(33.3)	29	(38.2)	37	(37)
50 - 59	4	(16.7)	21	(27.6)	25	(25)
60 - 69	5	(20.8)	4	(5.3)	9	(9)
70 - 79	0	(0.0)	2	(2.6)	2	(2)
Total	24	(24.0)	76	(76.0)	100	(100)
Median of age	49		46		49	

N is the number of patients

Table 2. Distribution of 92 Chinese NPC patients according to dialect.

Dialect	N	%
Cantonese	37	(40.2)
Hokkien	24	(26.1)
Hakka	24	(26.1)
Teochew	4	(4.3)
Hainanese	3	(3.3)
Total	92	100

Table 3. Distribution of 100 NPC patients according to occupation

Occupation	N	%
Professional	2	2
Administrative	2	2
Clerical	5	5
Sales	11	11
Service	4	4
Agriculture	3	3
Labourer	73	73
Total	100	100

he/she was inflicted with this disease. Most of them (30 or 88.2%) got information through either friends and relatives (16 or 47%) or through newspapers (14 or 41.2%). 13 of them had positive family history of NPC. 4 obtained information from medical staff known to them.

e. First Symptom

Presence of swelling in the neck (neck mass) was noted as the first symptom by 50 (50%) patients whereas there were 26 (26%) patients for whom the first symptom was nasal (in the form of blood stained nasal or postnasal discharge). There were 12 (12%) patients whose first symptom was aural, which included impairment of hearing with or without tinnitus in one ear. 11 (11%) had intracranial symptom; either headache (6%) or cranial nerve palsy (5%). There was one patient whose first complaint was generalised bodyache.

f. Stage of NPC at Diagnosis

All the patients were staged according to UICC staging classification (5), after CT Scan of the nasopharynx, skull base and cervical region, and complete metastatic work up (Bone Scan, Liver ultrasound and Chest X-Ray) to exclude distant metastasis to bone, liver or lung. As many as 80 (80%) belonged to Stage IV with 14 (14%) in Stage III and 3 each in Stages II and I.

II. Patient's Delay

It was revealing to find that 73 (73%) patients had consulted a doctor within 2 months of observance of the first symptom with as many as 47 (47%) visiting a doctor's clinic on the very first day they noticed a symptom. While there were 14 (14%) patients who took between 2 to 6 months and 13 (13%), more than 6 months to see a doctor. The overall median time to see a doctor (Patient's delay) was only 2.5 days.

a. In relation to age, sex, ethnic and dialect groups and awareness about NPC.

No significant difference could be allocated between various subgroups

b. In relation to occupation and educational level.

It was quite obvious that the worker/labourer group (76) took longer time (median delay of 12 days) to see a doctor, while those with no formal education (16) taking yet longer time (median delay 30 days) to do so.

c. In relationship to symptoms.

It was interesting to note that for those patients with nasal symptoms (26 patients) the median delay was 21 days, while for those with intracranial symptom (11) it was 14 days. However for those with neck swelling (50) the median delay was only 3 days and for those with ear symptom (12) there was no delay at all.

III. Doctor's Delay.

It was shocking to note that the median delay on the part of the doctors was as long as 127 days or more than 4 months. There were only 9 patients for whom the diagnosis of NPC was confirmed within 2 weeks of seeing a doctor. For 19 it took up to 2 months, for 37 between 2 to 6 months and for 35 (35%) i.e. more than one-third, it took anything between 6 months to more than one year.

a. In relation to first Symptom:

For those with nasal symptom (26 patients) the median doctor's delay was minimum (26 days), followed by those with intracranial symptoms (11) for whom it was 51 days. It was unbelievable to find that the median doctor's delay was more than 3 months (94 days) for those with neck swelling (50 patients) and for those with ear symptom (12) it was close to 9 months (266 days).

b. Doctor's delay in relation to type of doctor.

While none among this group of 100 patients consulted an ear, nose and throat surgeon to start with, there were 82 who attended the clinics of general practitioners (inclusive of 20 who first visited a Chinese traditional doctor). 18 went to see either the general surgeons (8), general physician (7), dental or maxillo facial surgeon (2) or a neurosurgeon (1).

Although it was interesting to note that median number of doctors consulted by these patients was 3.5, it had no obvious relationship to the first symptom or the doctor's delay.

Among the doctors consulted were those who had graduated from United Kingdom, India, Australia, Bangladesh, however further details were not extracted.

c. In relation to difficult diagnosis.

Difficulty in establishing the diagnosis was encountered in 18 patients who were subjected to nasopharyngeal biopsy more than once. 14 of them had biopsy taken twice and in 2 patients each it was done three times and four times respectively. The median doctor's delay was 144 days (close to 5 months) for those patients (14) who were biopsied twice and it was 576 days (about 11/2 year) for those with more than that (4 patients).

Nonetheless, it was surprising to find that even for those whose diagnosis was confirmed on first biopsy (82

patients) the median doctor's delay was as long as 92 days (more than 3 months).

Discussion

Needless to say, early diagnosis is the key to effective control of cancer in general but for NPC, early diagnosis can lead to "cure". Fortunately NPC is both radiosensitive as well as chemo responsive, so much so that for those at early stages the "cure" seems possible and for those at advanced stage better survival results are forthcoming. In fact, according to our NPC data bank, since the last 10 years not a single case of histologically confirmed NPC at UICC Stages I & II and treated with radiotherapy (RT) alone has died. For those at UICC Stage IV (non-metastatic) who received a combination of RT followed by chemotherapy (CT) there has been considerable improvement in overall survival(8) (80% 3 year survival), however there is room for further improvement. The fact remains that the chance of attaining effective control is best if NPC is diagnosed early, which has been the problem in the past9 and remains so at present (this study). It has been generally believed by oncologists in the developing world that cancer patients themselves visit the doctors at late stage, due to ignorance, lack of awareness, non-availability of medical services close by, financial difficulties, etc. The results of the present study has been an eye opener in the sense that in Malaysia so far as NPC patients are concerned, they did present themselves to their doctors within a very reasonable time (mean delay only 2.5 days), so much so that 47 (47%) of them consulted doctor on the very day they noticed a symptom. For those with ear symptom (12 patients), there was absolutely no delay while those with neck swelling the mean delay was only 3 days. Unfortunately for patients with these very important symptoms, which were clearly suggestive of NPC, the late diagnosis was due to doctor's delay. For those patients with ear symptom the median delay was close to 9 months (266 days) and for those with neck swelling it was more than 3 months (94 days).

If only the attending doctors had realised that the ear symptom in the form of unilateral hearing impairment with or without tinnitus, is one of the symptoms of NPC, which often comes on at its early stage, diagnosis for those 12 patients would not have been delayed to that extent. It was difficult however to ascertain as to why the median doctor's delay was to the extent of 3 months for those patients with neck nodes, which must be taken as secondary to NPC, particularly, if the patient is a Chinese, and in this series 92% of the patients were Chinese.

Although we did not go in depth investigating about the doctors who were responsible for the delay (82% of them were general practitioners), it was felt that those doctors who had received their undergraduate education in countries where NPC is rare like U.K, India, Pakistan, Bangladesh, Egypt, Australia, etc. might not have been taught this subject in great detail and would not have been exposed to NPC patients as they are commonly seen in Malaysia.

The authors would like to urge those doctors who wish to know of the fundamental clinical aspect of NPC, to read the articles, (10,11) particularly written for that purpose.

Acknowledgement

The authors would like to sincerely thank Dr C.E. Koay, presently a consultant ENT surgeon at Tung Shin Hospital Kuala Lumpur who, as a lecturer in the Department of Otorhinolaryngology, Faculty of Medicine, University of Malaya, had designed the questionnaire and imparted help at the beginning of the study, and to Associate Professor S.B. Yap of Department of Social and Preventive Medicine from the same faculty for providing assistance in the statistical analysis.

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INADVERTENT EXPRESSION OF DENGUE 2 VIRUS NS3-EGFP FUSION PROTEIN IN *ESCHERICHIA COLI* USING THE pEGFP-N1 MAMMALIAN EXPRESSION VECTOR

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ABSTRACT: Dengue 2 New Guinea C (NGC) virus NS3 protein, a potentially important virulence factor was cloned to the N-terminus of the *Aequorea victoria* enhanced green fluorescent protein (EGFP) using the pEGFP-N1 mammalian expression vector. During amplification of the recombinant plasmid in *E. coli*, transformants expressing the EGFP were detected *in vivo* when viewed using fluorescence microscopy. This inadvertent expression of the recombinant fusion protein was confirmed further by detection of the T7·Tag peptide cloned to the amino terminal of the fusion protein using T7·Tag specific monoclonal antibody. These findings represent perhaps the first reported expression of the T7·Tag-NS3-EGFP fusion protein using the pEGFP-N1 mammalian expression vector in *E. coli*. *(JUMMEC 1999; 1:41-46)*

KEYWORDS: Dengue, NS3, pEGFP-N1, fusion protein.

Introduction

The potential effects of specific virus genes on the host cells can be examined by cloning and expressing the genes within the host cells. The viral gene of interest can be cloned into a mammalian cell expression vector which normally contains inducible or constitutive viral promoter at the 5' end of the gene. Often times, to enable detection of the cloned gene expression, specific peptide sequence or protein is inserted either at the 3' end of the cloned viral gene or immediately after the promoter at the 5' end of the gene. These peptide sequences or tag proteins can be detected by using specific monoclonal antibodies. Most commercially available mammalian cell expression systems allow cloning and amplification of the recombinant plasmid to be performed in bacterial cells prior to transfection of the host cells. In most cases, no expression of the cloned gene is expected in the bacteria since in most mammalian cell expression vectors no bacterial promoter is included immediately upstream of the multiple cloning sites.

In an effort to investigate the potential effects of dengue 2 virus NS3 gene on the host cells, the virus gene was cloned into a mammalian expression vector, pEGFP-N1 (Clontech, CA, USA). This expression vector contains a strong constitutive CMV promoter for eucaryotic cell expression and no bacterial promoter immediately upstream of the multiple cloning sites. In addition, to facilitate detection of the cloned gene expression in transfected host cells, the dengue virus gene was cloned as a fusion partner to the EGFP protein which has been reported to fluoresce under ultraviolet light *in vivo* (1). It is reported here that during amplification of the recombinant T7·Tag-NS3-EGFP plasmid (pT7·Tag-NS3-EGFP), inadvertent expression of the cloned fusion protein in *E. coli* was detectable *in vivo* using fluorescence microscopy and by immunodetection method.

Materials and Methods

Virus infection and preparation of infected cells RNA

Dengue 2 New Guinea C (NGC) strain virus obtained from the American Type Culture Collection (ATCC, USA) was used in this investigation. Virus was propagated in the C6/36 mosquito cells as previously described (2). Briefly, semi-confluent cells (~ 70%) were infected with dengue 2 virus inoculum to give an estimated multiplicity of infection (MOI) of about 3 to 5 plaque forming unit (PFU) per cell. Approximately 7 to 8 days post-infection (PI) or when more than 90% of the infected cells have shown the cytopathic effects (CPE), cell cultures were frozen at -70°C. Crude virus inoculum was prepared by sequential centrifugation of the supernatant at 800 and 40,000 x g. The titer of the

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virus inoculum was determined by performing virus plaque assays using porcine spleen cells. Virus infection for RNA isolation was done as described above. Infected cells were harvested approximately 7 to 8 days PI and total RNA was isolated using the TRIzol™ Reagent (GIBCO BRL, Life Technologies Inc., USA) following protocols provided by the manufacturer.

Cloning of the NS3

Dengue 2 virus NS3 gene was amplified by the RT-PCR and cloned into the pGEM-T cloning vector (Promega Corp., Wisconsin, USA). It was noted, however, that the full length NS3 gene sequence was perhaps 'toxic' to the bacterial cells since no transformants were obtained after repeated attempts. To overcome this problem, the gene was initially cloned in two halves into the pET-23a(+) vector (Novagen, USA). The NS3 gene was amplified by the PCR as two separate segments using 2 sets of primers; NS3FXA (5'GGATCCATCGAAGGGCGCGCCGGAGTATTGT GGGATGTCCCTTCACCCCCACC) and NS3XR (5'CCATCTCTACTCGAGTTGAGATGTAT CCTCTAGC) which amplified the 5'-half of the NS3 fragment beginning at nucleotide number 4521 until 5440 (3), whereas, NS3NF (5'GCTAGCTAGAGGATA CATCTCAACTCGAGTAGAGATGG) and NS3NtR (5'GCGGCCGCCTTTCTTCCAGCTGCAAACTCC TTGAATTCC) which amplified the 3'-half of the NS3 beginning at nucleotide number 5409 until 6375. The two amplified fragments containing the NS3 *Xho* I restriction sites were then cloned separately into the pGEM-T cloning vector using the vector's T overhangs.

Construction of NS3-EGFP recombinant plasmids

Plasmids consisting of the 5'- and 3'-half of the NS3 were digested separately using the *Bam*H I-*Xho* I and *Xho* I-*Not* I restriction endonucleases respectively. The resulting 3'-half (975 bp) and the 5'-half (919 bp) of the NS3 fragments were then ligated to the pET-23a(+) vector (Novagen, USA) which had been digested with *Bam*H I and *Not* I, using three fragments ligation mixtures. The recombinant plasmids were then amplified, purified and the recombinant gene insert was excised using *Xba* I and *Not* I restriction enzymes. These restriction sites were chosen to enable ligation of the recombinant gene into the pEGFP-N1 vector using the compatible cohesive ends of the *Nhe* I and *Bsp* 120 I restriction sites of the expression vector. The excised fragment beginning at position 166 until position 276 of the pET-23a(+) vector consisted of a ribosome binding site (rbs) and a T7·Tag sequence at the 5' end which was intended to be used for detection of the fusion gene expression. The pT7·Tag-NS3-EGFP plasmid was then transformed into the Top10F' bacteria and cultured on LB/kanamycin plates for overnight at 37°C

Preparation of bacterial lysates and detection of the T7·Tag fusion protein

Detection of expressed T7·Tag-NS3-EGFP fusion protein was made by immunodetection using T7·Tag specific monoclonal antibody (Novagen, USA). Recombinant transformants were cultured overnight and then centrifuged at 10,000 x g for 3 min. The resulting pellets were resuspended in 1X sample buffer (62.5 mM Tris-HCl, 2% SDS, 10% glycerol, 0.01% bromophenol blue) and boiled for 7 min. Samples were then recentrifuged at 15,000 x g for 5 min, electrophoresed in 12.5% SDS-PAGE, and electrotransferred onto nitrocellulose membrane (MSI, Westborough, MA, USA). The membrane was blocked using blocking buffer (100 mM Tris base, pH 7.5; 150 mM NaCl) containing 5% skim milk and then developed using specific monoclonal antibody and conjugates as previously described (2).

Results and Discussion

Transformation of the Top10F' *E. coli* with the pT7·Tag-NS3-EGFP resulted in mixed transformants of large and small bacterial colonies (Figure 1). Since it was suggested earlier that the presence of the NS3 gene sequence was perhaps toxic to certain bacteria, it was possible

Figure 1. E. coli Top10F' transformed with pEGFP-N1 plasmid containing the T7·Tag-NS3 gene insert. Transformants consisted of a mixture of small (arrow) and big colonies.

that the resulting small colonies were also due to the toxic effects of the gene. To investigate this possibility, the presence of the gene insert was determined by screening the colonies with *Bam*H I restriction enzyme which digests the 5' and 3' ends of the cloned NS3 gene

to yield a fragment of approximately 1960 bp. It was found that only the small colonies contained the expected gene insert (Figure 2). When the transformants were viewed under a fluorescence microscope (Zeiss Axiolab, Germany), only bacteria from the small colonies appeared to be fluorescent green (Figure 3a), suggesting that the EGFP protein was expressed. Transformants which formed big colonies did not have the insert or show the presence of fluorescing bacteria. *In vivo* expression of the EGFP was not expected since no bacterial promoter was cloned immediately upstream of the T7·Tag sequence of the pT7·Tag-NS3-EGFP. Nonetheless, this result suggested that the recombinant fusion protein was inadvertently expressed *in vivo*.

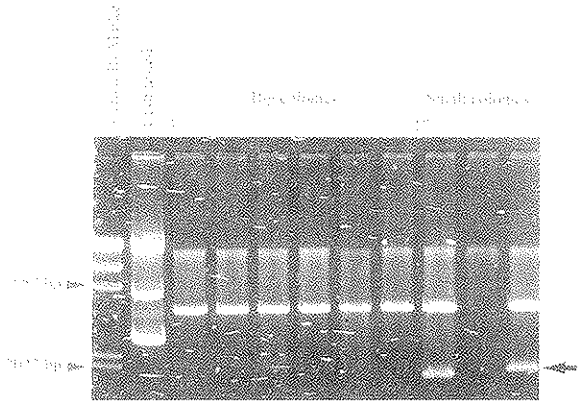

Figure 2. Restriction endonuclease digestion of plasmids from the small and big transformant colonies. Screening of the transformants were performed using *BamH* I enzyme. Arrow indicates the resulting NS3 fragments of about 1960 bp.

To confirm this possibility further, immunodetection was performed using monoclonal antibody specific against the T7·Tag peptide sequence, which was fused to the N-terminus of the NS3-EGFP. The monoclonal antibody was noted to recognize a polypeptide band of approximately 80 kD (Figure 4, Lanes 2-7) which was the predicted size of the T7·Tag-NS3 fusion protein. This polypeptide was present only in samples derived from the small colonies, suggesting that expression of the recombinant fusion protein somehow affects bacterial growth. A possible explanation for detection of only the 80 kD but not the expected full length T7·Tag-NS3-EGFP of about 102 kD is perhaps due to an intracellular cleavage of the fusion protein at a protease cleavage site (4) located at the carboxy end of the NS3. Nonetheless, since expression of the T7·Tag was detectable in the bacterial cell lysates and the bacteria also fluoresced when shown under ultraviolet light, it was apparent that the dengue 2 NS3 fusion protein cloned into the pEGFP-N1 eucaryotic expression vector was inadvertently expressed in *E. coli*.

The mechanisms leading to the expression of the fusion protein is not known. It is perhaps possible that the

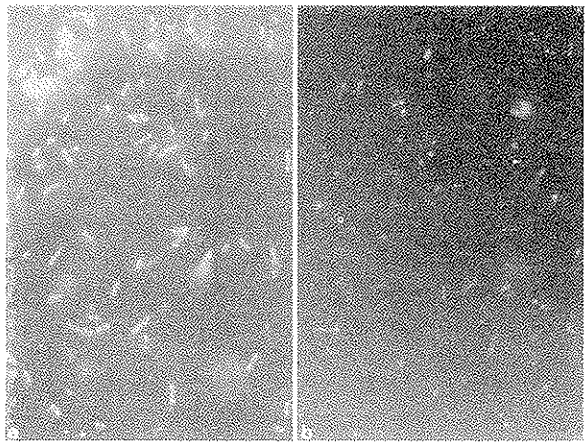

Figure 3. Expression of the pEGFP-N1 plasmid in *E. coli*. Bacterial cells transformed with the pEGFP-N1 plasmid carrying the T7·Tag-NS3 insert (a) and untransformed cells (b) were viewed with a Zeiss Axiolab fluorescence microscope using a single-pass filter set for FITC.

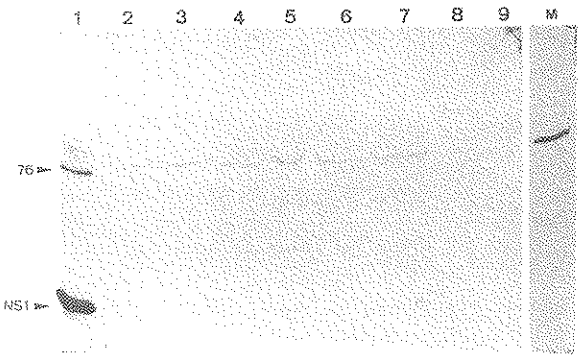

Figure 4. Detection of T7·Tag-NS3 by Western blot analysis using T7·Tag specific monoclonal antibody. T7·Tag-NS3 positive samples showed a band representing the expressed protein. Biotinylated protein marker (lane M), positive control for T7·Tag (lane 1) using T7·Tag-NS1 fusion protein which was cloned and expressed in the pET-23a(+). Positive clones (lanes 2-7), *E. coli* Top10F' transformed with pEGFP-N1 alone (lane 8), *E. coli* Top10F' (lane 9).

expression is mediated through the P_{amp} promoter which was the only bacterial promoter noted in the pEGFP-N1 plasmid. The presence of a ribosome binding site immediately upstream to the cloned fusion gene perhaps facilitates translation of the fusion protein. A possible immediate application of this finding is that it enables rapid screening of successful bacterial transformants during amplification of the recombinant plasmid. This will ensure that the cloned gene of interest has been cloned in frame to the EGFP and no stop codons were introduced prior to transfecting the recombinant plasmids into the mammalian host cells.

In summary, results presented here demonstrate inadvertent expression of genes cloned into a eucaryotic expression vector in *E. coli*.

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CAREER CHOICES OF PHYSICIANS IN MALAYSIA

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ABSTRACT: A survey of career choices was conducted for two batches of physicians applying for a medical speciality course in Malaysian medical schools. There were a total of 952 applications, with 477 males and 475 females. Surgery ranked highest, followed by obstetrics and gynaecology, family medicine and orthopaedic surgery. The minor specialities of otorhinolaryngology, psychiatry and pathology were the least popular choices. Questionnaires were sent to a random sample of 250 physicians in each batch to note factors affecting their choices of speciality. A total of 359 physicians responded, giving a response rate of 71.8%. Fixed hours of work and the ability to have direct contact with patients were relatively important factors for choice of speciality. Working as a clinical consultant was the most popular nature of employment while working in the health office, service consultant in a public hospital, a non-clinical lecturer in a university hospital and working in a private clinic were less popular choices for these physicians. *(JUMMEC 1999; 1:47-50)*

KEYWORDS: Career choice; medical speciality; doctors; Malaysia.

Introduction

The medical profession, presumably like all professions, is a gamut of many specialities. The choice of a speciality is a complex personal decision influenced by a multitude of factors. In the developing world, factors may differ from those operating in the developed countries. Malaysia continues to experience a shortage of doctors in certain specialities. There are shortages in service specialities like anesthesia, radiology and pathology (1). Deficiencies are also felt in the rural areas which involve primary health care and preventive medicine. The medical schools also have difficulties in recruiting medical graduates to non-clinical departments.

In Malaysia, postgraduate training in most of the medical specialities are conducted by the local medical schools. It is a four year program and graduates are awarded a Master of Medicine degree, which is recognised as a medical specialist qualification in Malaysia. Physicians apply to enter these courses through the Central Processing Unit for Universities in the Ministry of Education. The applicants are interviewed by a board comprising of representatives of the universities and the ministry. Presently, out of the four public medical schools, only three are conducting these courses.

This study was undertaken to determine the career preferences of physicians in Malaysia and to identify factors influencing their decisions. The results may be helpful to medical educators and health care planners in designing policies to attract manpower into the high priority specialities and also into the rural areas of the country.

Materials and Methods

A list of physicians applying to pursue a speciality course at one of the medical schools in 1995 and 1996 was obtained from the Central Processing Unit for Universities, Ministry of Education Malaysia. The list contains particulars of the applicants including the contact address of the physicians

A random sample of 250 physicians were selected for each year, giving a total of 500 physicians selected. A structured questionnaire was sent to the selected physicians and a stamped reply envelope was included. The questionnaire carried questions related to career preferences relevant to Malaysia. A Likert scale of 1 to 5 was utilised to score the importance of factors influencing their choices of speciality. Other questions focussed on the nature of employment and permanent station of work. The study involved 2 batches of postgraduate applicants in 1995 and 1996. A total of 359 physicians responded giving a response rate of 71.8%.

Results

There was a total of 952 applications to pursue a speciality course, with 403 in 1995 and 549 applications in 1996. The age range was from 24 to 44 years while working experience as a physician was from 1 year to

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17 years. There were 477 male physicians and 475 female physicians. The number of physicians opting for each speciality is shown in Fig 1. A total of 384 physicians (40.3 %) were attracted to the four established specialities of internal medicine, surgery, paediatrics and obstetrics and gynaecology. Surgery ranked highest amongst the specialities with 117 applications. Family medicine, orthopaedic surgery, public health and anaesthesiology were the other popular choices. The service specialities of pathology and the clinical speciality of psychiatry and otorhinolaryngology were the least popular choices.

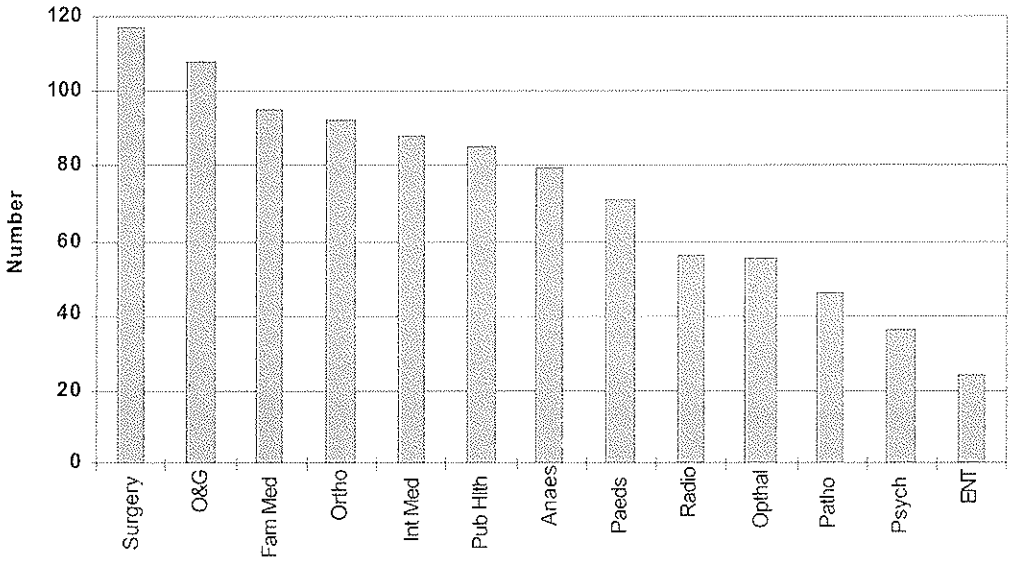

Figure 1. Speciality choices of Malaysian physicians, 1995-96

Fixed hours of work and ability to have direct contact with patients emerged as the most important factors (mean score = 4.2 and 4.1 respectively). Other factors like better financial rewards, and opportunities to do research and teaching were of lesser importance among the physicians, with a mean score between 3.4 to 3.7. Higher social status appears to be the least important for the physicians, with a mean score of 2.9.

When asked to select their desired nature of employment, a distinct bias towards working in the public health service as a clinical consultant in the hospital was noted, where 48.6% of the physicians had this option as the first choice and 21.9% in their top three choices (Table 2). Being a service consultant proved the least attractive, with only 5.1% of the physicians opting for it. The choice of working as an administrator in a hospital or in the health office was relevant only to applicants for public health.

Discussion

This study shows that a majority of physicians choose hospital and clinical-based specialities. Non-clinical specialities were less popular choices, similar to findings in studies done in other countries (2,3). In line with their clinically oriented career choices, clinical and academic careers in general and teaching hospitals were prime choices for vocational settings. 'Ability to have direct contact with patients', 'fixed hours of work" and 'opportunities to do research' were the most important factors in determining their career choice. These two factors may be incompatible with each other as most clinical specialities will involve working at odd hours of the day. A number of studies have shown that 'fixed hours' of work is more important for the female

Tabie 1. Factors determining choice of career of Malaysian physicians, 1995-96.

Factors	Importance Low 1	2	3	4	High 5	Mean score
Ability to have direct contact with patients	14	22	54	91	175	4.1
Offering better financial rewards	28	38	114	122	54	3.4
Fixed hours of work	53	56	93	92	62	4.2
Higher social status	58	46	144	84	24	2.9
Opportunities for teaching	29	36	99	117	75	3.5
Opportunities for research	21	37	78	131	89	3.7

physicians when family commitments were realised (4,5,6). With more female students entering Malaysian medical schools, and the resultant increase in the number of female physicians in Malaysia, this factor will play a major role in career choices. Thus, clinical specialities, which are considered 'light', such as family

Table 2. Choice of nature of employment of Malaysian physicians, 1995-96.

Location	Choices				
	1st	2nd	3rd	Total	(%)
Clinical specialist in a public hospital	173	48	13	234	(21.9)
Clinical lecturer in a university hospital	48	41	18	107	(10.0)
Private medical centre/hospital	55	86	42	183	(17.1)
Private clinic	10	28	20	58	(5.4)
Non clinical lecturer in a university hospital	6	25	26	57	(5.3)
Service specialist in a public hospital	34	15	6	55	(5.1)
Health office	5	7	12	24	(2.3)
Administrator in a hospital	12	80	113	205	(19.2)
Army	13	26	106	145	(13.6)

medicine, are anticipated to be popular choices, especially for the female physicians (7,8).

In terms of speciality choices, ironically, the 'heavy' clinical specialities were the most popular choice. Surgery was the most popular choice followed by obstetrics and gynaecology. Internal medicine, orthopaedics and paediatrics were also popular. Family medicine, public health and anaesthesiology were equally popular with the more established specialities. The response towards the established specialities may be due to several reasons. Medical practice has been and continues to be dominated by performances and personalities of the established clinical disciplines (9). Better financial rewards and opportunity for social prestige , which are important considerations in the choice of career, are fulfilled to a greater extent with the established disciplines.

Another major finding was the relative popularity of family medicine even though this is a new speciality in Malaysia. It was only recently that the Ministry of Health recognised the need for specialists in family medicine and it's postgraduate training has been offered in the local medical schools. This speciality is also a popular choice in Britain where 32% chose this speciality (10). Family medicine is able to provide a compromise between the desire to be a clinician, and opting for a practice which is not too heavy. Anesthesiology was also surprisingly a popular choice. Studies on career choices among Malaysian medical students noted this speciality to be relatively unpopular, together with pathology, and radiology (11,12). Radiology, psychiatry and pathology remain unpopular choices together with otorhinolaryngology. Perhaps the lack of emphasis and inadequate exposure to the 'minor' and 'service' disciplines in the undergraduate curriculum promotes this non-popularity. The chronic shortages in these specialities will certainly minimize the time for teaching, research and promotion of the speciality.

Employment as clinical specialists in the public hospital was the choice of only 21.9% of the physicians while the private hospital/centre is a choice for 17.1% of the physicians. Although the state continues to provide employment facilities, the private sector has provided better financial prospect, especially for clinical specialists over the last few years. The private medical industry has grown tremendously in Malaysia, and keeping physicians in the public sector is a problem. The pre-clinical departments in the universities attracted only 57 physicians (5.3%) while working in the service departments of hospitals attracted only 55 physicians (5.1%). This acute shortage of clinical and service specialists and clinical and pre-clinical lecturers in the universities has made it necessary to employ expatriate physicians on a contract basis from overseas.

Newly recruited physicians are usually posted to the rural clinics during the three years of compulsory national service. The lack of social amenities is responsible for the reluctance of these physicians to continue working in these rural clinics. However, with specialisation, these physicians are able to work in a more urban setting. Training in the communities during medical school will promote the interest in public health and family medicine, and working in a relatively rural area of the country (13,14,15)

The above findings highlight a number of implications in the speciality choice of physicians and the health care system in Malaysia:

- economic or financial incentives may be a viable alternative to be considered in areas of medicine where direct contact and social prestige are deficient to attract physicians. Eventhough the score for 'offering better financial rewards' was found to be low in this study, it will be simple to implement. It will attract those physicians that view financial incentives as important. Such incentives have already been in practice by the Ministry of Health Malaysia for paramedicals serving in the more remote areas of the country.
- Family medicine can fulfill many useful roles. Physicians can be made aware of the full potential that

this speciality can offer in modern medical practice. The speciality should be given its due recognition by the government.

- the role of the service specialities in the multidisciplinary care of patients needs to be emphasised during the training of medical students.
- physicians should be kept informed regularly by the Ministry of Health on manpower needs in the various medical specialities. This would enable the physicians to make realistic choices of careers, based not only on personal interest, but also on the current manpower requirements of the country.

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TEACHING ATTITUDES AMONG TEACHERS AT THE FACULTY OF MEDICINE, UNIVERSITY OF MALAYA

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ABSTRACT: This paper involves the obtained results of an "Elective Program" project which was carried out by Phase I Medical Students of the 1998-1999 academic year at the Faculty of Medicine (FOM), University of Malaya (UM). A questionnaire was designed to survey the attitudes of teachers at FOM-UM, the subject of choice of a 4-student group who were supervised by a faculty member. Students obtained a list of faculty members (teachers) of all academic departments from the Dean's Office and rehearsed their interviewing skills prior to collecting the data of the questionnaire, within a 1-week period. Respondents were 146 out of 275 in total (53%), which included all academic ranks and clinical and non-clinical teachers. Results showed that respondents were well qualified, have enough teaching experience and teach in a variety of forms. All teachers liked to teach and were motivated; however, 15% felt unhappy about their teaching and 6% did not think that their teaching was effective. The majority (96%) of teachers liked their teaching to be evaluated and many revealed several means to assist and motivate students. Teachers felt that there was room for improvement in the aspect of student-teacher interactions. Results of this project revealed that FOM-UM is well endowed by qualified, motivated and caring teachers who wish for better interactions with their students. *(JUMMEC 1999; 1:51-57)*

KEYWORDS: Elective program, Faculty of Medicine, questionnaire, medical teachers, new integrated curriculum, teaching attitudes, teaching methods, University of Malaya

Introduction

The Faculty of Medicine (FOM) at the University of Malaya (UM) started implementing a new integrated curriculum (NIC) with the beginning of the 1998-1999 academic year (1). Among the components of this NIC for Phase I Medical Students (first year) is an "Elective Program". In this component; a group of 4 students select a project, locate a supervisor and carry out such project within two weeks during one of their academic breaks (2). Such a project is to take place on the UM campus and/or its vicinity and without any major financial expense. The idea of such an Elective Program is to allow students to select any ideas or fields of interest (whether medical or otherwise) and have the opportunity to work as in teams to carry out their projects and the freedom to conduct such in various methods: e.g., interviews, field research, experimental work, questionnaires...etc. Also, in this Elective Program, students are required to make an oral presentation for 10 min to their fellow students and interested faculty members about their project and to submit a report about their project some time later.

We have chosen to study the attitudes of teachers in our FOM-UM about teaching as our project. We learned that our Faculty has 275 faculty members; 39 Professors, 89 Associate Professors and 147 lectures - the majority of them were assumed to be teachers (3). Thus, we felt that this project is of interest to both students and to faculty members, especially that we were not aware that a similar project was carried out in our FOM previously. The objectives of our project were:

1. To gain information about the teacher population in our FOM.
2. To learn about the teaching done by faculty members.
3. To study the attitudes toward teaching in our FOM.
4. To bring out problems related to teaching done in the Faculty.
5. To make students aware of how their teachers are concerned about them?

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We were required to submit a report about our project to the Coordinator of the Elective Program, which we have done. However, we also felt that the information obtained from our project is of general interest to the whole faculty – thus this article in the Journal of the University of Malaya Medical Centre (JUMMEC).

Material and Methods

We chose a topic for our project and sought a supervisor for our group: Professor Farouk El-Sabban, Department of Physiology, FOM-UM. We have confirmed our project and arrangement with our supervisor in writing by the 31st of October 1998. Our project was to begin and to be concluded between 4th –15th January 1999. We, with the help of our supervisor, designed a 2-page questionnaire to provide information relevant to our objectives. Our questionnaire (below) consisted of 21 questions. We divided the questions into 3 parts:

1- Information about the teachers, questions No. 1 – 11.
2- Attitudes toward teaching, questions No. 12 – 17.
3- Student-teacher interactions, questions No. 18 – 21.

Additionally, we included a space for any comments which teachers wished to make. We started working on our questionnaire earlier, in December 1998, as we were warned by our supervisor about how difficult is it to construct a questionnaire.

We obtained the name list of teachers from all academic departments in our FOM-UM (3). We divided the departments among the four of us and each had four or five departments to collect information from. We rehearsed interviewing skills with our supervisor and conducted personal interviews with as many teachers as we could in about 1-week period (4 – 12th January 1999). Each interview lasted between 10 – 15 minutes and each student filled out the answers to the questions being asked. Obtained data were entered on a spreadsheet (Microsoft Excel software program), were counted, grouped and analyzed. Results of our data analysis are expressed herein in a tabular form, from which our conclusions were drawn. Comments made by teachers were grouped into categories, dependent on their frequency. Results of our project were presented to fellow Medical Students and interested Faculty members in 10 min on 15th January 1999. We have submitted a report on our project to the Coordinator of the Elective Program in February 1999 – on which this article is based. A diary of our activities and involvement into this project is shown in Table 1.

Table 1. Diary of the project.

Date	Activity
30/10/98	Discussed the selection of a topic and a faculty member to be our supervisor.
	Chosen a lecturer for his consent to serve as our supervisor.
31/10/98	Members of the group and our supervisor discussed:
	a) The title of our project.
	b) Objectives of the chosen project.
	c) Methods that would be used for our project.
	The Elective Program form was submitted to the Elective Program Center.
7 – 30/12/98	Constructed a draft of the questions for our questionnaire.
4 – 12/1/99	Questions of our questionnaire were refined.
	Questionnaire was finalized and every member of the group had an original copy.
	Interviewing skills were practiced.
	Interviews were conducted.
	Transparencies were prepared for our oral presentation.
	Our presentation was rehearsed.
12 – 13/1/99	Each member entered all data from teachers into computer.
	All individual files were combined into one master file.
	We analyzed data from the master file and made tables from our analysis.
15/1/99	We made our oral presentation.
5/2/99	A rough draft of our report was prepared.
8/2/99	First version of our report was prepared.
9 – 26/2/99	Report was edited several times and a "final" version was ready for submission.
26/2/99	Report was submitted to the Elective Program Center.

Results

Information about the teachers

The population of the interviewed teachers consisted of 146 lecturers (Table 2). Seventy eight of the teachers were clinical and 68 were non-clinical teachers – 83 were males and 63 were females. Our population also consisted of 80 Lecturers, 54 Associate Professors and 12 Professors. The teachers possessed a variety of qualifications such as M.B.B.S., M.S., Ph.D. and others, which included: membership of Royal Societies of different specialties. The year in which teachers earned their last degree or qualification ranged from 1966 to 1999. Number of years of teaching at FOM-UM by our teachers ranged from 0.2 year to 35 years. The range of hours of teaching at our faculty was from 1.5 hour to 42 hr per week. These teachers do many forms of teaching; but most of them give lectures, followed by practicals then clinical scenarios and self-directed learning sessions. The form of teaching that the teachers do the least of is that of computer-assisted learning.

Attitudes toward teaching

Results of attitudes toward teaching are shown in Table 3. All teachers (100%) indicated that they like to teach.

Table 2. Information about interviewed teachers.

Item	Number (%) / Average (SD)	
Total number	146	(100)
Males	83	(57)
Females	63	(43)
Clinical	78	(53)
Non-clinical	68	(47)
Academic rank		
Professor	12	(8)
Associate Professor	54	(37)
Lecturer	80	(55)
Qualifications*		
Ph.D.	52	(36.7)
M.S.	49	(33.6)
M.B.B.S.	82	(56.2)
Others	106	(72.6)
Year of last degree earned	1988	+ 7.0
Years of teaching at FOM	9.3	+ 7.7
Hours of teaching/week	9.3	+ 7.4
Form of teaching done*		
Lectures	144	(98.6)
Self-directed learning	84	(33.1)
Computer-assisted learning	15	(10.2)
Practicals	115	(78.8)
Clinical scenarios	90	(61.6)

Numbers and percentages are of all obtained responses.

Table 3. Attitudes toward teaching.

ITEM/Question	Number	(%)
Do you like to teach?		
Yes	146	(100)
No	0	(0)
What motivates you to teach?*		
Promotion	14	(10)
Salary	12	(8)
Interest	129	(88)
Student-teacher interaction	105	(72)
Environment/facilities	49	(34)
Others	38	(26)
What form of teaching do you prefer?*		
Lectures	42	(29)
Self-directed learning	26	(18)
Computer-assisted learning	5	(3)
Practical	32	(22)
Clinical scenario	21	(14)
Others	84	(58)
Are you happy with your teaching?		
Yes	123	(85)
No	22	(15)
If not, why?*		
Do not like the topic	1	(0.2)
Student(s)	12	(8)
Environment/facilities	12	(8)
Promotion/professional aspect	7	(5)
Others	11	(8)
Do you feel your teaching is effective?	131	(94)
No	9	(6)
Do you like your teaching to be evaluated?		
Yes	140	(96)
No	6	(4)
If yes, by whom?*		
Peers	90	(62)
Administrators	22	(15)
Students	133	(91)
Others	13	(9)
How do you attract student's attention?*		
Make jokes	87	(60)
Speak louder	49	(34)
Keep quite for a while	33	(23)
Go on teaching	20	(14)
Others	97	(66)

* Numbers and percentages are of all obtained responses

The majority of these teachers were motivated about their teaching mainly because of their interest in teaching itself as well as because of enjoying the student-teacher interactions, followed by environment and facilities that the faculty provided. Neither promotion nor salary seemed to be the main factors that motivated them. Most of teachers whom we interviewed prefer lectures as a form of teaching – which was followed by practical sessions, self-directed learning sessions and clinical

scenarios. The least preferred form of teaching was the computer-assisted type. Examples of other forms of teaching teaching that they prefer are: tutorials, ward rounds and debates. When asked whether they are happy about their teaching, 85% said Yes. Those who said No indicated that the students are the main cause of their unhappiness, as well as the environment and the facilities, followed by not being satisfied with the promotion or because of some other professional aspects. Other factors that make them unhappy included not having enough time to prepare and deliver their lectures.

Out of 146 interviewees, 121 felt that their teaching is effective. When asked about if they like their teaching to be evaluated? 96% of them said Yes and the majority of this portion said that they would like the students to make the evaluation, followed by their peers, then by administrators. Other evaluators of teaching included the external examiners and visiting professionals. When asked about how do they attract the students attention when they teach, most would make the effort to crack jokes, followed by speaking louder, keeping quite for a while and the rest would just go on with their teaching. Other ways to attract the students attention included asking questions and sometime tell a story that relates to their teaching.

Student-Teacher Interactions:

Results on the aspect of student-teacher interactions are presented in Tables 4 and 5. About 56% of teachers were satisfied with their interactions with the students, but the remainder (44%) were not satisfied (Table 4). Dissatisfaction about this aspect was mainly because the students do no ask questions, followed by coming late to class, not coming to class at all, as well as talking in class. Students who fail in the teacher's topic or sleep in class were not sources of dissatisfaction for teachers. Another reason was that the students do not make an early preparation before coming to class. When asked about if students come to see them about what they have taught?, most of teachers said Yes and majority who said Yes said that the students come to see them sometimes (i.e., not at a specific time during the academic year), followed by near examination time and only a small number of interested students come to see them "most" of the time (Table 4).

When asked whether they have ever failed to answer any of the students questions, most of teachers said Yes. The majority who said yes, admit to the students that they do not know the answer, followed by promising to provide an answer when they are sure. Telling the students to look up the answer in the library came up next and giving away and answer even when they are not sure received the least response. Another way to respond to this situation was to refer students to another colleague (Table 4).

Table 4. Student-teacher interactions.

Item/Question	Number	(%)
Are you satisfied with your interactions with students?		
Yes	82	(56)
No	64	(44)
If not, why?*		
Student are late for class	23	(16)
Talking in class	16	(11)
High absenteeism	16	(11)
Sleeping in class	8	(5)
Failing your topic	9	(6)
Not asking questions	55	(40)
Others	34	(23)
Do student come to see you about what you have taught?		
Yes	124	(85)
No	22	(15)
If yes, how often?*		
Most of the time	17	(12)
Sometime	98	(67)
Near examination time	34	(23)
Have you ever failed to answer any of the student's questions?		
Yes	103	(72)
No	40	(28)
If yes, how do you respond to that?*		
Admit that you do not know	92	(89)
Give an answer, even when unsure	17	(17)
Promise to provide answers when sure	87	(84)
Tell them to look up in the library	53	(51)
Others	23	(22)

*Numbers and percentages are of all obtained responses.

For the purpose of enhancing the student's learning, most of the teachers do not mind spending an extra class time with the students (Table 5). Those who responded by either dislike or indifferent were almost equal. The idea of taking the students to the library does not catch the teachers interest. Teachers indicated that the students are "grown ups" who should know how to take care of themselves. There were still teachers who felt indifferent about this and some of them even said they like it. In regard to providing the students with revision questions, most of teachers liked to do so while the rest said they disliked it or were indifferent. The majority of teachers like to loan books and notes to students and those who said dislike and indifferent were almost equal. When asked about being sensitive to student's personal problems?, the majority of teachers (83%) indicated that they like to be sensitive to the student's personal problems. Only a small percentage felt indifferent and a very few teachers disliked it.

Table 5. Information on techniques to enhance student learning

ITEM/QUESTION	Like Number (%)	Dislike Number (%)	Indifferent Number (%)
For the purpose of enhancing student's learning, how do you feel about the following ?			
Spend an extra class time	73 (51)	34 (24)	36 (25)
Take student to the library	27 (19)	84 (59)	32 (22)
Provide revision questions	82 (57)	37 (26)	25 (17)
Loan books & notes to students	67 (47)	42 (29)	34 (24)
Be sensitive to student's personal problems	118 (83)	2 (1)	22 (15)

* Numbers and percentages are of all obtained responses.

Comments

Teachers were asked to make comments at the end of the interview. We had a lot of comments and each of the comments has its own point of view and merit. It was enlightening to know that 85 out of 146 (58%) faculty members have made comments. Below are the comments that were obtained, which we have divided into 5 major categories.

1. Student-teacher interactions: We obtained 28 comments related to this category. Most of the teachers said that the students are lacking in discussion, as well as not asking questions. Along with this, there were also comments on the students being not that interactive, i.e., they are being passive and non expressive. Also, teachers hoped that the students would give feedback to them regarding their teaching efficiency.
2. Student-related comments: We obtained 20 comments related to the students. Teachers indicated that the students are not paying attention in the class, not expressing enthusiasm, not being self-learners, not active in discussion, absent from classes and that the students need not be "spoon-fed". There were also teachers who suggested that a student with an exceptional educational performance should receive a bonus.
3. Questionnaire-related comments: We obtained 11 comments regarding our questionnaire. Some teachers felt that our questions were not suitable, difficult to answer, rigid, lack adequate options, and that some questions had no specific objectives.
4. Faculty-related comments: Eleven comments had been made concerning the Faculty. Some teachers wished for a hefty increase in salary. They also felt that the Faculty should be more responsible towards enhancing interactions between the faculty members and the students. Some teachers expressed that Department Heads should have an equal teaching load like others. Other teachers felt that some colleagues need more training in teaching (especially for the self-directed learning and discussion-type sessions). Also, it was expressed that the administration needs to improve teaching facilities and improve the student-teacher ratio.
5. Project-related comments: We obtained 7 comments regarding our Project/Elective Program and the teachers gave both a thumb-up!

Discussion

In this Elective Program, there are various titles for students to choose from and to carry out under the guidance of supervisors. Our group chose to research the attitudes of teachers towards teaching in our FOM-UM and selected a supervisor by ourselves. We felt that this project is unique, of a general interest, especially that a similar project has not been done before. Through this study, we were able to reveal how our teachers felt about their teaching. We wished to share our results and thoughts about our project and the Elective Program with those who are in our academic environment.

Besides having an outlet to do something different and of interest, we felt that the spirit of cooperation among our group was both emphasized and enforced. Additionally, we learned about the different thoughts and processes involved in the design and completion of their project. The required oral presentation gave us an opportunity to public speaking and to learn about what is involved in preparing for an oral presentation? Thus, such an elective program allows students, in that early stage of their medical education, to work cooperatively and to get the feel for what their future profession entails.

We designed the questionnaire and conducted personal interviews with as many teachers as we could within the allowed duration for our project. We collected information from 146 respondent teachers, which accounts for 53% of the total number of faculty members. Responding teachers were balanced between both sexes and between clinicians and non-clinicians. However, respondent Professors were under represented (8 vs. 14% of faculty members), perhaps

because of heavy academic and clinical duties which made them unavailable for our interviews. On the other hand, Associate Professors were over represented (37 vs. 32%), for which we have no specific explanation. Meanwhile, percentage of interviewed Lecturers matched their percentage in the Faculty, 54 vs. 55%. It must be pointed out that because such interviews were conducted during the first 1/3 of January 1999 and during an academic break, we felt lucky to collect information from those 146 teachers.

All interviewed teachers were found to be qualified and earned more than one degree. Many of them earned other qualifications than the options given. For instances, Masters in Public Health (MPH) and Bachelor of Science. The M.B.B.S. holders are the second highest followed by Ph.D. and M.S. The percentages of Ph.D. and M.S. degree holders were almost equal. On average, teachers have earned their last degrees about 10 years ago and have had that length of time as experience in teaching at our FOM. Most teachers are busy with their teaching and a few pointed out that they have a packed teaching schedule. Lectures and practicals constituted most of the medical student teaching. Clinical scenarios came next, followed by self-directed learning. The least practiced method was the computer-assisted learning, perhaps because there are not enough computers being available to students.

All teachers liked to teach but not all (15%) were happy with their teaching. Responses given by unhappy teachers were mainly because of students as well as because environment or facilities. Students were said to be passive-learners, non-interactive and non-prepared while the environment and facilities were not sufficiently conducive for teaching. Almost all teachers (88%) were motivated to teach because of their interest. This is not surprising, as all liked to teach. Another good motivating factor of teaching was the student-teacher interactions. We realized that teaching would be ineffective unless there are interactions between students and teachers, as through such interactions teachers would be able to know how well their students comprehend their subject matter and would be in a better position to determine how students can be helped. We noticed that only less than 10% of teachers chose salary as one of the motivating factors; however, we feel that teachers should know that salary is not supposed to be a major motivating factor. We were surprised to note that promotion was not a highly motivating factor, as it is generally understood that good teachers ought to be rewarded for their good performance.

As to the preferred form of teaching, the majority of teachers put 'others' apart from the options given. Examples of the 'others' were: tutorials, ward rounds and bedside teachings. A common notion was expressed, which was: "the easiest way of teaching is to give a lecture". There was almost an equal number of teachers who preferred self-directed learning and clinical scenario sessions. However, very few of our teachers seemed not to prefer computer-assisted learning. However, it was indicated that some teachers have good knowledge of computers and possess skills. Perhaps, this form of teaching will be prevalent when more computers become available to students.

Almost all teachers felt that their teaching was effective. This was hinted at by referring to the years of teaching in this Faculty. Only a few of them (6%) did not feel so. This could be because none of students came to see them to ask questions or because they were not being promoted for such a long time. A small group of teachers (4%) did not like their teaching to be evaluated, possibly because this small portion was confident enough with what they teach and did not require any feedback from others. Teachers felt that students are the best to evaluate their teaching. We were happy to learn about this fact, as students are the recipients of their teaching. There were also teachers who liked peers and administrators to be evaluators of their teaching. They may have felt that this can be considered as their technique, mechanism or strategy to be promoted.

Teachers use many ways to attract student's attention in class. The majority of teachers put 'others' as one of their options. Examples of 'others' were: giving anecdotes which related to the topic, asking students something about the topic and pointing out that the topic is important and may be asked in the examination. Techniques to draw student attention varied, but the fact is that teachers are interested in the student welfare and success. We feel that making jokes is good since this will make the students not feel bored with the topic or with the speaker. So does speaking louder, in order to make the student listen to the taught subject without falling asleep.

The percentage of teachers who are satisfied with their interactions with students surpassed those who were not by 12%. Teachers who were not satisfied mostly indicated that such was because students are passive and do not ask questions. Through observation, students here like to take lectures or teaching for granted and do not seem to go deeper into a topic. For them, lectures or teaching were totally enough of what they should know. The second cause to teacher dissatisfaction was the late comers for class, who would not only interrupt teaching but also other students. We admit that this is a habit that should be abolished from a medical student's life.

Surprisingly, the majority of teachers indicated that students came to see them regarding what they had taught. However, a busy schedule of students in completing many writing works partially prevented them

from seeing the teachers at most of the time. Instead of that, students felt freer to see them sometimes. Logically, there would be more students coming to see teachers near examination time to get as many tips as possible and to revise the topics with them. However, this did not occur here and the reason for this is unknown.

Approximately one-third of the interviewed teachers had never failed to answer any of student's questions. Perhaps, this shows that they had stronger understanding and wider knowledge in their fields. However, for those who failed to answer, it does not reflect negatively on them – as it is honest to admit that they do not know. The majority of teachers ticked this option, which was followed by promising to give the answer when sure about it. There were also teachers who would give an answer even though they were not sure and tell the students to look up in the library to verify such an answer. The point here is to encourage students to go to the library and to "push" them to be independent learners. Other responses given were to refer them to other colleagues or search for the answer on the spot. No matter what technique or response the teacher has used, it seems that they show willingness to help students.

For enhancing the students leaning, the majority of teachers liked to spend an extra class time, provide revision questions, loan books and notes to the students and lastly be sensitive to students' personal problems. This implied that this faculty has caring and friendly teachers. The average percentage of teachers who liked the above items was almost 59%. From the data (Table 5), we found that the idea of taking students to the library was not the teacher's favourite, as it was felt that students are mature enough to go by themselves.

From the comments made by teachers, the following may improve some of the current inadequacies:

1. The Faculty should organize more programs and activities, which involve both students and faculty members and, perhaps, these can enhance student-teacher interactions.
2. In order to increase the level of students interest's, teachers may include the latest findings from research which is related to the topics they teach.
3. The faculty should provide training sessions for teachers so that they can teach better especially for the self-directed learning, problem-solving sessions and practicals.
4. Technical problems should be lessened when the teaching is on, such as: electricity outage, breakdown of air-conditioning, malfunctioning overhead projectors...etc.
5. Faculty should provide supplies and utilities which are needed by teachers, for example: laboratory tools, equipment and resources for preparing slides and coloured transparencies.

Conclusion

Generally; teachers of our Faculty, who are adequately qualified are happy with their teaching – but they are not that satisfied with their interactions with the students. They hope that there will be more student-teacher interactions in the future and that the students will become more active in their learning process. Teachers expressed willingness to help students in a variety of ways. Therefore the students in this Faculty should feel very lucky that they have both caring and generous population of teachers.

Appreciation

There are many people to whom we would like to express our gratitude. Firstly, to all the teachers whom we interviewed for their full cooperation and support. Secondly, to our families for their support and encouragement. And lastly, but not least, to our fellow students, friends and faculty members for being present during our oral presentation.

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LOW BIRTH WEIGHT BABIES IN SITIAWAN, PERAK - RURAL HEALTH SURVEY 1997

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Introduction

The single most important determinant of newborn survival and future growth is the birth weight of the infant. According to the World Health Organisation (WHO), low birth weight contributes to an estimated 9.1 million infant deaths which occur each year. (1) It not only contributed to about 13.5% of all births at the maternity hospital in Kuala Lumpur but also to 74.8% of all deaths in 1985 (2).

Low birth weight is defined by WHO for international comparisons as "less than 2500g, irrespective of the gestational age" in the 29th World Health Assembly. The frequency of low birth weight varies from society to society with a much greater prevalence in the countries of the developing world e.g. Malaysia, where low birth weight infants run greater risks of malnutrition and are victims of infection such as respiratory tract infections and gastrointestinal tract infections. This further impairs their growth and development, and thus leads to further physical shunting. Those who manage to cross the bridge of increased risk of morbidity and mortality in infancy, would carry the problem over into their adult life, and thus hinder their participation in social and economic development.

No single factor can be implicated in the high incidence of low birth weight. Kramer (3) in a review article has identified 43 factors as possible determinants of low birth weight, including socio-economic status, parity, maternal age, height, weight, gestational weight gain, ante-natal care and infections just to quote a few examples. In Malaysia, studies show that the Indian, babies are the most likely to be low in birth weight and the Chinese babies are the least likely. This statement is supported by the evidence that 20.3% of Indian babies born weighed less than 2.5 kg whereas only 8.5% of Chinese babies had low birth weight. These figures were obtained from a study conducted on all babies born in the year 1985 who weighed 500g or over at the maternity hospital in Kuala Lumpur.

The Manjung Rural Health Survey (RHS) group had proposed to undertake a thematic project on birth weight of babies in Sitiawan. It is believed that birth weight data can be a useful indicator for evaluating health programmes.

Materials and Methods

The study sample was obtained from the two health clinics, namely Mother and Child Health Clinic, Health Office situated in Sitiawan and the other Mother and Child Health Clinic at Kampung Koh, located in a predominantly Chinese area. The data was contained in the ante- and postnatal records. Altogether there were 649 consecutive births between January 1994 and January 1997. Out of these 583 singleton, normal delivery cases were selected for the purpose of this study.

Further, only data for 1995 was considered as it had sufficient number of cases, i.e. 391 records. From these, 323 cases which contained most of the variables formed the final sample.

These data were specific to the population of mothers who were delivered at the Manjung Hospital and to the recording techniques of the hospital. The sample were analysed with respect to the ethnicity of the mother, maternal age, maternal height, maternal employment, parity, number of ante-natal visits, and the gestational age of the baby. The infant birth weight and gender were also studied.

All this data was transferred to a data transfer sheet and then entered into the computer using a database package dBase III Plus. An epidemiological package (EPI-INFO ver 5.0) was used for the purpose of statistical analysis. The data was inspected for transcription errors and out of range values. All the continuous variables were examined for normality distribution. Appropriate test of significant test was used to test the consistency of the data with the Null Hypothesis at the significant level of 0.05. Also included in the analysis was the reporting of the odds ratio with 95 % confidence interval.

Results

Sample data

There were altogether 391 records (ante- and postnatal cards) of births during 1995 from the two health centres in Sitiawan. These two health centres served mostly mothers from Sitiawan and Manjung townships, and a nearby Kampung Koh, about 3 kilometres from Sitiawan. Based on the inclusion and exclusion criteria, 323 singleton normal births were studied.

Birth weight distributions

With the exception of one extreme value, i.e. 1.6 Kg, the distribution of the birth weight is nearly symmetrical. (Figure 1) Most of the values tend to be closer towards the centre

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of distribution, with the mean (std. deviation) of 3.19 (0.49)kg .

The distributions for the Malay, Chinese and Indian also reveal symmetric distribution even though it is slightly skew towards the left for the Indian infants.

As shown in Table 1, there seems to be some difference in the mean birth weights between the three ethnic groups, with Chinese and Malay were on average heavier compared to the Indian. Also, it is of interest to find that Indian babies' weight tend to be slightly more variable compared to the Malay and Chinese.

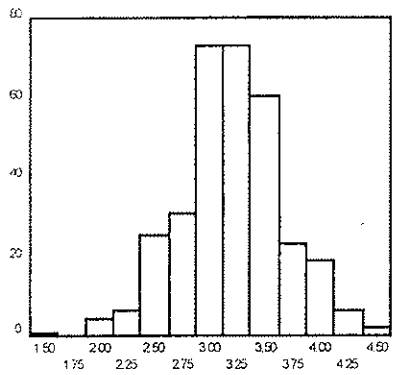
The relationship between mothers' characteristics and the birth weight

In order to examine the relationship between some of the characteristics collected in this study with low birth weight, the data on birth weight were classified either as low birth weight LBW (< 2.5 Kg) or normal birth weight (=>2.5 Kg). Each of the mothers' characteristics: ethnicity, employment status, height, parity, number of ante-natal visit, and gestational age was cross-tabulated with tile birth weight ('Low' versus 'Normal').

The overall incidence of LBW was 6.5 percents. As shown in Table 2, it can be seen that for ethnicity, mother's height, parity, and gestational age - the difference in the proportion of LBW among the various categories were statistically significant. The magnitude of its 'effect' can be seen from the odds ratio. For instance, if the mothers' height is less than 145 cm the risk of LBW is about 5.2 times (95% C.I. : 1.5, 17.6) compared to mothers' whose height is 145 cm or more. However, there were insufficient evidence to suggest that employment, and the number of antenatal visit were associated with LBW.

Table 1. Summary statistics for the birth weight (Kg) for the three ethnic group

Ethnicity	No.	Mean	Std. Dev.
Malay	121	3.26	0.42
Chinese	117	3.23	0.40
Indian	85	3.05	0.47



Distribution of birth weight of infants at two health centres, Sitiawan for the year 1995

Discussion and Conclusion

There were some differences in the mean birth weights among the three ethnic groups. The Indian babies on average seem to be lighter compared to the Chinese and Malay. This finding seem to be supported by studies done at Maternity Hospital Kuala Lumpur (2) and in Singapore. (3) These differences may be explained by the type of diet eaten, especially among those in a lower socio economic group. Apart from these factors which may explained some of these differences, the genetic predisposition among ethnic groups cannot be ruled out.

The overall incidence of LBW was 6.5%. This figure was much lower than those found elsewhere. (2, 4) This may not be reflective of the actual incidence as the sample were taken among the mothers who stay within the township of Sitiawan, where the health centres were located.

In terms of LBW among the three ethnic groups, the Indian showed the highest incidence (14.1%), while the Chinese being the lowest (1.7%). In terms of odds ratio, the risk of LBW among Indian, and Malay compared to the Chinese were 9.5, and 3.5 times respectively.

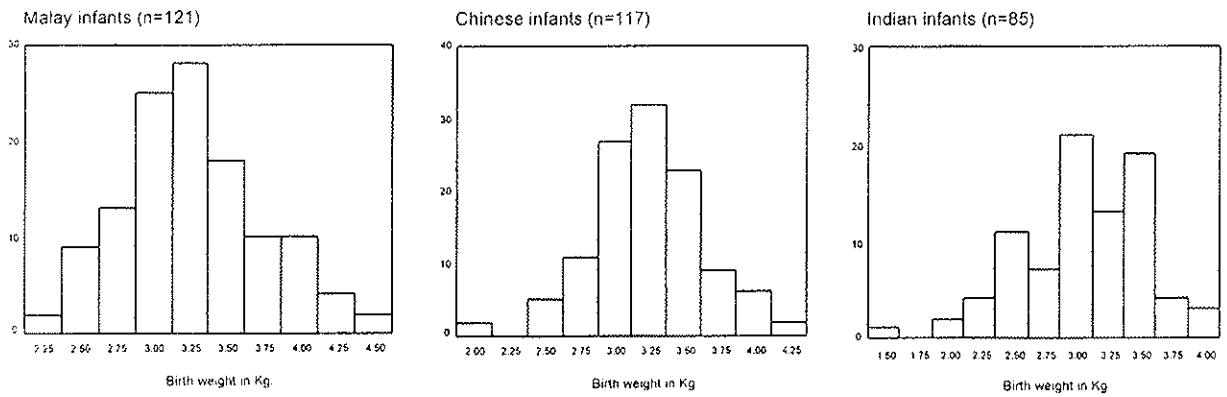


Figure 1. The distributions of birth weight (Kg) for the three ethnic groups.

In this study some of the maternal characteristics were examined for its association with LBW. As for the mothers' height, the association was statistically significant (p=0.004). We found that mothers whose height were less than 145, had 5.2 times the risk of having LBW babies (95% C.I. 1.5, 17.6). This may have contributed indirectly to the differences in the incidence of LBW among the three ethnic groups seen above. However, as for the pre-pregnancy weight the difference in the proportion between those with less than 50 Kg (8.2%) and those with 50 kg and more (6. 1 %) was not statistically significant (p=0.504).

As seen from other studies, birth weights were lower among lower socio-economic groups. In this study we examined mothers' employment status as a proxy measure for socio-economic status. The differences of LBW between working (3.0%) and non-working mothers (3.0%) was not statistically significant (p = 0.083) with the odds ratio of 2.8 (95% C.I. 0.8, 10.0). It must be stressed that the use of mother' employment status was rather inadequate as the type of occupation, level of education or income were not known.

As for parity, there was a significant association. The risk was lower for multipara (0.3) and grand multipara (0.8) compared to primipara. This finding was similar to the study carried out by Hashim, *et al. (2)*

The minimum requirement for ante-natal visits set by the Ministry of Health is eight. From the study done by Trivedi *et al* (5) there was a significant association between ante-natal care and birth weight. In this study we tried to find out whether mothers who had less than 8 visits to be more at risk of having LBW babies. However, the finding was not statistically significant (p=0. 145).

Gestational age was also thought to contribute to the incidence of low birth weight. From our finding, those mothers whose gestational age was less than 38 weeks, the proportion of LBW was significantly much higher (26.4%) compared those with gestational age of 38 weeks or more (2.3%), with the accompanying risk of about 15 times.

However, the findings from this study should be interpreted with caution because of the limitations and errors already mentioned. Furthermore, the analysis of the data is limited in the sense that it does not take into

Table 2. Relationship between mothers ethnicity, employment status, height, parity, no, of antenatal visit, gestational age and birth weight.

Characteristics	Birth weight				Total		p-value	O.R. 95% C.I
	Low		Normal					
Ethnicity								
Chinese*	2	(1.7%)	115	(98.3%)	117	(100.0%)	0.002	1.0#
Malay	7	(5.8%)	114	(94.2%)	121	(100.0%)		3.5
Indian	12	(14.1%)	73	(85.9)	85	(100.0%)		9.5
Employment								
Not working	18	(8.1%)	204	(91.9%)	222	(100.0%)	0.083	2.8
Working	3	(3.0%)	98	(97.0%)	101	(100.0%)		(0.8, 10.0)
Height								
< 145 cm	4	(23.5%)	13	(76.5%)	17	(100.0%)	0.004	5.2
> 145 cm	17	(5.6%)	287	(94.4%)	304	(100.0%)		(1.5, 17.6)
Parity								
Primipara**	9	(13.0%)	60	(87.0%)	69	(100.0%)	0.019	1.0#
Multipara	9	(4.0%)	216	(96.0%)	225	(100.0%)		0.3
Grandmultip	3	(10.3%)	26	(89.7%)	29	(100.0%)		0.8
Antenatal visit								
< 8 visit	10	(9.3%)	97	(90.7%)	107	(100.0%)	0.145	1.9
=> 8 visit	11	(5.1%)	205	(94.9%)	216	(100.0%)		(0.8, 4.7)
Gest. Age								
< 38 weeks	14	(26.4%)	39	(73.6%)	53	(100.0%)	0.000	15.2
=> 38 weeks	6	(2.3%)	254	(97.7%)	260	(100.0%)		(5.5, 41.9)

Footnote: *Chinese and **Primipara were used as baseline for calculating odds ratio.

95% C.I. was not calculated. Some of total does not add up to 323 cases due to missing data.

account of the multiplicity of factors that may influence the outcome (LBW) as well as the inter-relationship between the factors themselves. (6,7,8)

There are several limitations in this study. The data was secondary in nature as such there was no standard procedure in the measurement, e.g. birth weight. Thus, some of these variables were subjected to errors. Some of the records were incomplete, e.g. gender, where 81 records with no information about sex of the infant.

There was a selection bias, as the sample was obtained only from the two health centres. This may not be representative of the population at large. For example, those who delivered in private hospitals and clinics were not included. Moreover, both of the health centres were located in a more 'urbanised' areas.

Other variables, e.g. place of stay (urban or rural), education level, and dietary history could not be studied as these were not collected routinely.

However, this project has given us the opportunity to carry out a small scale study on the available data. It is quite obvious that the data from clinic records could be used for the purpose of examining health issues. In this situation, the birth weight data can be analysed to see the trend which can provide a picture of the health status in the community, specifically in the area of maternal and child health. Nevertheless, we take caution in the interpretation of these data.

Acknowledgement

We would like to express our gratitude to the Medical Officer of Health of Manjung district, Dr.Vimala Sothirajah for her permission to carry out this thematic project as part of the rural health posting requirement. Also our thanks to Sister Rogayah bt. Abd. Mutalib for her help in accessing the ante and postnatal records. We would like thank our fellow station colleagues who have helped to transfer the data and helped in the analysis.

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List of Students, Manjung Rural Health Posting 1996.

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CANNABIS-INDUCED MANIA

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ABSTRACTS: Hypomanic episodes have been reported in two patients who were known to have abused cannabis. The nature of its presentation, possible association and treatment modalities are discussed herewith. A greater awareness of such a condition can put clinicians in a better position to give appropriate treatment imediately, and thus prevent any kind of re-occurrence of such a condition especially in vulnerable patients. *(JUMMEC 1999; 1:62-63)*

KEYWORDS: Cannabis, hypomania.

Introduction

The use of cannabis as a social drug in Malaysia is illegal, and therefore, it is still classified under the "hard drugs" by law, similar to that of opiates. However, despite the stringent law against its use, it is still easily available especially in places where other illegal drugs are being abused. Thus, we can see the reason why many youths still resort to the use of cannabis as a social drug. Although cannabis is not known to produce any kind of severe dependence syndrome, nevertheless, several studies have shown it to cause or even precipitate psychosis (1, 2). Since the continuous use of cannabis can either aggravate or precipitate a relapse, thus it is important for clinicians then to be able to identify how long a duration this drug had been abused by a particular patient and be in a position to advise the vulnerable patient to abstain completely. The following two case-reports illustrate the nature of psychosis which can be induced by the abuse of cannabis.

Case I

Mr. S., a 28-year old Malay man was admitted to Ward 5B of the University Hospital for a three-day period. A review of his medical history revealed that patient had wandered away from home and exhibited some kind of abnormal behaviour. Associated with this, patient was noted to have had poor sleep and was suspicious of his family members. Patient's history of drugs showed that he had been abusing cannabis for the past eleven years and this was confirmed by his wife. The day prior to patient's abnormal behaviour, he had smoked about two sticks of cannabis. A review of the patient's family history revealed that his father had been treated for psychotic disorder. The mental status examination of the patient at the time of admission revealed patient to be euphoric as well as exhibiting grandiose delusions. Patient thus believed that he had the ability to cure other people's illness. Nevertheless, patient's orientation and memory were intact. A diagnosis of cannabis psychosis was made based on the clinical findings available. Patient was thus treated with Haloperidol 5 mg tds and Benzhexol 2 mg tds and he recovered finally after two weeks of inpatient treatment.

Case II

The second case of cannabis-induced psychosis was found in Mr. D., a 26-year old, single, Chinese man who had been known to have abused cannabis for the past thirteen years. A review of this patient's history revealed that he had been admitted to the University Hospital, Kuala Lumpur on two previous occasions since 1989, and was diagnosed to have suffered from bipolar mood disorder. However, during the previous episode, patient's drug history was not assessed and thus the abuse of cannabis could not be elicited. It was only after his third admission that patient was found to be abusing cannabis since there were no other drugs being abused by him at that particular period.

The history of cannabis abuse was confirmed by the patient's girl-friend since she acknowledged co-habitating with him. A review of patient's family history did not show any kind of mental illness in the family, but the mental status examination revealed that he suffered from a pressure of speech and expansive mood. He had lots of ideas about business deals and experienced grandiose delusions. He claimed to be the richest man in Malaysia, owning lots of properties. His orientation and memory were intact at that time. Nevertheless, patient's diagnosis was thus changed to cannabis-induced psychosis and like the first case, his psychotic symptoms subsided after treatment with Haloperidol 10 mg bd after a duration of two weeks.

Discussion

Cannabis-induced psychosis can occur in any form, but based on a literature review, it is supposed to occur mainly in the form of either schizophrenia-like psychosis or acute organic psychosis rather than hypomanic (3). On the other hand, when you analyse the latest findings available in the above two case reports, one can note the great contrast seen in both the cases where both patients showed or exhibited hypomanic episodes. In fact, in the case of Mr. D, all his presentations in the past had always been hypomanic.

The possible association of the abuse of cannabis and that of psychosis itself had been debated for several years now due to the fact that the results tend to vary from one subject to another. Nevertheless, there have been at least six types of associations which had been postulated in trying to explain the manifestations of the psychosis. These explanations include the direct toxic effect to the brain and the induction of a latent psychosis (4). Two different forms of associations are also possible in explaining the cause of psychosis as can be seen in Case I and II. For Mr. S, the latter explanation is due to patient probably inheriting some form of psychosis from his father which then manifested when he abused cannabis. This is in great contrast to what had happened to Mr. D (Case II) where patient neither recalled any history of psychiatric illness nor was he exposed to any kind of genetic predisposition like the other case. Furthermore, there seems to be a temporal relationship between the intake of cannabis and that of the occurrence of the psychotic states. It is therefore possible, that this particular form of psychosis is probably due to the direct toxic effect of cannabis and a psychosis *de novo*.

Therefore, the best treatment one can resort to is by administering antipsychotics where the psychosis improved tremendously in both the cases after they were treated with Haloperidol. Nevertheless, it is important to note that patients should be advised to refrain from abusing cannabis, otherwise there could be a possibility of a relapse if cannabis is abused again as highlighted in Case II.

It is hoped that these two case-reports would create some form of awareness among clinicians especially psychiatrists about this particular condition if a good history on drug-intake is assessed in every patient whom we suspect of abusing cannabis as a social drug. A delay in diagnosis can probably lead to another relapse, and perhaps might even further lead to a chronic form of psychosis as we have seen highlighted in these case-reports.

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