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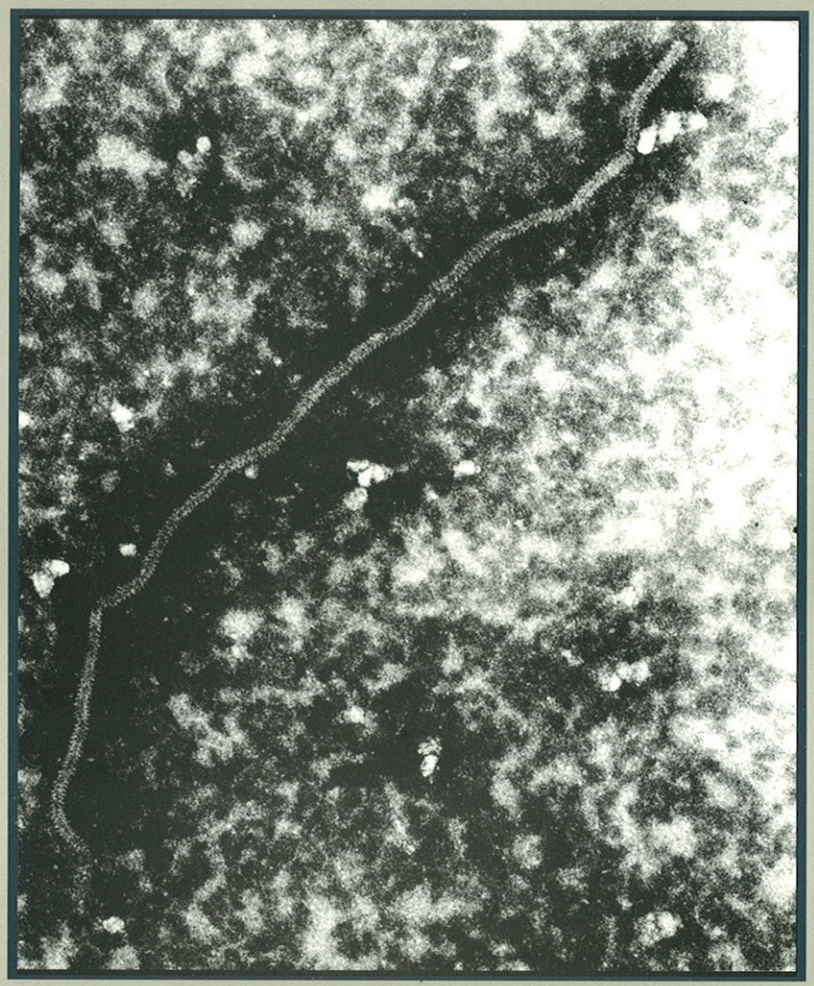

Vol. 4 No. 2 December 1999

Journal of the
University of Malaya
Medical Centre

Journal of the University of Malaya Medical Centre
JUMMEC

Volume 4❖Number 2 December 1999

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Publisher

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

Cover

The front cover depicts a negatively stained nucleocapsid of the Nipah virus, showing the characteristic herring-bone appearance typical of members of the paramyxovirus family. This electron micrograph (magnification : 65,000x) was taken at the Centers for Disease Control and Prevention (CDC), National Center for Infectious Diseases, Division of Viral and Rickettsial Diseases, Infectious Disease Pathology Activity, Atlanta USA.

Courtesy of Dr. Chua Kaw Bing and Dr. C. Goldsmith

Printed by

Printing Unit, Faculty of Medicine, University of Malaya, Kuala Lumpur

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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.

References: Number references consecutively in the order in which they are first mentioned in the text. References in the text should be indicated by a figure within parenthesis. The titles of journals in the list should be abbreviated according to the Index Medicus. Authors are responsible for the accuracy of all references. Examples of correct forms of references are given below:

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ii) ***Personal author(s) of book:***
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iii) ***Chapter in book:***
Weinstein L., Swartz MM. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, Eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders; 1974; 457-72.

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Figures: Graphs, drawings and photographs should be submitted as clear, glossy prints measuring 12 cm by 17 cm. Figures should be identified on the back with the title of the article and figure number (in light pencil) and an arrow to indicate the top. Legends to the figures should be submitted on a separate sheet. Explain all abbreviations and symbols used.

Letter of Consent: Submissions must be accompanied by a letter of consent, signed by ***all*** authors, containing the following text:

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SETTING UP A PAIN CLINIC FOR CANCER PAIN RELIEF - THE CANCER PAIN CLINIC

Cancer Pain Relief requires a dedicated team whose goal should be to obtain satisfaction from attempting to relieve the intractable, unrelenting pain of a cancer patient who more often than not is unable to sleep because of pain and is dying in pain. The Pain Clinic should preferably be a Therapeutic Pain Palliation one rather than a diagnostic clinic. The cancer patient in pain is a complex entity; besides the pain experienced the spectre of death hangs over his or her head, environmental factors (family, work or employment commitments) bring in psycho-social and religious influences. One does not treat the organ or system involved in the pain, one has to treat the patient as a whole human being bearing in mind the related factors that have produced this complex entity.

A Pain clinic dedicated to the cancer patient in pain needs to be set up with a panel of specialists brought in as and when relevant - the panel should comprise those directly involved in relieving pain in a cancer patient. The Pain Clinic for cancer pain is a multidisciplinary one involving various fields-.

- Anaesthesiology
- Oncology
- Radiotheraphy
- Neurosurgery
- Nursing
- Counselling - Psychology
- Religious.
- Physiotherapy

In many centres this Pain Clinic is sited within a hospital with back-up facilities such as physiotherapy (including reflexology, massage and muscle spasm relaxing techniques), pharmacy, a minor operating theatre and a few "observation" beds.

To set up a Pain clinic for the cancer patient the following are required:

1. A specialist in Pain Relief (The Anaesthesiologist can fulfil the role)
2. A dedicated Nurse
3. The physical space for a clinic equip with
   - ➢ Examination couch
   - ➢ Facilities for medical recording (clinical staff and a computer)
   - ➢ A telephone and a handphone
   - ➢ Facilities to bring in relevant panel specialists for consultation
   - ➢ and or pain management

The Cancer Pain Clinic should be able to provide the following modalities for Pain Relief

1 Non-Invasive Pharmacology
   - ➢ analgesics, anti-depressives, anxiolytics, antiemetics, chemotherapy

2. Invasive Pharmacology
   - ➢ neural blockade
   - ➢ as Diagnostic/Prognostic procedures,
   - ➢ Therapeutic blocks and prophylactic blocks

3. Neurosurgical procedures including radiofrequency/thermocoagulation ablation

4. Radiotherapy

5. Non-Phamacological Adjuvant Therapy
   - ➢ Transcutaneous Electrical Nerve Stimulations (TENS)
   - ➢ Massage, Reflexology
   - ➢ Acupuncture
   - ➢ Physiotherapy
   - ➢ Counselling for the dying

Costing

1. Clinic space (preferably within a Hospital)
2. Examination couch, desk, phones
3. Filing facilities (including a computer)
4. Dedicated pain specialist (on retainer fee?)
5. Dedicated Nurse
6. Physiotherapist
7. Panel of relevant physician specialists on referral basis
8. Pharmacy and equipment back-up facilities
   - ➢ drugs, needles, syringes, pumps

9. Minor Operating Theatre facilities with resuscitative equipment
10. Observation beds (1 or 2) for post-procedures care.
11. Radiology back-up facilities

- ➢ Image-Intensifier for guidance of certain invasives blocks e.g. coeliac ganglion block
- ➢ Scanning and imaging facilities

7-11 should be available from the back-up hospital or hospitals.

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RECENT ADVANCES IN GERIATRIC MEDICINE - A REVIEW

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ABSTRACT: The rapid aging of populations worldwide demands major changes across all aspects of health care for older persons. Geriatric medicine which is that branch of of medicine which is concerned with the clinical, preventive and rehabilitative aspects of care of older persons, has much to offer in relieving the suffering and increasing the disability free years they can enjoy. Recent advances in Geriatric Medicine based on well designed randomised trials and meta-analysis that are clinically significant to the practicing physician are reviewed in this article. *(JUMMEC 1999; 2: 67-73)*

KEYWORDS: Recent advances, Geriatric Medicine, Older persons.

Introduction

Geriatric Medicine is that branch of Medicine concerned with the clinical, preventive and rehabilitative aspects of care of older persons. According to the United Nations estimates, the population of the elderly in the world will reach 590 million by the year 2000 of which 60 % will be residing in developing countries. In Malaysia, of the estimated population of about 18 million in the year 2000, approximately 10.3% or 1.84 million would be older persons aged 60 years or older. Physicians in managing older persons with illnesses strive to relieve their suffering, increase their disability free years they can enjoy and hence improving their overall quality of life. In recent years there has been many methodologically rigorous studies relevant to the medical care of older persons have been published. A review of the clinically significant recent advances in geriatric medicine is presented.

Ageing and oxidative stress

Oxidative stress is one of the mechanisms of aging and it has been shown that aging involves defects in the mitochondrial DNA which promote oxidative stress mediated cell damage (1). In recent years numerous trials have been completed involving the use of antioxidants like Vitamin E, Selenium, β-carotene and Vitamin C in the management of Alzheimer's disease, heart disease and in reduction of incidence of cancer. In a 2 year randomised placebo controlled trial, 2000 IU of Vitamin E per day given to patients with moderate Alzheimer's disease delayed 50% the combined endpoint of death, admission to an institution, inability to perform the activities of daily living, or severe dementia (2).

In the Cambridge heart antioxidant study, the active treatment group receiving Vitamin E 400-800 IU per day death from cardiovascular causes or non-fatal myocardial infarction was significantly reduced (3). However a similar Finnish study found no significant changes in the rates of coronary events and a significantly higher rate of coronary events in those participants randomised to receive β-carotene (4). An observational study reported a followup of 7 years of over 34486 post menopausal women who had a high dietary intake of Vitamin E who showed a significantly reduced risk of death from coronary disease (5). The clinical trial data for the regular use Vitamin C, Selenium and β-carotene in the prevention of cancer or reduction in risk of coronary events is less favourable.

Importance of inflammation and role of NSAID in the elderly

Inflammation has a major role in many of the disease processes that affect the physical function and cause disability in the elderly. Investigators in the SOLVD study (6) and other studies (7) have shown the association of proinflammatory cytokines such as tumour necrosis factor a and interleukin 6 with poor prognosis and increased severity of heart failiure. Cardiac cachexia causing wasting of skeletal muscle often seen in older people with cardiac failure is associated with excess of cytokine production. Aspirin through its anti-platelet effects has been proven of benefit in cardiovascular disease in the elderly and there is now increasing data that aspirin may inhibit inflammation in atherosclerosis. In the Physicians health study (8), the reduction in the risk of acute myocardial infarction associated with taking aspirin was greater in people with high concentrations of C-reactive protein than those with low values. The

protective effect of NSAID use on the cognitive decline in older persons and the reduction of risk of Alzheimer's disease was highlighted in 2 studies (9,10). However more definitive studies need to be done in this area before recommending the use of NSAID in the prevention of dementia. For Alzheimer's disease, the commonest cause of dementia, two cholinesterase inhibitors, donepezil (Aricept) and rivastigmine (Exelon), are now licensed for the symptomatic treatment of mild to moderate cognitive impairment [minimental state examination score of 10-26]. Trials (11,12) suggest that in some patients these agents improve cognition, global function, and behavioural function, but there are as yet no data as to whether they delay deterioration or improve outcome.

Heart disease, dyslipidaemia, hypertension and stroke in older people

Coronary Heart disease (CHD) is the most important part of the broad spectrum of disease conditions affecting the heart and circulation that progresses dramatically as the age advances. CHD contributes heavily to the disability and death especially in the elderly persons. A systemic evaluation of risk associations, focussing on the initial development of CHD in subjects aged 65-94 years in Framingham and other studies, showed that the majority of risk factors established in middle age also maintained significant associations with CHD in older persons, but with some differences related to sex. Hypertension particularly elevated systolic blood pressure, emerged as the dominant risk factor for CHD irrespective of sex. Serum total cholesterol alone lost statistical power as a predictor for CHD, particularly in older men, but predictive strength for serum lipids was restored when high density lipoproteins were considered in the analysis. Cigarette smoking was not associated with risk of overall CHD incidence but remained a risk factor for coronary death. ECG left ventricular hypertrophy and non-specific repolarisation abnormalities were related to enhanced CHD risk. Glucose intolerance and diabetes mellitus made independent contributions to CHD risk particularly in older women.

Systolic hypertension

Data from the systolic hypertension in the elderly program has shown that treating isolated systolic hypertension with diuretic drugs can reduce the risk of heart failiure over time (13). The reduction in congestive heart failiure events is greatest in patients with a history of myocardial infarction or electrocardiograhic evidence of this. Results from the same group has shown that diuretic drug treatment of isolated systolic hypertension in patient's with moderate type II diabetes was at least as effective as treatment with other types of hypertensive drugs in reducing stroke, non-fatal myocardial infarction and coronary heart disease and all other major cardiovascular events. Data from another large trial the Syst-Eur trial (14) showed that among elderly patients with isolated systolic hypertension, antihypertensive drug treatment starting with nitrendipine reduces the rate of cardiovascular complications. Treatment of 1000 patients for 5 years with this type of regimen may prevent 29 strokes or 53 major cardiovascular endpoints. The same group in a related analysis found that that the calcium channel blocker nitrendipine, given as a single antihypertensive medication, prevents cardiovascular complications in older patients with isolated systolic hypertension. A meta analysis of trials of antihypertensive therapies has shown that treatment with diuretics given in low doses to older adults was associated with reduced risks of stroke, coronary heart diseas,congestive heart failiure and total mortaility (15). The Hypertension in the Very Elderly Trial (HYVET) is an ongoing multicentre, open, randomised, controlled trial(16). The aim of this trial is to investigate the effect of active treatment on stroke incidence in hypertensive patients over the age of 80 years. Secondary end-points include total cardiovascular mortality and morbidity. Patients are to be randomised to 3 groups-(i) no treatment; (ii) treatment with a diuretic (bendrofluazide); or (iii) treatment with an angiotensin converting enzyme (ACE) inhibitor. It is expected that this trial will provide with the answers whether to treat hypertensives above the age of 80 years with mild to moderate hypertension. Many other trials are also in progress in the U.S. and Europe to determine which hypertensive agents are better at preventing major complications of hypertension. The effect of anti-hypertensive treatment on cognitive function is still uncertain. Although the MRC trial (17) and the SHEP trial (13) showed no impact on cognitive function the data from the Kungsholmen project (18) and the Syst-Eur Trial (14) are more promising. Extrapolating from the results of Syst-Eur Trial, treatment of 1,000 hypertensive patients for 5 years could prevent 19 cases of dementia. More large scale and definitive studies are needed to answer the question of the prevention of cognitive decline with antihypertensive treatment.

Dyslipidaemia

The predictability of CAD by serum cholesterol appears to decline with advancing age. In an ongoing longitudinal community study of cardiovascular disease in Australian elderly, 60 years or older [The Dubbo Study] (19), hypercholestroleamia due to elevated LDL cholesterol was predictive of initial and recurrent CAD in men and women 60-69 years, but not predictive in older subjects. Hypertriglcerideamia was predictive of initial and recurrent CAD in men 60-69 years only, and in all women 60 years and older Controlled trials of lipid

therapy have not been conducted specifically in the elderly. However in men and women aged 60-69 with established CAD in the 4S (20) study achieved similar CAD prevention to younger subjects. In the WOCSOPS trial (21) demonstrated benefit from pravastatin in hypercholestroleamic men up to the age of 65 years but evidence of similar benefit above the age or in women is lacking. Hence although the case for lipid intervention in still older subjects with established CAD is justified on empirical grounds, the available evidence leads to the conclusion that dyslipideamia should not be treated in asymptomatic, elderly free clinical CAD of above the age of 70 years.

Stroke

Recently published large clinical trials (22) of heparin and aspirin in acute stroke - the International Stroke Trial, Chinese Acute Stroke Trial, and Trial of ORG 10172 in Acute Stroke Treatment - fail to show a net benefit from heparin. The rates of recurrent ischemic stroke in the control groups of these trials were low, ranging from 0.6 to 2.2% per week. The low rates of recurrent stroke observed in these groups, coupled with the morbidity and mortality associated with i.v. heparin in this patient population, argue against routine use of i.v. heparin in the acute stroke period. Aspirin's benefit in preventing vascular outcomes is well established (23). It reduces the relative risk for stroke, myocardial infarction, and vascular death by about 25% compared with placebo. Almost 10 years ago we learned that ticlopidine is more effective than aspirin (about 12% relative risk reduction for stroke or death). However, ticlopidine has important adverse effects. In 1996, the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial showed that clopidogrel, a new thienopyridine similar to ticlopidine, is also more effective than aspirin (by a similar amount) and is as safe as aspirin. Also in 1996, the European Stroke Prevention Study 2(ESPS-2) showed that dipyridamole alone prevents stroke and that when combined with aspirin it is more effective, probably comparable to ticlopidine and clopidogrel. Dipyridamole combined with aspirin reduced the relative risk for stroke or death by about 13% compared with aspirin alone. Both clopidogrel and dipyridamole are safe but will cost more than aspirin. Aspirin also appears beneficial for acute stroke treatment. The Chinese Acute Stroke Trial (CAST) (24) and the International Stroke Trial (IST) (25) demonstrated that aspirin given at the time of an acute ischemic stroke reduces the risk for early death (about 5 less/1,000 treated), recurrence or death (about 10 less/1,000 treated), and dependence (about 5 less/1,000 treated). Overall, the benefits of aspirin in acute stroke treatment and stroke prevention are definite but modest. Combination therapy with antiplatelet agents that act through different mechanisms is a promising way to maximize the benefits of antiplatelet treatment. All the randomised controlled trials comparing the outcome of patients with stroke cared for in a specialist stroke unit with the outcome of those cared for in general medical wards were examined and showed that stroke units reduce the risk of death or living in an institution at a median of 12 months afterstroke (26). However there is some evidence that elderly patient's with stroke may benefit from care in geriatric assessment or rehabilitation units as much as care from stroke units (27). However the most important factors contributing to the effectiveness of the stroke or rehabilitation units will be their organisation and the presence of a multidisciplinary team that is knowlegeable and enthusiastic about treating stroke. Rudd *et al* showed that in a randomised controlled trial (28) early discharge from the hospital after stroke with specialist rehabilitation at home is feasible without an increase in readmission rates or stress to carers. This study has shown that considerable reductions in the use of hospital beds are achievable with the development of an effective rehabilitation team in the community and may provide an opportunity to cut costs.

Interventions to improve healthy ageing

Cardiovascular disease is still the most important cause of morbidity and mortality in older persons and interventions to reduce blood pressure by 6mmHg and blood cholesterol by 10 % will reduce the risk of heart attack or coronary artery disease by 15% and 30% respectively. Diets high in fruit, vegetable intake, high complex carbohydrates, non-starch polysaccarides and reduced saturated fat and total fat intake has been found to be especially protective for cardiovascular disease in older people. Similiarly the risk of fractures can be reduced by ensuring that older people have adequate dietary intake of calcium and vitamin D. Physical activity has been shown to protect against cardiovascular disease, osteoporosis and fractures, diabetes, breast and colon cancer. Exercise programmes in the elderly can not only improve their balance but resistance exercises for the legs are especially useful in helping them rise from the chair and increase their walking speed. A combination of upper body resistance exercises which can increase the range of activities of daily living and flexibility exercises that protect against falls are important interventions in the elderly. In a randomised controlled trial (29) of general practice programme of home based exercises showed that strength and balance retraining exercise improved the physical function and was effective in reducing falls and injuries in women 80 years and older. Exercise also provides some performance improvement and pain relief in patients with knee osteoarthritis. In a 18 month randomised controlled trial (30) of 463 community dwelling older persons mean age 68 years old, with pain and functional limitation from knee osteoarthritis, both aerobic and resistance exercise

training improved performance and diminished pain in these patients with knee osteoarthritis. These exercise regimens were well tolerated with 2 % adverse effects (falls and fractures).

In a randomised controlled trial of prevention of falls in the elderly (PROFET) (31), Close J *et al* assesed the benefit of a structured interdisciplinary assessment of people who have fallen in terms of further falls. The study shows that an detailed medical and occupational-therapy assessment of this high-risk population with referral to relevant services if indicated; can significantly decrease the risk of further falls and limit functional impairment. External hip protectors or safety pants have been shown in open randomised nursing home study (32) to reduce the rate of hip fractures by 50 %. The risk of fracture in older people can be reduced by increasing their low bone mass by ensuring adequate intake of Vitamin D and calcium. Alendronate-α biphosphonate has emerged as alternative to hormone replacement for women who are unable or unwilling to take the drug and it has been shown to reduce risk of vertebral fracture and preserves bone mass at all sites of major osteporotic fracture. In a randomized double blind placebo controlled trial (33) of 2027 post menopausal women with osteoporosis taking 5-10 mg/day of a biphosphonate-alendronate, treating 35 (95%CI:22-85) women with alendronate for three years prevented 1 clinical vertebral fracture; treating 52 (95% CI:28-234) women prevented one wrist fracture.

Hence healthy life expectancy is often influenced by chronic disabling conditions like cardiovascular disease, osteoporosis, or serious injuries associated with falls which can be prevented or postponed by appropriate interventions throughout life.

Hazards of hospitalisation in older persons

Functional decline is a common problem during and after acute hospitalization in older adults. Sager *et al* (34) showed that one third of older adults lose the ability to perform at least one ADL after acute medical hospitalisation and 40% had of these patients had not regained preadmission ADL/IADL function 3 months later. Patients with hospital acquired ADL declines were more likely to be re-hospitalized or newly institutionalized at 3 month followup. In another study of hospitalized patients (35) researchers found that 15-18% of patients developed delirium during the first 9 hospital days. Use of physical restraints, malnutrition(albumin<3.0 gm/dl), more than 3 medications added in 24 hours, use of a bladder catheter, and iatrogenic events were identified as independent risk factors for the precipitation of delirium in the hospitalized older adults. Falls by inpatients are associated with increased duration of stay in hospital and a greater chance of unplanned readmission or discharge to residential or nursing home care. Oliver *et al* (36) by identifying five factors significantly associated with falls have devised a simple risk assessment tool (STRATIFY) to predict which high risk elderly patients will fall and hence target prevention programmes towards this group.

NSAID usage and its complications in older persons

Estimates of attributable risk suggest that non-steroidal anti-inflammatory drugs are responsible for between one quarter and one third of hospital admissions for upper gastrointestinal bleeding in older people (37) In U.K. it is estimated that NSAID inclusive of aspirin cause about 5000 upper gastrointestinal bleeding episodes needing admission with about 800 deaths per year. A result of meta-analysis(38) showed that compared with 11 other NSAID's, ibuprofen at doses<2400mg/d has the lowest risk for serious gastrointestinal complications requiring hospitalization. However the risk of hospitalization increases with higher doses. Another meta-analysis (39) showed that treating eight (95%CI:4-112) short term NSAID users or 12 (95%CI:6-100) long term users with misoprostol will prevent one endoscopic gastric ulcer in each group. Usual doses of H^2 blockers were ineffective in preventing NSAID-associated gastric ulcers. In a double blind placebo controlled RCT (40) famotidine at doses of 20 mg po bid, did not prevent NSAID associated gastric ulcers, but high dose famotidine (40 mg bid) prevented NSAID-induced endoscopic ulcers in arthritis patients. Treating 10 (CI:5-143) patients for 24 weeks with famotidine 40 mg bid, prevents one NSAID-associated gastric endoscopic ulcer. Cyclooxygenase-2 (COX-2) inhibitors are being evaluated in clinical trials or are in development. These agents appear to inhibit only the COX-2 isoenzyme, which is produced largely during inflammation and is responsible for the biosynthesis of prostaglandins and other mediators of inflammation as well as sensitizers to pain. Because COX-2 inhibitors do not inhibit COX-1 isoenzyme activity at pharmacologic concentrations, they are devoid of many of the toxicities that are typical side effects of NSAID. Short term studies in dental pain, osteoarthritis, and rheumatoid arthritis found that the COX-2 inhibitor celecoxib was an effective analgesic (41) but did not cause gastroduodenal erosions. It has the potential to provide analgesia and antiinflammatory action in patients with arthritis without the side effects of NSAID. Further studies are in progress to substantiate these findings. With these results in mind older patients with painful arthritis should be treated initially with acetaminophen or a nonacetylated salicylate. If this is not effective the lowest effective dose of ibuprofen should be started with adequate prophylaxis with either misoprostol or high dose famotidine in high risk patients. The newer COX-2 inhibitors would be a

more suitable and safer alternative in many older patients with arthritis in the future.

Comprehensive geriatric assessment

Comprehensive geriatric assessment is a multidimensional, interdisciplinary diagnostic process intended to determine an elderly person's medical, psychosocial, functional capabilities and problems. Controlled trials in a number of countries have documented benefits from different types of in-home assessment and treatment programs for various subgroups of elderly persons. The concepts of in-home comprehensive geriatric assessment (CGA) consists of a regular follow-up, health education, and preventive care in a community. The intervention includes yearly in-home CGA by geriatric nurse practitioners (GNPs), who provide, following discussions with physician geriatricians, lists of specific recommendations for health and well-being enhancement. The GNPs provide follow-up visits quarterly and regular telephone contacts to improve compliance. In 3-year randomised trial involving 202 older people enrolled in an in-home comprehensive geriatric assessment (CGA) and preventive care program, Cho *et al* (42) found that although functional status was similar at baseline, the presence of certain target conditions in this sample was associated significantly with functional decline in (IADL) instrumental activities of daily living and (BADL) basic activities of daily living during the 3-year period. Four conditions (gait/balance disorders, depression, unsafe home environment, and coronary artery disease) were associated with significant declines in IADL, and four conditions (gait/balance disorders, depression, hypertension, and urinary incontinence) were associated with significant declines in BADL. These findings may help identify older persons at risk for greatest functional decline despite participation in CGA and may also suggest the need for more effective intervention strategies in these individuals. Secondary analysis of the same randomised trial (43) showed that preventive in-home geriatric assessment in well functioning community dwelling older people delayed the onset of disability in them. The effectiveness of outpatient CGA consultation coupled with an adherence intervention on 15-month health outcome was tested in a randomized controlled trial by Reuben *et al* (44). This study showed that a combined approach in an outpatient setting can prevent functional and health-related quality-of-life decline among community-dwelling older persons who have specific geriatric conditions.

Conclusion

Practising clinicians should be aware of the recent advances of geriatric medicine highlighted above as important studies have shown that chronic inflammation has an important role in the abnormal processes related to aging, including changes in body composition, congestive heart failiure, and possibly dementia. Increasing oxidative stress is a key aspect of aging as studies suggest that Vitamin E supplementation reduces coronary events associated with atherosclerosis and may slow the processes underlying Alzheimer's disease. John Glenn's (aged 77 years) recent nine day journey to space aboard the space shuttle Discovery (45) promises to expand human knowledge about the aging process. Many of the biological changes that occur in the weightless environment of space are similiar to those that occur on earth as one ages. Research about the changes in the physiological systems in the ageing body in space will help us learn more about aging-related frailties and conditions, such as osteoporosis, cardiovascular deconditioning, and sleep disorders in older persons. Increasing research into the clinical interventions of common geriatric syndromes by way of methodologically rigorous studies will provide the evidence base that will relieve suffering in old people and increase the number of disability-free years they can enjoy.

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GROWTH HORMONE DEFICIENCY IN ADULTS

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ABSTRACT: Adults with Growth hormone (GH) deficiency is now being recognised to display many distinct clinical, metabolic and psychological abnormalities. It has been demonstrated that GH deficient (GHD) adults display features of multiple insulin resistant syndrome (MIRS) which predispose the GHD adults to increased cardiovascular morbidity and mortality. These features include central obesity, insulin resistance and glucose intolerance, hypertension, dyslipidaemia that includes a reduced level of high density lipoprotein cholesterol, an elevated triglyceride level and small low density lipoprotein cholesterol size. Furthermore, GHD adults are found to have a lower bone mass and a reduced sense of well-being.

Replacement of GH in these GHD adults has brought about a major improvement in psychological well-being and central obesity. The improvement of some of the lipid abnormalities is however more modest. Insulin resistance, the corner stone of MIRS, is however not altered by GH replacement. Long term data is as yet unavailable to assess if GH replacement reduces cardiovascular mortality and morbidity in these subjects. *(JUMMEC 1999; 2: 74-80)*

KEYWORDS: Growth hormone, Hormone deficiency, Diabetes mellitus, Central obesity, Hyperlipidaemia, Hypertension.

Introduction

Growth hormone (GH) deficiency in childhood are characterised by short stature, delayed bone maturation, excess adiposity with a predominant truncal distribution, reduced lean body mass and fasting hypoglycaemia, all of which are improved or normalised with GH treatment (1).

The incidence of pituitary insufficiency is not fully known and is found not only in patients with pituitary or parapituitary tumours but also in those who has been exposed to previous radiation, the field of which includes the pituitary for example head and neck malignancies, nasopharyngeal carcinoma and cranial irradiation for brain tumour or childhood leukaemia. Traditionally, adults with hypopituitarism are only replaced with sex steroids, corticosteroids and thyroxine where clinically indicated, although GH deficiency is common in these patients (2). However, GH deficiency in adults also represents a specific clinical syndrome characterised by a wide range of clinical features as reviewed by Cuneo *et al* (3) and more recently by us (4).

Overall mortality was found to be two fold higher in hypopituitary patients than in the general population, despite appropriate conventional hormone replacement, largely accountable for by an increase in mortality from cardiovascular disease (2,5). This increase tended to be more prominent in women (2,5). This may be due to the similarity between the metabolic aberrations associated with GH deficiency and Multiple Insulin Resistance Syndrome (MIRS) (4) and is discussed below.

Cardiovascular system

The increased cardiovascular mortality is supported by the findings of increased atherosclerotic plaques in the carotid arteries (6), reduced aortic distensibility (7) and ischaemic-like electrocardiographic ST segment changes on exercise testing in GH deficient (GHD) adults (8). Hypertension is also found to be more common in GHD and hypopituitary adults (9,10), which is in keeping with the premature atherosclerosis found in these patients. GH replacement has resulted in a reduction in the diastolic blood pressure in the GHD adults although no data is available on long term cardiovascular morbidity and mortality to date (4).

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Fibrinogen and plasminogen activator inhibitor-1 (PAI-1), fibrinolytic factors that are also independent atherogenic risk factors for cardiovascular disease, are found to be higher in GHD adults compared with matched healthy controls (11). This observation further supports the atherogenic tendencies in GHD adults. The elevated PAI-1 level decreases after 2 years of GH replacement, but the fibrinogen levels remain high (12).

However, the role of GH in the regulation of cardiac function is not fully defined. Dilated cardiomyopathy is associated with GH deficiency (13). An increase in left ventricular mass, stroke volume and cardiac output, and a reduced peripheral vascular resistance has been documented in GHD adults given GH replacement therapy (13). Interestingly, even GH sufficient adults with idiopathic dilated cardiomyopathy seem to respond positively to GH therapy (14). However, this is yet to be confirmed in a controlled trial to establish GH as an effective therapeutic agent in patients with idiopathic dilated cardiomyopathy.

Body composition

GHD adults have an increased fat mass (FM) and a reduced fat free mass (FFM) compared to healthy subjects matched for age, sex and body mass index (BMI) (15, 16). The increase in waist circumference and waist to hip ratio (WHR) (15, 16) suggests that the increased adiposity found in GHD adults is centrally distributed. This was confirmed independently, using dual energy X-ray absorptiometry (DEXA) (17), and magnetic resonance imaging (16). Importantly, visceral fat is ~ 30 - 35% higher in the GHD adults compared to the controls whereas subcutaneous fat is only ~ 11% higher (16). This visceral fat, which is metabolically more active, may be responsible for the metabolic abnormalities found in both GH deficiency (4) and MIRS (18). This visceral fat is also more prominent in the female GHD adults compared to their male counterparts (16), the significance of which will be discussed in Section VI.

There have been numerous studies documenting the beneficial effect of GH on reducing FM and increasing FFM in GHD adults (4, 19). These changes tend to be GH dose dependent (4, 17). The reduction in whole body FM in GHD adults in GHD adults receiving GH replacement is mainly due to a marked decrease in central or visceral fat in GHD subjects, as determined by change in WHR (17, 20) and DEXA (17, 21). Furthermore, these body compositional changes induced by GH are more pronounced for young, lean male subjects (12, 21, 22), and appear to be more pronounced in subjects with adult onset rather than childhood onset GH deficiency (23). This reduction in central obesity should potentially reduce the increased cardiovascular risk of GH deficiency in adults, especially those with adult onset disease.

Muscle strength

The reduced FFM found in GHD adults results in a mild to moderate reduction in muscle strength concordant with the reduction in muscle mass (19). The increase in FFM induced by GH replacement therapy is more evident in the limbs (4, 21). This corresponds with an increase in quadriceps isometric muscle strength following 12 or more months of treatment (19). Similar improvements are also seen in exercise capacity (19).

Insulin resistance

A. Insulin sensitivity in GH deficiency

Hypopituitary and GHD adults are traditionally thought to be insulin sensitive (24). Most of these early data were derived from animal studies and were supported by the observation of fasting hypoglycaemia in children with GH deficiency which was normalised following GH replacement therapy (25). However when insulin sensitivity was measured by the glucose decay rate obtained during an insulin tolerance test, GHD children were not more insulin sensitive than normal children (26). Subsequently, Bougneres and co-workers (27) demonstrated a diminished hepatic glycogen store in untreated hypopituitary children which might have accounted for the proneness to spontaneous fasting hypoglycaemia in hypopituitary children.

Fasting glucose was not found to be different between hypopituitary GHD adults and matched control subjects (3, 28, 29). Cuneo and co workers noticed a higher fasting insulin level in obese GHD adults, suggestive of insulin resistance in these subjects (3). Furthermore, Beshyah *et al* demonstrated that the prevalence of abnormal glucose tolerance was higher in GHD hypopituitary adults (44%) than in a control group (21%)(28) and was accompanied by insulin resistance in the GHD adults. GH is known to increase insulin secretion directly. Theoretically, it is possible that GH deficiency may reduce the capacity of the β cell to respond to the insulin resistant state and maintain glucose tolerance, as supported by the increased prevalence of abnormal glucose tolerance when glucose tolerance was formally tested (28). However, despite the foregoing discussion, retrospective epidemiological studies have not demonstrated an increased prevalence of diabetes mellitus in GHD adults (9, 10).

Using a variety of measurements, a significant and major reduction in whole body insulin sensitivity was demonstrated in GHD adults (17, 25, 29, 30). It must be noted that the GHD adults in the studies were overweight with mean BMI ranging from 26.4 to 28.5 kg/m^2. It is interesting to note that the insulin resistance was related only to the degree of GH deficiency and not to the number of pituitary hormones that were defi-

cient (25). In a subsequent study, we found that, whilst glucose turnover and partitioning of whole body glucose utilisation into the glycolytic flux (GF) and glucose storage (GS) pathways were normal in GHD adults basally, insulin activation of glucose uptake in the periphery was markedly decreased, and that this insulin resistance was due primarily to a reduction in insulin stimulated exogenous GS (29). This was closely associated with a major defect in the insulin activation of muscle glycogen synthase (GlySyn), the rate limiting enzyme for GS (29). The insulin resistance increased in severity with the duration of GH deficiency and was associated with alterations in fasting TG levels, insulin levels and abdominal obesity, thereby closely resembling the abnormalities seen in MIRS (29). In fact, the degree of reduction in the insulin activated Rd, GS and GlySyn found in GHD adults (29) was similar to that seen in obese and NIDDM subjects (31).

The mechanisms responsible for the peripheral insulin resistance in GHD adults are not entirely clear but a key contributor must be the markedly reduced GlySyn in GHD adults. The increased visceral FM present in GHD adults (16) may serve as a depot for increased FFA flux (18), thereby raising FFA levels which in turn induce insulin resistance. It is probable that an altered Randle-FFA cycle might have contributed to the decreased insulin sensitivity, particularly in the GS pathway (25). Alternatively, there are data to support a direct influence of FFA on cellular membrane structure with possible alterations to insulin receptor binding and in vivo insulin action (25). The latter mechanism would support a hypothesis that the influence of FFA on muscle GlySyn insulin occurs at an earlier step in the insulin signal transduction cadence, such as insulin receptor or kinase activation (20, 25).

IGF-I levels have been shown to reflect basal GH secretion in hypopituitary and normal subjects (32). The observed positive correlation between IGF-I levels and insulin sensitivity in GHD adults (29) suggests that the impaired basal GH secretion may be an aetiological factor in the insulin resistant state, similar to that described for obese subjects (33). In addition, IGF-I levels are closely linked to the duration of GH deficiency and this would support our observation of a significant relationship between the duration of GH deficiency and impaired insulin action (29). Thus, it seems likely that the duration and the severity of GH deficiency are important in the development of the insulin resistant state found in GHD adults (25, 29). Therefore it can be hypothesised that GH deficiency leads to central obesity, which in turn serves as a depot for an increased FFA flux that induces insulin resistance through the Randle cycle of substrate competition.

Despite the profound insulin resistance described above, pancreatic β cell function is found to be impaired (25, 30). This may explain the increased incidence of impaired glucose tolerance in GHD adults (28).

B. The effect of GH replacement

In acromegaly and GH treated children and adults, a decrease in insulin sensitivity has been demonstrated (29). Weaver *et al* (17) reported an increase in both the fasting glucose and insulin levels after 6 months of GH replacement indicating a deterioration in insulin resistance. However, this deterioration in insulin sensitivity is only transient and with longer duration of GH replacement, most studies have demonstrated a return of insulin sensitivity back to the level prior to GH replacement (23, 25). The transient raised level of FFA with GH replacement also implicates FFA in the mechanism of GH-induced insulin resistance, certainly in the short term (25). This occurred despite a significant sustained reduction in abdominal FM. The partitioning of total body glucose disposal into the two major intracellular pathways of glucose metabolism namely, glycolysis and glucose storage, and the activities of glycogen synthase were unchanged by GH replacement therapy (23).

The impact of GH therapy in GH deficiency on b cell function is not entirely clear. The earlier studies in b cell function assessment (17, 25) following GH therapy generally indicate increased insulin responses to oral glucose. This is not unexpected given the persistence or even worsening of the insulin resistance with GH therapy (see above). The net impact of the continuing insulin resistance in these GH treated GHD adults on overall carbohydrate tolerance in the long term is uncertain, although the majority of studies have not found a deterioration of glucose tolerance (25, 34).

In summary, long term GH replacement in GHD adults has resulted in a slight reduction or no change of insulin sensitivity in these subjects despite the favourable effects on body composition, especially the reduction of abdominal obesity. The reason for the persistence of the insulin resistance is not known but may be related to the chronic GH-induced alterations of FFA metabolism.

Lipid abnormality

A. Growth hormone deficiency

GH has been shown to be important for the normal expression of LDL receptors in rat liver (35). Numerous recent studies have documented alterations in serum lipids and lipoproteins in hypopituitary and GHD adults, although no apparent uniformity in the lipid abnormalities has been observed. Hypercholesterolaemia and hypertriglyceridaemia associated with elevated low density lipoprotein (LDL) and reduced high density lipoprotein (HDL) cholesterol levels have been described

(4). De Boer and co-workers (15) also found that both the total and LDL cholesterol levels were higher in those with multiple pituitary hormone deficiency than those with isolated GH deficiency. The subjects with multiple pituitary hormone deficiencies in the study were more GH deficient as assessed by IGF-I and maximum GH response to stimulation tests. Thus, it is probable that GH secretory status and possibly duration of GH deficiency have an impact on total and LDL cholesterol. The inverse relationship demonstrated between IGF-I and LDL cholesterol levels further support this contention (15). It seems that the degree of hypercholesterolaemia found in hypopituitary and GHD adults is mild (9, 15, 28). De Boer and co workers found that only patients with severe GH deficiency have an increased risk of developing clinically relevant hypercholesterolaemia (15). In addition, O'Neal and coworkers showed that in GHD subjects the lipid abnormality is associated with smaller, denser LDL particles (36). Thus the increased cardiovascular mortality found in long standing hypopituitary subjects on conventional replacement therapy (2) is due not only to the altered lipid levels but also to a higher prevalence of small, dense LDL particle (36) which are highly atherogenic.

The lipid abnormalities noted above seem to be more prominent in female than male subjects (9, 28, 36). The similar WHR in the female and male GHD adults (11, 36) indicates a comparative higher central fat distribution in the female GHD adults and would support the observation of a more atherogenic lipid profile in female subjects (9, 28, 36). In addition, a higher prevalence of glucose intolerance (28) and mortality rate (2, 3) were found in the female GHD adults. In NIDDM, females also have a relatively greater excess risk of cardiovascular disease than their male counterparts (37), perhaps reflecting the more adverse effect of glucose intolerance on lipids and lipoproteins, including LDL size in women (38). Importantly, both GH deficiency and NIDDM are characterised by insulin resistance and a similar dyslipidaemic pattern, including small dense LDL particles. Thus, the expected positive effect of female gender and oestrogen supplementation on lipid profiles and cardiovascular risk in female GHD adults is blunted (36).

Obesity, especially abdominal obesity, is associated with increased TG and LDL cholesterol levels, and a reduced HDL cholesterol level in healthy and NIDDM subjects (39). Abdominal obesity is also present in GHD adults and as discussed above may account for a similar lipid profile abnormality in GHD adults. Nevertheless, it is important to note that in pituitary sufficient individuals, small LDL particle size is also associated with insulin resistance (40). A similar association has been also demonstrated in GHD adults (36) which further supports the hypothesis that patients with GH deficiency and MIRS have similar pathophysiology.

B. The effect of GH replacement therapy

A reduction in total and LDL cholesterol levels in GHD adults receiving GH replacement was found in some but not all studies (4). It has been noted that a greater reduction in total and LDL cholesterol was seen in those subjects with higher pretreatment levels (41). A GH dose dependent effect, as seen on body composition changes, was not seen on changes in total and LDL cholesterol levels. Hypertriglyceridaemia, a common abnormality in GHD adults, was not found to be significantly improved by GH replacement, although normalisation of the TG levels in GHD adults with high pre treatment TG levels was observed in one study (42). As expected, the LDL size did not change with GH replacement (21).

Lp(a) was found to be elevated after GH replacement in a time and dose dependent manner (4). This is supported by the high Lp(a) levels found in acromegaly and in normal healthy subject undergoing GH therapy (4). On the other hand, no increase in Lp(a) was demonstrated after 2 months of GH replacement in GHD adults (43). The lack of concordance in the findings of the studies may be due to the fact that the increase in Lp(a) is not found in all the GHD adults undergoing GH replacement, for example 6 out of 21 subjects in one study (41). These data are therefore consistent with the view that Lp(a) response to GH replacement is determined by genetic factors, and thus only 'susceptible' subjects will adversely respond to GH replacement therapy.

In summary, GH replacement in GHD adults results in a decrease in total and LDL cholesterol levels, especially in those individuals with high pretreatment levels. Dramatic improvement in HDL cholesterol levels is less certain. The atherogenic small, dense LDL particle size associated with GHD adults does not appear to be altered by GH replacement. Finally, Lp(a), an independent cardiovascular risk factor, seems to increase in some subjects in a GH dose- and time-dependent manner. It is therefore premature to conclude that GH replacement in GHD adults has a net benefit with respect to the total in vivo lipid profile, and longer term studies of the impact of GH on cardiovascular morbidity and mortality are required in GHD adults.

Bone mass

Reduced bone mass has been documented in adults with GH deficiency, particularly in those with adult onset disease, as supported by epidemiological evidence of an increased fracture rate (19). GH replacement increases bone turnover, but continuous therapy for at least 12 months is needed before an increase in bone mass is observed. The important question is whether

the increased rate of osteoporotic fractures observed in GHD adults can be reduced with GH replacement. So far no such data is available.

Psychological well-being

Decreased psychological well-being has been reported in GHD adults (3, 19). GHD adults have been reported to have less energy, greater emotional lability, more difficulties with sexual relationships, and a greater sense of social isolation (19). In double blind controlled trials, GH replacement was found to improve mood and energy levels. This improvement in psychological well being has now become one of the main indications for GH replacement in GHD adults.

Conclusion

GH deficiency in adults is associated with alterations of body composition, psychological well-being and metabolic disturbances characterised by insulin resistance; dyslipidaemia which includes a decreased HDL cholesterol, increased TG levels and the prevalence of small, dense LDL particles; an increased incidence of carbohydrate intolerance and risk of future ischaemic heart disease, all features of MIRS. The central feature of this syndrome, insulin resistance, was found to be related to both the severity and duration of GH deficiency, and to serum TG levels (29). It is unclear at this point as to why GHD adults display such a close resemblance to patients with MIRS.

Given the protean metabolic effects of GH and the clear relationship between the features of GH deficiency, and duration and severity of GH deficiency, GH replacement therapy should improve the features of GH deficiency in adults. The improvement in lipid parameters in GHD adults is more evident with higher doses of GH, but there is little or no change in other metabolic features. Increasingly, there is a move towards using a lower dose of GH due to a lower side effect profile. Certainly, this lower dose of GH replacement has resulted in a reduction in the metabolically active abdominal fat on the one hand but an increase in Lp(a) on the other. The insulin resistant state found in GHD adults may worsen with GH replacement, even at the lower doses (17, 21). Thus, there may be only a small overall net positive impact on the features of MIRS by GH replacement therapy in GHD adults. However, this does not compromise the subjective and objective improvement in sense of well being and energy perceived by many GHD subjects on GH replacement (3, 19). Nevertheless, the dose and route of administration of GH may confound the true physiologic impact of GH replacement therapy on various metabolic parameters as the GH profile is far from physiological in subcutaneous GH injection as compared to the normal pulsatile GH secretion. Future studies will need to define the appropriate GH dose, optimal duration of therapy, metabolic effect of physiologic pulsatile GH versus subcutaneous GH administration and thus the route of GH administration. More recently, using a much more sensitive assay, it has been demonstrated that far from being absolutely GH deficient, GHD subjects are able to secrete GH at smaller amplitudes (Toogood *et al*, 1998). Thus, GH secretagogue is being investigated to see if these agents can be used to augment the attenuated GH secretion. These agents are certainly more convenient to use as they can be administered orally, unlike GH which like all the peptide hormones has to be given parenterally. Intense research is now underway to assess if these agents can alleviate the features of GH deficiency more physiologically and therefore with less side effects.

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THE ROLE OF NUTRITIONAL SUPPORT IN ACUTE PANCREATITIS: A REVIEW AND PROPOSAL OF A CLINICAL PATHWAY FOR MANAGEMENT

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ABSTRACT: The aim of this review is to critically analyse the available literature and to propose a rational, safe and cost-effective clinical pathway to provide nutritional support in acute pancreatitis. This pathway is proposed based on assessment of peer reviewed literature and existing generally accepted knowledge.

Acute pancreatitis is a heterogeneous disease and the outcome is variable. The role of nutritional support is controversial. Acute mild pancreatitis (80%) usually does not require nutritional support unless the pre-existing nutritional is poor or complications occur. Contrary to this acute severe pancreatitis is associated with severe catabolism and a high complication rate. Nutritional depletion rapidly occurs. It is logical to support the nutrition once the patient is haemodynamically stable. Although enteral nutrition should be administered whenever feasible, it is not always possible or advisable. Aggressive, hypercaloric parenteral nutrition administered via central venous line is not recommended. A combination of initial peripheral parenteral nutrition with fat in appropriate amount, and gradually switching over to enteral feedings is safer and cost-effective. It also avoids central line associated sepsis. The roles of newer specific therapeutic diets to enhance the immune status in patients with acute pancreatitis are not well established. *(JUMMEC 1999; 2: 81-87)*

KEYWORDS: Acute pancreatitis, Enteral nutrition, Parenteral nutrition, Immunonutrition.

Introduction

Acute pancreatitis is a disease that results in autoactivation of pancreatic enzymes, leading to inflammation and autodigestion of the gland, and peripancreatic tissues. It is common in adults and uncommon in children. In adults biliary tract disease, alcoholism and trauma are the common causes (1). In children the causes are more diverse. Congenital anomalies, trauma, viral infections, drugs, and worm infestation are the leading causes (2). The resulting inflammation varies from mild oedema of the pancreas to severe pancreatic necrosis and abscess formation, and may later result in loss of endocrine and exocrine function. In 80% of the cases, the disease is mild and usually resolves)ân a week (3). The presence of organ failure or evidence of pancreatic necrosis on dynamic CT scan differentiates severe pancreatitis (20% of the cases) from mild cases. They have a more protracted course and higher mortality and are more likely to require nutritional support. In 25% of these patients pseudocysts, intestinal and pancreatic fistulas, pancreatic abscesses and pancreatic ascites can occur (1,4,5,6,7).

Metabolic response to pancreatitis

Severe pancreatic inflammation leads to metabolic abnormalities similar to sepsis. Energy expenditure is increased further when infectious complications occur (4, 5, 8). Indirect calorimetric studies have shown an increase in Resting Energy Expenditure. A hypermetabolic state occurs in about 65% of them. In 35% there may be normometabolism and in 10% there may be hypometabolism (3,9,10).

During the hypermetabolic state the energy expenditure and oxygen demand are increased. There is increase in gluconeogenesis. In addition peripheral and hepatic insulin resistance occurs and results in hyperglycaemia. Cataboiism and protein breakdown especially from skeletal muscle raises the concentrations of aromatic amino acids, decreases levels of branched

chain amino acids, and accelerates ureagenesis (3,9,11). Skeletal muscle glutamine level reduces considerably to as low as 15%, and serum glutamine levels may drop to as low as 55% of normal (3,4). Hypocalcaemia and hypomagnesaemia may occur. Ten to 15% may develop hypertriglyceridaemia (1,4). Most hypertriglyceridaemia seen in association with pancreatitis are related to metabolic abnormalities secondary to illness, rather than as a primary causative factor (12).

Why nutritional support ?

The net result in acute severe pancreatitis is marked catabolism, and if not supported leads to, or, aggravates pre-existing malnutrition (4,7,13). In Feller's series 42% of 200 patients developed severe malnutrition and it was regarded as a complication of acute pancreatitis (14). Nutritional depletion may increase the risk of, or may modify the response, to infection and may lead to increased morbidity and mortality.

Review of the literature suggests that there is no level I evidence that nutritional support is beneficial in acute pancreatitis (3,5,12,15,16). Most of the studies are in acute severe pancreatitis, there are few studies comparing TEN with TPN (5, 18,19,20). It is difficult to draw definitive conclusions from these studies because each one uses different criteria to indicate severity (Ranson's or Imrie or Glasgow), and different levels of score in the APACHE II system, varying from >7 to >9 to indicate severity. The study population is also not adequate in each group. It is difficult to demonstrate that a difference is truly present when the study population is small (Type II error). In addition there are no prospective randomized controlled trials (PRCT) comparing TPN vs TEN vs No treatment, or TEN vs no treatment. Although some of the studies have shown improvement in nutritional indices and other parameters (5,7,18,19,20), there is no dramatic effect on outcome. These studies are also inadequate to prove that nutritional support has no benefit at all. However, some evidence in patients with acute pancreatitis (3,6,7,13,14) and other disease processes (Trauma and sepsis) (21) suggests, that failure to achieve adequate nutritional support worsens outcome. It is not logical to starve patients beyond 5 to 7 days, especially, if the pre-existing nutritional status is not good and the disease runs a protracted course. Koretz suggests that one can wait for 10 to 15 days in critically ill patients (22). However, Koretz himself agrees that this long duration of starvation may not be advisable if there is pre-existing malnutrition (23). In general there is no definitive primary therapy for pancreatitis. The treatment is mainly supportive. Nutritional support should be an important component of this overall supportive care. Although its specific role in influencing the outcome is not known at present, use of nutritional support seems reasonable in patients with moderate to severe pancreatitis and especially if the pre-existing nutritional status is poor and the disease is likely to run a protracted course or if complications develop and/or operative measures are indicated.

Both Parenteral and enteral nutrition have been used in patients with complications with limited success (24,25,26,27). Placement of Nasojejunal tube may be difficult or impossible in the presence of pseudocyst or abscess. In addition enteral nutrition should be stopped if pain or ascites increases or pseudocyst increases in size. TPN is safer during this phase (7,24). "Nutrition support for patients with severe pancreatitis may prevent nutrient deficiencies, and preserve lean body mass and functional capacity when nutrient intake falls below needs" (28). The role of nutritional support is not a definitive therapeutic intervention, but is an adjunct to primary therapy, and is an essential component of supportive care in severe and complicated cases (6,7,28,29,30).

Objectives of nutritional support

In general, the objectives of nutritional support in acute severe pancreatitis are:

1) To maintain nitrogen balance or more often to minimise nitrogen imbalance, 2)To support the acute phase inflammatory response till the patient recovers and hypermetabolism resolves, 3) to preserve body functions that are functioning normally, and to facilitate recovery of those that are failing, 4) To prevent specific nutritional deficiencies.

Who needs nutritional support ?

This depends on:

1. pre-existing nutritional status
2. severity of the disease

The pre-existing nutritional status may be good or poor, and the disease may be mild or severe. The severity of the disease is assessed by Ranson's criteria, APACHE II Score and Dynamic CT scan Grade (Balthazar criteria, 31). Based on these two factors, there are three groups of patients (3,4,32):

Group I : Good nutritional status + Mild pancreatitis

Group II : Poor nutritional status + Mild pancreatitis

Group III : Good or Poor nutritional status + Severe pancreatitis

Group I patients without complications usually resolve in 5 to 7 days and do not require total parenteral nutrition (TPN), or total enteral nutrition (TEN) via a tube. Oral diet with less fat is considered safe to start with. However, there is no theoretical or practical support

for less fat. A well balanced, nutritious and balanced diet should be given (11). Too early return to full oral feeding may aggravate symptoms. Feeding should be gradually increased from day 5 to 7 (3,4). Group II and III patients need early nutritional support by parenteral and/or enteral route. In patients with poor nutritional status early nutritional support is safer as studies have shown that in patients with poor nutritional status, the acute phase response is only 40 to 50% of normally nourished patients (13,33).

When to start ?

Once the patient is haemodynamically stable with appropriate supportive therapy (approximately in 5 to 7 day's time), a definitive decision is taken to support the nutrition. The approximate expected length of stay can be assessed by the severity of disease, nutritional status, development of complications, and appropriate supportive therapy is planned. However, there is no place for aggressive nutritional support from day 1 as advocated by some authors (5,21,34).

Route of nutritional support

Until recently, TPN was considered as the gold standard in the management of severe pancreatitis (3,7,34,35,36). The aim being to 'put the gland to rest' (3,4,34,35,36). The major question is how pure is the gold in the standard?

Although bowel rest certainly decreases pain, no clinical trial has proven that it decreases the morbidity or mortality of the disease (4,15,23). The stimulation of the gland depends on the type of feed and the level at which it is delivered through the gastrointestinal tract. Oral normal diet causes maximum stimulation. Jejunal elemental diet causes minimal stimulation. TPN with or without fat produces the least or no stimulation (4,11,34,35,36,37). However, recent studies indicate that during an acute attack of pancreatitis the gland may not respond to any form of stimulation (11).

Currently, the trend is changing in favour of enteral nutrition. Intrajejunal elemental or semielemental diet is preferred whenever feasible. The single most advantage being cost (11,18,19,20,34,35,36,38). TEN may improve the gut barrier function and therefore may reduce bacterial translocation. This may reduce the development of systemic inflammatory response syndrome (SIRS), multisystem organ failure (MOF), and sepsis (39,40,41). However, at present no definitive conclusive evidence is available to show TEN is superior to TPN in preventing development of MOF and sepsis in acute stress states (42). Analysis of two recent PRCT studies claiming that TEN is superior to TPN does not clearly support their claims. Based on scoring system, initial CT score and laboratory findings, Windsor *et al* claimed that compared to parenteral nutrition, enteral nutrition decreases the acute phase inflammatory response and decreases disease severity. This study (20) includes mild to severe cases (only 13 out of 34 were severe cases). The average APACHE II score is higher in patients receiving TPN. In addition the main etiological factors causing pancreatitis is also different in those receiving TPN or TEN. Whether this will have any effect on the outcome has to be studied. The disease also seems severe in TPN treated group (3 out of 7 had surgery). In addition the number of patients with severe disease are small. From this limited study, it is difficult to conclude that administration of TPN adversely modulates the inflammatory response and outcome compared to TEN which favourably modulates it, as other studies have shown no advantage for TEN in critically ill septic patients(42).

Kalfarentzos, et *al* (18) claimed that enteral nutrition is superior to parenteral nutrition in acute severe pancreatitis. The numbers in this study were small. The pancreatitis related complications were higher in the TPN group. From the pathological description, it appears that the pancreatitis itself was more severe in the TPN group, with more cases having pancreatic necrosis. The serial CT grade is not available. The outcome in this study is probably due to the severity of the disease rather than due to TPN.

From these studies it is difficult to conclude that TEN is superior to TPN. However, these studies showed TEN is safe and as effective as TPN. Further prospective multicenter randomized controlled trials (PRCT) in a larger number of patients are needed. Because of the heterogeneous nature of the disease and the patients who develop it, it will be difficult to conduct a satisfactory randomized prospective study. The limitations are: 1) ethical concerns with randomizing patients to a control group without TPN or TEN, 2) heterogeneity of the variables influencing outcome, and 3) difficulty in stratifying patients according to degree of malnutrition, 4) obtaining adequate numbers. However, the evidence is more persuasive that in severe and/or protracted disease, especially in alcoholic patients with an already compromised nutritional status the prompt use of parenteral nutrition may well be crucial for survival, especially if complications occur or operative measures are indicated (12,13,14,30,35,36).

Review of the literature shows both advantages and disadvantages for TPN and TEN (6,7,12,15,35,43) (Table 1 & 2). Availability, cost, and expertise of the team will also influence the route of delivery. The cost of TEN is less compared to TPN. It is only marginally less in some series, if all the cost factors are taken into consideration. In one series the approximate cost of administering nasojejunal elemental feedings (US $ 1200 per week) is only minimally less than the cost of central

TPN (US $1400 per week). The cost estimates include professional fees for line placement, cost for diet delivery and expense of nutritional assessment and monitoring (3). In another study the cost for nasojejunal tube placement is US $600, and the cost of Central line placement is US $500 (44). The minimally higher cost of TPN is therefore not a viable argument against its use.

What type of parenteral nutrition products to be given and by what route?

In general central venous "aggressive" nutritional support with fat is commonly practised. The risk of sepsis is greater with central venous administration. Studies have shown that aggressive hypercaloric nutrition is not utilised well by critically ill patients, and may be harmful (45). Recently, the degree of hypermetabolism in critically ill adult and paediatric patients has been modified downward (45,46,47,48,49,50). Indirect calorimetric studies have confirmed that the previous estimated requirement (3000-4000 calories/24hour) was very high and actual measured resting energy expenditure is around 1400 calories/day in adults. The current recommendations for critically ill patients are: Total calories 25 kilocalories/kg/day. Water requirement : about 1mL of water per kilocalories administered is sufficient. 30 to 70% of the calories can be provided as glucose and 15 to 30% of total calories as fat. Protein should form 15 to 20% of the total calories. Approximately 1.2 to 1.5gm protein is sufficient at the start and may be increased to 2.0gm per kilogram if there is SIRS. BUN, blood sugar and serum triglycerides should be monitored (51).

What type of jejunal feeds to be used - semielemental or elemental ?

Though elemental feeds are believed to be absorbed better and pancreatic stimulation is probably less when compared to semi-elemental formulas, studies show semi-elemental feeds with low-fat are better utilised, and absorbed well, and the effect on pancreatic stimulation, is probably only marginal without any adverse effect on outcome (11,15,38,39). In addition, it costs less than elemental diet and is more easily available.

TPN or TEN ?

The question is not whether TPN is superior to TEN. Although the cost of enteral nutrition is relatively less, one may have to use both in the same patient due to the severity of the disease. Judicious use of both TPN and TEN is recommended, as this will avoid wastage of nutrients, and is more cost-effective. The advantages and disadvantages of both parenteral and enteral nutrition should be considered carefully in each patient (32).

Table I. Advantages and disadvantages of TPN

Advantages
1. Rapid ability to achieve goal calories
2. Relative ease of gaining accesses to peripheral or central venous route.
3. Lack of pancreatic stimulation
4. Avoidance of the proximal gut, which may be relatively obstructed by inflammatory mass or ileus.
Disadvantages
1. High cost
2. Failure to use the gut may be harmful
3. May exaggerate the stress response to pancreatitis
4. Increased incidence of line sepsis ?
5. Technical complications of central venous access
6. Increased frequency of hyperglycemia
7. Caution: Use of lipids - if there is hypertriglyceridemia

Table II. Advantages and disadvantages of TEN

Advantages
1. Minimal or insignificant stimulation of pancreas may not be harmful
2. Cost is less one third to one-fourth of TPN (marginal in some series)
3. May improve gut barrier function, improves mucosal nutrition, reduces bacterial translocation and may reduce SIRS, MOF and sepsis
Disadvantages
1. Placement of Naso Jejunal tube endoscopically or by fluoroscopy in a conscious, sedated critically ill patient is needed.
2. Not always successful.
3. Risk of aspiration in a patient who is not intubated
4. Proximal dislodgement of the tube may aggravate pancreatitis
5. Advancement to goal calories takes time.
6. If not tolerated, wastage of feeds is possible.

Based on this a practical clinical pathway for nutritional support is proposed. Although this pathway is proposed for acute pancreatitis, it is applicable to all critically ill patients.

Clinical pathway for management

With the present state of knowledge from the literature a Nutritional Support clinical pathway for acute pancreatitis is shown in Figures 1 and 2. The aims are to provide a rational approach to the patient with acute pancreatitis that is cost–effective and safe.

a) In Group II patients with mild pancreatitis, nutritional support is started from day 3 to 5 after carefully assessing the disease status and the need.

b) In severe pancreatitis with or without complications, starting parenteral nutrition with fat by peripheral route by 5 to 7 days is safer during the acute phase. The patient's progress is assessed frequently. After a period of 5 to 7 days a decision is made on whether to continue TPN or start TEN or to use both. If the patient is stable switching over to Jejunal feeds appears more appropriate and cost-effective (32).

When TPN or TEN is used, insulin supplementation may be needed. Hypertriglyceridaemia can occur and serum triglyceride levels should be monitored. If surgery is performed nasojejunal tube positioning is easier. In children, transpyloric jejunal placement, which is more secure and safer is preferred to surgical jejunostomy or needle-catheter jejunostomy (52,53,54). In adults complications have been reported in up to 25% with surgical or percutaneous jejunostomy procedures (39).

Though sepsis due to central line infection has been reported to be high with TPN patients, recent PRCT did not show any significant difference (55). In addition, catheter infection rate is high with triple lumen central lines (56). However, the overall incidence of sepsis is higher in acute pancreatitis, and it is believed to be due to neutrophil dysfunction and decreased phagocytosis by hepatic Kupffer cells (57,58). Peripheral parenteral nutrition with fat is a safe alternative, cost-effective and avoids central line associated sepsis.

In children pancreatitis is usually secondary to trauma, drugs (cytotoxics), viral infection or worm infestation. The severe cases are started on peripheral parenteral nutrition for 5 to 7 days followed by nasoduodenal or naso-jejunal semielemental or elemental diet for a week and gradually weaned off to oral feeds (2,52,53,54). If complications occur, either TPN or TEN as appropriate is provided for a longer time.

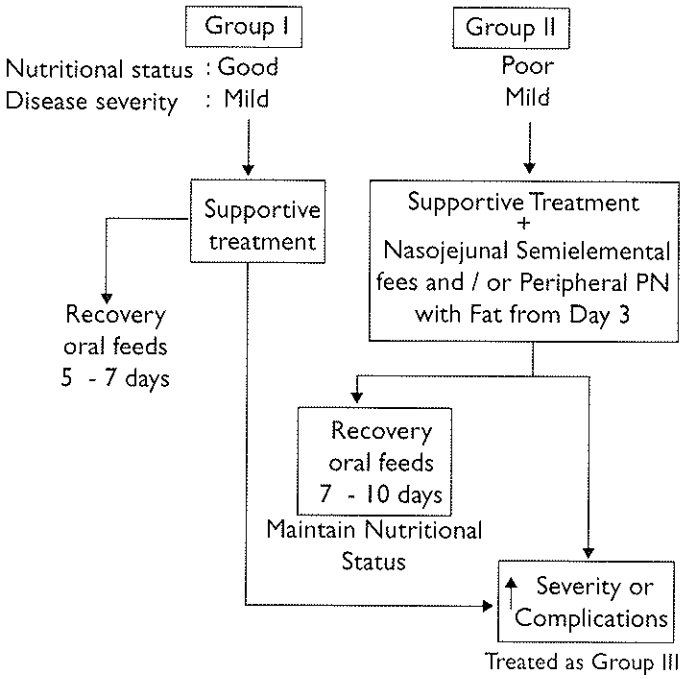

Fig 1. Clinical pathway for a practical approach to nutritional support in mild acute pancreatitis based on nutritional status and disease severity

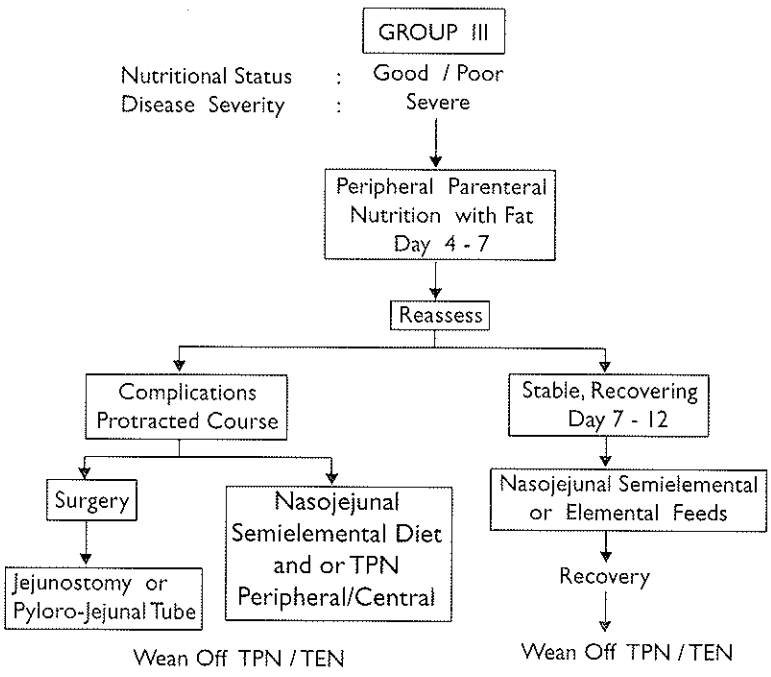

Fig 2. Clinical pathway for a practical approach to nutritional support in severe acute pancreatitis

Future trends

In future, substrate specific nutritional needs of the gut, liver and immune system, which act at cellular level, may be used to improve the outcome. Supplements like glutamine, branched chain amino acids, omega-3 fatty acids, dietary RNA (Immunonutrition) and modified structured lipids have been tried, but studies conducted so far have not substantiated any advantages of such substitutes (3,4,11, 59,60,61). The major questions in feeding the critically ill patients that still remain unanswered are:

1. How to feed the sick cell during acute stress? In

other words, how to supply what will be utilised by the sick cell?

2. Whether supply of nutrients improves the function of the sick cell or is it a recovering sick cell that is utilising the supplied nutrients more appropriately?

3. Whether nutrients have specific therapeutic value or are given for nutritive value?

Until these questions are answered specifically the place of nutritional support in acute severe stress states like sepsis or pancreatitis will remain controversial.

To obtain the real answer further strictly controlled multicenter prospective randomized trials are needed. This includes age range, type of center, hospitals with comparable facilities and patient care, using the same criteria, types of nutrient products supplied, etc. Age range is important because still we do not know whether the immune and metabolic response to acute stress is similar in a healthy 30-year-old and a 60-year-old patient. Are they comparable? In addition a study conducted in a Veterans hospital is not comparable to a study conducted in Mayo clinic and this is even less applicable to a hospital in Malaysia. We have to conduct our own PRCT, with adequate number of patients before any definitive conclusions can be arrived at for local patients.

Conclusion

Critical analysis of the literature shows that nutritional support in acute pancreatitis is essentially part of the overall supportive management and not a form of primary therapy. The question is not "how to feed the gland which is eating itself?", but to know "how to feed the whole organism safely?". At present initial peripheral parenteral nutrition and subsequent enteral feeding will be a safe, cost-effective, and practical approach when nutritional support is needed in acute pancreatitis.

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MEDICO-LEGAL RESPONSIBILITIES OF THE MALAYSIAN MEDICAL GRADUATE AND THE TEACHING OF UNDER-GRADUATE FORENSIC MEDICINE

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ABSTRACT: The requirement of the medical graduate, tabled in the objectives of undergraduate medical education, as envisaged by the Malaysian Medical Council, call for the all round basic doctor to be able to handle any medical emergency, as well as meet the requirements of law in examining, documenting and reporting on the common offences of the Penal Code, where medical documentation is required of law for the purposes of dispensing justice. However, in tabling the amended requirements of the undergraduate syllabus on the lines of those followed in some of the more developed nations, we seem to have lost this perspective. The authors discuss, based on his previous experience from another former colonial country viz. India, where the objectives of the undergraduate training is the same, and the influences on the legal profession bear a common origin and governance, the relevance of some of these topics, coming under the ambit of Forensic Medicine and Toxicology as an undergraduate subject, in the day-to-day practise of medicine in and out of government service. While this issue has been the frequent topic of discussion in international conferences and symposia, where the decline in the standards of medico-legal work in the countries attending have been blamed on the fall in the standard of undergraduate teaching, due recognition of the pitfalls of the deletion or whittling down of the course content, independent of the overall overhauling of the syllabi of medical schools, to keep up to the trends of overseas universities, has not been accorded in the planing of the course revisions, resulting in a deletion of a vital aspect of daily practise of medicine. *(JUMMEC 1999; 2: 88-93)*

KEYWORDS: Medico-legal; Undergraduates

Introduction

The word Forensic derives from the practise of the ancient Greeks in bringing all disputes, including those involving the infliction of injuries and the apportioning of blame and/or compensation in the "forum" before the assembled publicans and elders - civic and legal matters by those with public responsibility- for adjudication. In Latin the word forensis means "of the forum" and therefore the practise of medicine in this regard came by the term Forensic Medicine. Historically, Forensic Medicine was earlier known as Medical Jurisprudence, and in certain cases also as State Medicine. In some countries, it is today known as Legal Medicine.

The forensic aspects of medicine has always held a position of importance since the ancient times and there are many codifications to guide the practitioners of medicine as to the opinions that are expected of them in these judicatory proceedings. Manu, the first traditional king and law-giver of India, codified legal and medico-legal matters in his "Manu-Smriti"(3102 B.C.) and defined the offences, findings and punishments for various offences such as adultery, carnal knowledge with force or upon an unwilling maiden, unnatural offences, mental incapacitation due to intoxication/illness/age and unfitness to make a contract, etc (1). The "Vedas", the sacred literature of India, were written between 3000 B.C. and 1000 B.C., of which the "Rig Veda" mentions prohibition of relations of marriage and of incest, illegitimacy, etc. while the other Vedas mention crimes and their determination of - incest, adultery, abduction, infanticide and foeticide, murder, drunkenness, and their

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punishments, as well as the diagnosis of various forms of poisoning and their management were also prescribed.

In ancient Egypt, legal provision for punishing improper treatment of patients and causing their deaths, as well as sexual perversions, diagnosis of poisoning, etc. were prescribed, as described in the works of Homer, Herodotus, and Diodorus; while Imhotep (3000 B.C.), grand Vizir, Chief Justice and Physician to king Zoser of Egypt is considered as the first medico-legal expert for combining the science of medicine and law.

The first legal code of Babylon written by the King "Hammurabi" in 2200 BC prescribed punishments as well as civil and criminal liabilities of physicians, and the determination by examination of adultery, rape, incest and violent deaths. Hippocrates' (460-355 BC) role in the ethical aspect of medical practise cannot be forgotten, while Aristotle (384-322 BC) fixed the animation of the foetus at 40 days, and advocated abortion as a means of population control. The "Lex Aquilla" (572 BC) deals with lethality of wounds and their gravity, The murdered body of Julius Caesar (100-44 BC) was examined by a physician, Antistius, who opined that of the 23 wounds, only one of them was fatal; while Pliny the elder (23-79 AD) wrote describing the recognition and medico-legal importance of conditions such as superfoetation, suspended animation, sudden natural death, suicide, signs of maturity of a foetus and age of menopause, amongst others.

Shushruta (200-300 AD), the father of Indian surgery, in his "Shushruta Samhita" wrote unique chapters on duties and responsibilities of physicians, injuries, diagnosis of poisoning and poisoners, the treatment of poisoning, pregnancy and delivery, types of weapons and the diagnosis of the injuries and sequellae, etc.

The "Justian Code" of Emperor Justinian (AD 483-565), besides describing many of the medico-legal issues, instructed that "physicians are not ordinary witnesses" but that they give 'judgement' rather than 'testimony', thus creating the role of the medical man as an impartial "Expert Witness", thus being the earliest European Code on Forensic matters. Charlemagne (AD 742-814) brought about uniformity in the law practised in all his empire captured by his Germanic tribes, and instructed the judges to seek medical opinion when trying cases of wounding, infanticide, suicide, rape, bestiality, etc.

In 1250, "Hsi Yaun Lu" in China or "Instructions to coroners" gave detailed instructions to coroners relating to establishing the event of various medico-legal causes by examination of the corpse, etc. as well as instructing them on all medico-legal matters including the matter of inquests in such cases.

In France, the trend was laid by the 12th century bishops of Maine and Anjou who are said to have regular medical experts in their employment for forensic cases, while the Pope gave the faculty of Montpellier the right of autopsy in 1934, from where we have the works of two noted medical jurists, Brouardel and Tardieu.

While a systematised law code on providing medical evidence in violent deaths was prepared in Maine, Germany, in 1507, it was the Criminalis Carolona of Charles V in 1532 which established all over Europe especially over his empire, the importance of medical evidence in substantiating these issues, and allowed the opening of bodies for the same, making them mandatory. The medical profession suddenly started taking a keen interest in these matters, organising discussions, and writing monographs on these subjects. During the 17th it became a separate subject for special instruction, and by the 18th century, chairs were created in German Universities for Legal Medicine; Liepzig University being the first to establish a chair for it in 1720. Subsequently the French followed suit, with chairs in Forensic Medicine in Paris, Strasbourg and Montpellier in 1790, and a full professorship in Legal Medicine in Vienna in 1804.

In Great Britain, the first chair in Forensic Medicine was established by 1807 at Edinburgh, while Glasgow had the chair at its University in 1839. London had its first professor of Medical Jurisprudence by 1834. Currently there are Crown Office Pathologists in each district, as well as Forensic Pathologists, who take care of the medico-legal post-mortems, while the living cases of assault and battery, rape and other sexual offences, intoxication cases including 'drunken-driving', etc. are catered to by the Police Surgeon, who is a specialist in Clinical Forensic Medicine. Subsequently these experts of Forensic Medicine attend courts and inquests, and also appear in litigations as expert witnesses, either for the prosecution or the defence.

In America, the Coroner (a person, usually a lawyer with some experience in medical matters, appointed to investigate deaths, whether suspicious, or of sudden but natural origin, so as to ascertain or rule out the role of any other person in the death) was replaced by the Medical Examiner system; the Medical Examiner, being an Expert in Forensic Medicine, who has under his office, the complete crime team, including Forensic Chemistry, Toxicology, Ballistics, Fingerprints, and other allied departments, so that when his department gave a report at the end of the investigation, he was, - being well versed in Forensic Medicine, as well reasonably well versed in the other branches of Forensic Science, able to sum up and give a complete picture of the death or injury, how caused, by whom, in what manner, and also recommend, based on his skill and knowledge, where the police or other investigation agencies should go from there.

Thus the medical profession has, throughout the world, recognised the importance of Forensic medicine, or Legal Medicine, or Medical Jurisprudence, depending on which state or country one is in, and emphasised its teaching through the years to medical students through the centuries, so that, crimes do not go unreported, or un-investigated, because of the ignorance of the medical practitioner, called upon to either treat the patient, or to certify his/her death. That is precisely what any criminal would want, and has aimed for in the past, in using poisons such as arsenic (which in its symptoms mimics cholera) or strychnine (which mimics epilepsy or tetanus in its symptoms), or even thallium (which has a whole host of disease-presentations that it may mimic) to poison people, and to get death certificates of some natural disease, averting suspicion from themselves.

Legal expectations from the medical graduate

Any medical graduate, is required to provisionally register, to undergo the necessary training, so as to have his/her name entered in the register of medical practitioners within the country, as required by the Medical Act 1971. For this purpose, he/she has to first apply to the registrar, Malaysian Medical Council, to be provisionally registered, for the sole purpose of obtaining the experience required for full registration (2); provided that he/she has a recognised M.B.B.S. or equivalent degree, as listed in the Second schedule, or the degree in medicine and surgery is deemed suitable for registration by the minister after consultation with the Medical Council, after the candidate passes a prescribed test for this purpose - along with evidence that he/she has been selected for employment in an approved hospital or institution in Malaysia for a period of not less than one year, in medicine and surgery in a resident posting (3). After the provisional registration, on the satisfactory completion of this resident medical posting, he/she would be awarded a certificate to this effect (an applicant having qualifications other than those in the schedule, and applying for registration after the approval of the Minister and after clearing the prescribed qualifying test, would have to continue in service in a medical resident capacity, to the satisfaction of the Director General for a further period of not less than two years in such post/s as directed to serve at the latter's discretion (unless the Council, on the basis of the applicant's further qualifications, feel that that the person has the experience which is not less in scope and character that that prescribed (2), when they may exempt the applicant from the further 2 years of service (4)), after the satisfactory completion of which, he/she will again be entitled to a certificate to this effect (2).

Only a person who has satisfactorily completed the requirements as mentioned in the previous paragraph, by being provisionally registered and having served in a resident medical capacity, can apply to be fully registered as a medical practitioner in Malaysia (5). During this period of service, he would been deemed to have been fully registered under the Act, so as to undertake employment and service successfully (6), and shall be considered as a public servant within the meaning of the Penal Code (7), thus requiring to carry out all the duties and bear all the responsibilities incumbent upon such a person. Only fully qualified practitioners are entitled to carry on the practise of the speciality they are registered as qualified in, or to charge or recover through any court of law, reasonable fees for his services, or visitations, etc (8), provided he/she has a valid annual practising certificate at that time, and is the only one whose signature on a certificate or document required by any written law is considered to be valid (9). Wherever the word "legally qualified medical practitioner" or "duly qualified medical practitioner" features in any testimony or statement, it is understood that it connotes a fully registered medical practitioner, for this purpose (2).

Thus the medical graduate, immediately on clearing his final examination and the compulsory rotatory internship, has to serve the government as a government medical officer, for a period of one to three years, depending on his basic qualification.

The Criminal Procedure Code (F.M.S. 6) spells out that when a police officer is investigating a death of a person who committed suicide, or was killed by another person or animal, machinery or by accident, or died in suspicious circumstances suggesting that another may have committed an offence, or died a sudden death or was unexpectedly found dead (11), then the police officer at once informs the nearest Government Medical Officer, and, unless it is necessary for the magistrate who would later conduct the inquest, to come and view the body in situ, take or send the body to the nearest Government hospital or other convenient place for holding a post-mortem examination of the body by a Government Medical Officer (12). It now becomes the duty of the Government Medical Officer to make a post-mortem examination of the body as soon as possible, and extend the examination to dissection of the body and analysis of any portion where required, to arrive at the cause of death (13). The Government Medical Officer is required to draw up the report on the appearance of the body and conclusions therefrom, and issue a certificate of the cause of death, sign and date it and transmit it to the officer in charge of the police district (14), where the "cause of death" denotes not only the apparent cause of death - ascertained by inspection or post-mortem examination of the dead body, but also all matters necessary to enable an opinion to be formed as to the manner in which the de-

ceased came by his death, and also whether his death was the result of, or was hastened by the unlawful act or omission of any other person (15).

The Penal Code recognises that injury (16) to mind or body (also legally defined as hurt (17)) carries a grave implication when grievous (18), as compared to the infliction of just (simple) hurt, with the offences (19) of grievous hurt carrying a much enhanced punishment; besides being 'seizable offence' (20), which allows the police officer or the Penghulu to arrest without a warrant of arrest. Besides, if the injury, whether simple or grievous, were to be inflicted by a 'dangerous weapon', then not only is the punishment enhanced, but in this case, even infliction of a simple hurt (i.e. that which is not in the eight categories of grievous hurt) would be considered to be a siezable offence. Sometimes, the clinching of the evidence in a court of law in an alleged case of attempt to murder (21) or attempt to commit culpable homicide (22) requires proper documentation of the injuries and the opinion on the weapon- as to whether the latter could have inflicted these injuries on the injured (the same question has also to be addressed in an alleged case of murder, when the weapon is produced before the doctor during or after the autopsy).

These then are some of the situations that the law has to take recourse to early and prompt, detailed expert reports from the medical men to further prosecute in these cases.

Besides these, there are even graver offences where the proper knowledge of the subject of Forensic Medicine is required for the recognition and proper documentation of offences such as rape (23) and other unnatural offences (24), where the awareness of the precautions in the collection and preservation of evidence as well as proper documentation, as well as taking adequate precautions during the course of examination, in a medico-legal sense makes or breaks the case for the prosecution even if she was a genuine victim of rape or he/she - a true victim of an unnatural offence. During the course of examinations of these and other Clinical Forensic Medicine cases, one soon learns to differentiate cases of malingering from the cases of genuine assault, or battery or violence cases, including torture, domestic violence and child abuse.

Recognition of poisoning is another domain, especially linked to Forensic Medicine, where the timely recognition of the case to be a typical case of poisoning, initiates appropriate tests in this direction, such that many a homicidal poisoner has put behind bars due to the diligence of the Forensic Pathologist in the not too distant past. In certain cases, an accused of a crime may take the plea that due to the fact that he was intoxicated, either with alcohol or with some unwholesome substance - he was not able to understand the nature and consequences of the act or omission to be wrong or contrary to law (25), and the intoxicating substance had been administered to him without his consent or knowledge or was rendered temporarily, or otherwise, insane, from the intoxication. Of course, the law would consider our medical expert's opinion on these effects, firstly - whether it can be agreed that he was intoxicated at the time of the alleged offence, and that it would have lead to his loss of reasonableness, or resulted in a state of insanity, whether temporary, or otherwise; as well as whether, if the above has been established with the help of medical and other evidence.

Where intoxication is established, and the law requires him/her to form an intention to commit the crime, the ability to form such an intent in the midst of the alleged intoxication will be taken into account, so tha tif he could not, it would not, therefore make it the offence described (26).

Then there is the offence of attempting to cause hurt by administering a poison with intent to commit an offence (27), which again requires that the poisoning be diagnosed by the doctor.

This interest in Toxicology has developed, in many countries, into a healthy interest in the antidotal management of poisoning, amongst the Forensic Experts, as well as the undergraduate teaching of this vital discipline in the Speciality, in most of the Asian colonial medical schools. In India, many medical colleges have their Forensic departments named as "Department of Forensic Medicine & Toxicology" and the undergraduate students are tested on not only many of the above mentioned subjects after somewhat extensive teaching and training (since the objectives are the same i.e. that any graduate doctor, or registered medical practitioner, as defined in the Code of Criminal Procedure 1973 (of India), can be asked, if recognised by the State government for this purpose [i.e. to conduct autopsies], to do a post-mortem examination of a dead body (28) in similar circumstances as in Malaysia), but is also given a reasonable grounding of Medical Ethics, and the law relating to medical men, etc. as part of this discipline. Members of this speciality are often called to be part of the ethical committee in their institutions, since they are daily imparting to the undergraduates the ethical aspect of practise vis-à-vis the law.

Besides, there are a host of offences, such as negligently doing an act likely to spread infection of any disease dangerous to life (29), or the offence of molestation, or outraging the modesty of a person by using criminal force (30) which would require the documentation of the injuries inflicted, and the expert opinion that these are likely as a result of assault or force and the type of weapon used in this case, and if a weapon is recovered in the case, whether it could have caused the injuries noted on the injured; or in the case of the former of-

fence of spread of infection, that such an act would ordinarily spread the potentially dangerous infection and that it is a known dangerous infection spread by this mode, are opinion required of medical men.

In the west, the pathological component of medical duties are fulfilled by specialists trained in Forensic Medicine, who, as Medical Examiners in the United States, and Crown Office Pathologists or Forensic Pathologists in the United Kingdom, who, possessing postgraduate qualifications in these spheres, are recruited only to serve this function, and are available in every district, so that there is no requirement of the average registered medical practitioner (as in India) or the Government Medical Officer (as in Malaysia) to be required to do this exacting and responsible legal duty in both these countries. Thus, Forensic Medicine has, by and large, been removed from the extent it is still taught, for instance, in India, from the undergraduate curriculum.

In India, to encourage some of the best of manpower, both in the form of experts as well as technical staff to take up this speciality, some state governments such as the state of Kerala have passed orders (31), assigning additional designations to those of the assigned teaching/non-teaching posts of the trained and specialised Medical staff - viz. Police Surgeons, and assigned additional official perks (proportionate to Heads of Dept's viz. Official vehicle and residence, etc.) as well as declare additional emoluments as honorarium for each Medico-legal examinations done, including postmortems, to be proportionately divided as gazetted, amongst all the staff/ doctors involved in the case and its reporting. The source for the funds would be the Ministry of Home (since the medico-legal duties, being a duty/function undertaken for the home department-through the respective Director-General of Police's office- the department indenting for this service). This model is now being emulated in many of the other states in India.

In Malaysia, the requirement for the medical graduate, working as a Government Medical Officer, is to be well versed in the medico-legal situations and problems encountered in his day-to day practise of Government service and their solutions, which also extend to the diagnosis and management of poisoning and its proving, if discovered as a cause of death. He may also be called upon to examine and report on many other situations such as the juvenile offenders and instances of injuries to the 'Protector' of custody cases (32), as well as immigrants brought for examination to establish that they are not harbouring any communicable or infectious disease, under the Immigration Act.

However, due to the designing of the undergraduate syllabus on the pattern of western undergraduate syllabi, this aspect of undergraduate teaching is accorded least priority, and in fact faces the first onslaught in the deletion of teaching man-hours, so that not even the bare essence of Forensic Medicine, Ethics or Toxicology is being taught, so that there is no question of further creating awareness of the clinical aspects of Forensic Medicine.

While the courts have till date been lenient in the service offered by our Forensic Examinations before it, the increasing number of acquittals before it may turn the tide, bringing the preparedness of our so-called Forensic examinations to be judged, and at times found wanting, from our country's medical service function. That such a step is unheard of is an erroneous, as evidenced in India, in the state of Gujarat, where the Hon'ble High Court of Gujarat, responding to a criminal appeal (33), issued guidelines to the Gujarat State Government which became the subsequent instructions in the circular issued by the State Government, addressed to all Deans and Directors of Medical institutions and Medical Colleges and the Registrars of the Universities (34). To summarise briefly, it instructed all medical officers to themselves record the history as it is, as told by the patient, or his near and dear one accompanying him/ her, as well as record his/her dying declaration of the course of events that lead to these injuries in their vernacular, while additionally noting the exact time and date, and the compos mentis of the patient when he is giving this history, himself. These should be taught to the undergraduate student during his training - that it is the duty of the doctor treating to take down these. The Deans/ Directors and Registrars of Universities were, in addition, instructed to be seized of the fact that Forensic Medicine in India, is taught in the Second Professional, i.e. by middle of fourth year of their M.B.B.S. (a five year course excluding internship), they have cleared this subject, and therefore hardly any practical training was imparted to them. Therefore they should have at least a two weeks posting in Forensic Medicine during their internship, so that they acquire these vital skills at "jurisprudential work". They also asked that the same course be held in a phased manner as a refresher course, at regular intervals, by the Deans of Medical Colleges, in consultation with concerned Additional Directors and Commissioners of Health, Medical Services and Medical Education, to cover all medical officers serving, from time to time.

This is a laudable judgement for the teaching and training of Forensic Medicine, since Gujarat is a state where Medico-legal practise is of a high standard; where state recognised Medical Jurists (who are trained experts of Forensic Medicine) are allowed to have private consultations and who write medico-legal examination reports privately, for a fee charged, which the courts accept on an equal footage as that made by any Government Medi-

cal Officer sitting at his official desk; and yet the courts responded to the felt need that in the particular case as well as others before it, the standards of Medical Jurisprudence were declining, and the educators need to rectify this.

Before such a legal step is initiated, to the detriment of the teaching institution concerned, and the creating of doubt as to the standards of technical training and meeting the goals required in the training of the students, some thought as to how to rectify this needs to be accorded priority, so that our students are adequately prepared for their responsibilities currently thrust upon them. An amendment in the situation as it is, can only come about when, like in the West, every district has its trained Medico-legal Jurist/ Forensic Medicine expert or a combination of a Forensic Pathologist and a Police Surgeon posted in each district of each state.

Conclusion

The curriculum of Forensic Medicine should have, besides proper orientation of the student towards recognising cases of foul play, and the various forms of suspicious or unnatural deaths, and a reasonable idea of how to go about proving them through a post-mortem examination, or clinical examination and reporting; an initiation of the processes of law they would be dealing with in their day-to-day existence, and the role of medical men in various situations where the law calls on them to assist it; or to recognise in time- poisons and poisoning and their management; various ethical aspects of practise and malpractice suits arising out of their (medical) duties/practise, - their defence against them; as well as their role in a trial, the norms in evidence giving /taking in any investigation or trial, and an overview of the legal system they will be part of, to name a few. Some hands-on experience towards making of a medico-legal report of a living- injured patient or a post-mortem examination should also be envisaged, so that in the long run, the graduate does not suffer when called upon to undertake these duties when assigned to him, from inadequate training.

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PROBLEM-BASED LEARNING (PBL): MAKING AN IMPACT IN EDUCATION

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ABSTRACT: Problem-based learning (PBL) is an educational reform that is now becoming a household word in higher education, particularly in medical schools. Many medical schools have implemented a full problem-based learning curriculum (PBLC) while some have included PBL into selected units of the course in an otherwise conventional curriculum (embedded PBL) and others run their tutorials in a PBL manner within a modified conventional curriculum (hybrid curriculum). Yet there are others who claim that small components of PBL in a conventional curriculum are not PBL at all. Thus amateurs in the subject matter find difficulty in evaluating the logistics and outcome of these variations. This article focuses on the general characteristics of PBL and how this learning method can help enhance independent learning and critical thinking, whether in a full, embedded or hybrid curriculum. The extent of PBL to be included and which of the three types is to be adopted depends on the objective of the undergraduate medical course as determined by the faculty, resources available, limitations, feedback on the existing curriculum and various other factors. *(JUMMEC 1999; 2: 94-98)*

KEYWORDS: Problem-based Learning (PBL); Embedded PBL; Hybrid PBL; New Integrated Curriculum (NIC).

Introduction

Medical education has evolved mainly through the need to produce trained doctors in the scene of a rapidly developing science and technology, and rapid changes in the disease spectrum. The future doctors will be exposed to massive information and will be applying skills unforeseen at present. In order to cope with the information overload, educational institutions strive to educate doctors capable of adapting to change, new ideas and development, and possessing the attitude of continuing medical education throughout their professional life. The problem-based learning approach has been advocated by many educationists as one of the processes that can help accomplish this task. The Problem-Based Learning Curriculum (PBLC) in medical education was first implemented in the McMaster University School of Medicine, Ontario, Canada in 1969. Since then various medical institutions have implemented the PBL curriculum. These include Harvard University, University of New Mexico, University of Southern Illinois and Michigan State University in USA, University of Sherbrooke in Canada, and University of Newcastle in Australia. There are however many institutions that include PBL as complementary components in certain aspects of the course or parts of their course (1,2).

Recently, universities in our region such as National University of Singapore, University of Hong Kong and Universiti Malaysia Sarawak (UNIMAS), started a similar concept in medical education. Universiti Sains Malaysia (USM) introduced PBL from the second year onwards, in an integrated curriculum (3) while Universiti Kebangsaan (UKM) introduced small PBL components into an otherwise conventional medical curriculum (4). In the 1st Asia Pacific Conference on PBL held in Hong Kong in December 1999, more than 230 participants worldwide met to present their papers on various aspects of PBL in a variety of courses. Although most papers referred to the medical course, others included pharmacy, nursing, economics and business studies, education and science. The Medical Faculty of the University of Malaya is taking several steps in the process of introducing PBL style tutorials or components into the New Integrated Curriculum (NIC) that was first implemented in 1998.

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The new integrated curriculum (NIC)

The undergraduate medical programme at the Faculty of Medicine, University of Malaya, Kuala Lumpur, enrolled its first batch of students in 1963. Since then several reviews and improvements have been carried out on the medical curriculum (5, 6). The most recent curriculum planning was done based on the twelve reforms of the Edinburgh Declaration, reiterated at the World Summit on Medical Education held in Edinburgh in 1993 (7). These include relevant educational settings, a curriculum based on healthcare needs, emphasis on disease prevention and health promotion, lifelong active learning, competency-based learning, teachers trained as educators, integration of science with clinical practice, multi-professional training and continuing medical education. Therefore the NIC was planned with the additional objectives of producing graduates with better attitude, communication and leadership skills, and to develop interest in continuing education and medical research (6).

The NIC is made up of three major strands that span through a 5-year programme. The strand on the Scientific Basis of Medicine forms the core knowledge, with the additional strands of Personal and Professional Development (PPD), and Doctor, Patient, Health and Society (DPHS) introduced to achieve the additional objectives. Phase I takes up just over a year, Phase II consists of 1. 5 years and Phase III is covered in 2. 5 years. The lectures in the Phase I and Phase II programmes were synchronized within most systems in the scientific basis strand. The PPD strand is made up of a week of nursing practice, 2 weeks of electives, and lectures or seminars in the Attitude, Character and Ethics (ACE) programme and the Management programme. The DPHS strand consists of some core lectures and a Community and Family Case Studies (CFCS) programme, where a patient is allocated to two students to be followed through the 5 years. More patient-oriented and other self-directed learning packages were introduced as a complementary strategy to promote active learning, and the mode of assessment modified. The also course contains some problem-based learning (PBL) components. The cases selected for the PBL tutorial component in the present Phase II attempts to integrate aspects of all the three strands in patient care. The consideration for the inclusion of PBL was more focused on the first and second year of the programme as it was considered more didactic than the clinical years.

What is problem-based learning (PBL)?

This is a difficult phrase to define as it has been claimed that there are variations of PBL. However after going through various publications (1, 8, 9, 10) and personal communications (11, 12, 13), in general the most fundamental concept for PBL is any learning environment that drives the student to learn new knowledge and skills, working in small groups. During the process of trying to understand and seeking possible solutions to the problem or case given, the students acquire (a) integrated factual knowledge in context, unconstrained by subject divisions, (b) skills in self-directed learning, clinical reasoning and teamwork, and (c) self motivation. In the context of medical education PBL is a learning process where various ***patient-centred problems are used as a starting point*** for the students ***to learn how to acquire knowledge in the basic and clinical sciences*** in an ***integrated manner*** along with ***reasoning skills***, clinical or otherwise. During this process, with the guidance from their tutors and resource persons the students gradually become ***independent learners***. The learning process is considered as more student-centered and self-directed.

The PBL approach is in contrast to the more familiar "case approach" widely used in most conventional curriculum, where the problem or patient's case is used as a means to integrate previously learned knowledge obtained mainly through structured lectures. Thus this mode of learning is not considered as PBL by some (10, 14). In instances where PBL is incorporated as part of or is complementary to an otherwise conventional curriculum a selected part or topic in the medical curriculum could be organized so that the students learn through the PBL process. This type of curriculum has been referred to as an embedded PBL curriculum. Examples of PBL environment may include research projects that compel the students to learn new knowledge instead of mere integration of previously learned knowledge. Such environment does exist in the NIC, specifically the electives (15) and Community and Family Case Studies (CFCS), although in the latter programme the learning objectives are made known and not fully decided by the groups of students involved (16).

In a PBLC such as the one conducted in McMaster, Harvard and Calgary the students will learn only using the activities mentioned earlier. The factual knowledge is not obtained through exhaustive lectures. Small group tutorials and independent study constitute the main activity while laboratory work and formal clinical skill sessions are kept to a minimum. Lectures are a novelty, being very general in presentation and used only for the students to identify their own learning issues individually and as a group (11, 12). Lectures and demonstrations are considered as optional enrichments for students. The learning process is totally integrative in nature with no subject divisions such as Anatomy, Physiology or Biochemistry or identification of clinical or pre-clinical knowledge.

The PBL learning process

The PBL learning process includes the following features (17, 18):

1. The trigger: The students encounter the patient-problems (ie. the triggers) first before they learn the basic science or clinical concepts, and not after. The problems, given to the students one at a time in small groups, are designed accordingly; either to focus on a certain organ system or to be more general to allow free enquiry. Whichever is the case the design of the problems must ensure that there are overlaps in coverage so that the different groups of students will eventually acquire the basic knowledge expected at the end of each course.

2. Brainstorming: Using the problem given, the students will initially rely on their previous knowledge that is relevant, and from there identify their learning needs and objectives for the given problem as a group. They then decide on how to acquire knowledge on the issues raised. Members of the group will decide on how to distribute their workload and responsibilities, the time required to gather the information and the number of meetings required. During this process they learn to

- work as a team,
- be responsible for the group's achievement,
- recognize contributions from other members of the team.

Ideally the tutorial groups should consist of no more than six students.

3. Discussion and hypothesis generation: After the students have gathered their information from various sources, they meet to discuss and share what they have learnt, hypothesize on the issues raised, and evaluate their progress.

The tutor's role in these sessions is only to monitor progress and interaction (11, 19, 20). The tutor may intervene if there are personality conflicts to be resolved, the discussion is losing direction or becoming a deadlock. This should be done appropriately without dominating the group. An ideal tutor should get to know the students in the group, create an environment that is friendly and non-threatening, foster cooperation rather than competition, give constructive verbal feedback, and listen, observe and act when required.

Small group session, time and schedules

It has been stressed that in PBLC more unscheduled time is required compared to the conventional medical course (11, 13, 18, 20). This time is required for:-

- the small groups of students and their tutors to work out their own educational plan
- the students to organize meetings to work out the given problem
- the students to work out their own self study plans

These activities, organized in the unscheduled time, are important since each group takes varying length of time and number of meetings (with or without their tutor) to achieve maximal learning from each problem given. The problems are also of varying complexity and the number of learning issues raised varies. Each learning issue also requires a certain amount of time to comprehend. Weekly meetings are arranged between the students and their tutors. This is to provide an avenue for the students to talk about the course, problems they have encountered, suggestions for changes in the course, and comments on learning resources and learning methods.

In this case several guidelines were suggested to facilitate learning. It was recommended that the staff involved provide an overview or helpful way of handling difficult concepts or facts. Secondly, new or important facts or concepts could be presented in lectures, including those that may have future significance for medicine.

Advantages of PBLC compared with conventional curriculum

The advantages of the PBLC approach are mostly related to the process of learning itself.

1. Posing a problem before the students learn the facts motivate them to learn because the knowledge to be acquired is considered relevant (17,18).

It could also be argued, as in the case of the NIC at UM, that presenting clinical scenarios (cases of patients) by clinicians at the beginning of the various systems lectures could show relevance to what is to be learnt. Feedback from students of NIC and the previous curriculum agrees with this assumption. The difference with PBLC however is that with the scheduling of extensive lectures students become passive learners, especially the less motivated ones. In fact, surveys done in 1994, 1996 and 1998 indicated that they would prefer to have the clinical scenarios presented after the systems lectures. Exposing and training the students to some PBL process may modify this attitude. However, it has been noted, at Queen's University in Ontario, Canada, that even mature students tend to readjust and become passive learners when extensive lectures are scheduled after PBL tutorials (21).

2. Active learning in the context of the need to understand and solve a problem tends to store integrated knowledge with better understanding rather than rote learning. Students develop and use the scientific and medical reasoning process as they learn (14).

In the NIC, problems are also given for the students to solve. However in this case, since the students have already acquired some knowledge prior to the given

problem, solving it is mainly an activity that promotes greater understanding and integration of the subject matter. The case used can be extended into a PBL if it requires the student to seek new knowledge to solve or understand some aspects of the problem. To promote active learning, the students need to identify their own learning objectives and this can be promoted by excluding questions that induce rote learning. This shift was noted during the Phase II integrated or multi-disciplinary PBL tutorials that were started in December 1999 at the Faculty of Medicine, University of Malaya.

Where does NIC stand?

As mentioned earlier, within the realms of the Phase I and Phase II, the NIC does contain some aspects that allow students to progressively meet some of the objectives of PBL through various activities, although they may not be considered as pure PBL. These include:-

(1) elective projects, where students in groups of four (in Phase I) or two (in Phase II) undertake a project under the supervision of a faculty member,

(2) CFCS, where pairs of students learn through interacting with the patient, his/her family and the community associated with the patient.

(3) selected patient/paper cases in Phase I, although the focus of the problems tend to be more subject-based, where the students need to acquire new knowledge in the said subject independently so as to understand or solve the problem.

(4) integrated or multi-disciplinary PBL tutorials in Phase II, which will also be introduced in Phase I in the near future.

Areas of concern on the implementation issues for teachers changing to a problem-based learning concept

Tony Dixon (13) mentioned that changing from something familiar to another that is relatively new is unsettling. This is especially so for teachers who had been raised with the traditional concepts in education, where the teaching is didactic and mostly teacher-centred. To accept PBL one has to undergo three paradigm shifts, that is, a change in the understanding of education, a change in the understanding of subject content and a change in the understanding of the system/arrangement that promotes education. Most common issues raised towards PBL are:

1. Teachers question the non-uniformity of knowledge acquired between groups.

A common concern amongst teachers is that in PBLC the different groups of students will not acquire uniform information. In the old paradigm, the teacher giving the lecture is the main source of information. With that is the belief that since the same content of knowledge is transmitted to all the students thus all will have acquired the same information. However if one could read each of the students' minds one would then discover that this perception is not true since the amount the students "absorb" depends on their previous knowledge, attentiveness in class, interest in the subject matter and various other factors.

2. *Subject specialists worry about depth*

Another common concern is that the students may not have a solid foundation in PBLC and that the information acquired by students is in bits and pieces, not according to subject's priority sequence. In the old paradigm, who decides when and how much should be given? Is it the curriculum committee, the various departments or the individual lecturers? When it comes to implementation a variation of the three is in play. How then does a student cope with the information overload from each of the specialized disciplines, especially in this new era of information and technology?

The new paradigm consists of a holistic approach, promotion of understanding and interaction with the environment, and the ability to adapt and change as they learn. Learning in context promotes integration of subject matter, and any conflict that may arise promotes learning. Learning in context also allows selection of knowledge to be learnt and thus reduces rote learning. Communication, teamwork and early interaction with patients promote the element of care. In all these the teacher facilitates and helps the students through discovery learning.

3. *Facilitators feel inadequate when materials to be dealt with are outside their subject specialty.*

This is a valid apprehension and one that has to be overcome not only through training workshops but also by facilitating the students through the PBL tutorials, and learning with and from them. Learning is best done through experience, both for the students and the facilitators.

Prepared tutors' guides may help the tutor to gauge whether the group has identified most of the learning objectives suggested for the learning package. Self and group evaluation which is carried out at the end of every group meeting may help to reduce this apprehension.

4. *Teachers felt that Asian students do not have the confidence to discuss in a PBL format.*

During a PBL regional workshop held in the Faculty of Medicine, University of Malaya, in November 1999, the Phase II students were asked to volunteer for the PBL tutorials training session. It was observed that the students present were able to carry out independent group

discussions. During the group feedback, in their respective tutorial groups, a number of students were quite direct in informing the "tutors" of the unnecessary interruptions they had during the tutorial. It was noticed that once the students see that their opinions are valued they tend to be more vocal and would contribute to the development of the programme. Feedback from the workshop questionnaires indicated that the teachers were apprehensive about their students' ability to handle self-directed learning in PBL and so were the students.

Conclusion

PBL is a process or arrangement that is taking an important role in medical schools and various other courses in our region. The reasons for this are many and some have been mentioned earlier. Some institutions will continue to use the pure model or PBLC while others will make various modifications to suit their resources and limitations.

Future challenges in the curriculum change

Several strategies have to be considered to meet future challenges. Problem-based learning requires a high degree of faculty commitment and collaboration. As mentioned earlier, how much PBL could be included depends on the objectives of the medical course. At present PBL components can be developed to hybridize with the system-based lectures within the NIC. Learning packages for PBL have to be prepared by academic staff and some form of recognition has to be awarded for their time and effort. Therefore remuneration system has to be reviewed. PBL will cause disorientation to the teachers and to the less motivated students, thus initial training is necessary. Both the student and teacher need to understand the PBL process to ensure success of implementation. Needless to say the method of assessment will have to be improved in various aspects including the criteria that determine the pass or fail mark and the type of questions asked. Questions that require encyclopaedic answers will defeat the purpose of PBL and will influence the way the students learn.

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MALNUTRITION AND HELMINTH INFECTIONS AMONG PRE-SCHOOL CHILDREN IN ORANG ASLI RESETTLEMENT VILLAGES IN KELANTAN

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ABSTRACT: A survey of malnutrition and helminth infections among 268 pre-school children living in the Kuala Betis Orang Asli resettlement villages in Kelantan. The prevalence of helminth infections was 47.4%, with *Ascaris lumbricoides* being the most common helminth (43.9%), followed by *Trichuris trichiura* (29.7%) and hookworm (6.3%). The prevalence of *Ascaris lumbricoides* and *Trichuris trichiura* infections increased with age, with the higest prevalence found in the 6-7 yeas age group. The overall prevalence of stunting, underweight and wasting were 61.7%, 60.4% and 17.5% respectively. Both stunting and underweight were significantly higher among the infected children. Factors associated with helminth infections in the pre-school children were older age group, poor water supply and households with more than 5 members. Routine regular deworming is recommended based on the World Health Organisation recommendations for schoolchildren. *(JUMMEC 1999; 2: 99-103)*

KEYWORDS: Helminth infections, Malnutrition, Orang asli, Malaysia

Introduction

Both malnutrition and helminth infections are still widely prevalent in developing countries, especially in the disadvantaged communities (1). Although the mortality of helminth infection is low, the consequences include malnutrition and poor growth of the infected children (2). Most children in many developing countries suffer either undernutrition or malnutrition at some time during the first 5 years of life (3). The children typically start to acquire the infections as soon as they begin to crawl and explore their environment (4). In disadvantaged communities, where the basic needs for food, housing, clean water supplies and good sanitation are not met, the poor growth of the children occurs once they start weaning between 6 to 24 months. The most critical period then, to prevent malnutrition and thereby reduce malnutrition related problems, is during the pre-school period. The contribution of helminth infections to malnutrition of the children in such disadvantaged communities has to be determined as there are now effective, safe and inexpensive anthelmintic drugs available for mass presumptive treatment of children.

The study is a one year prospective, placebo-controlled, double blinded study on the impact of helminth infections on the nutritional status of pre-school children in Kuala Betis, Kelantan The primary purpose of this study was to determine whether there is an causal relationship between helminth infections and malnutrition among the pre-school children in a disadvantaged community in Malaysia. In this paper, we report on the baseline cross-sectional survey, looking into helminth infections and the association with several socio-economic and nutritional parameters among the pre-school children in Kuala Betis, Kelantan.

Materials and methods

The study area, Kuala Betis, is an orang asli resettlement community, consisting of several villages situated near to each other. The orang asli were resettled in these villages from the interior. There were also a few malay settlers living nearby in a malay village. Most of the villagers were rubber tappers, with a poor socio-economic background. The sanitation in these villages was also poor, and the river was their main source of water. There were very few toilets available and the villagers normally use the nearby bushes.

A total of 397 pre-school children were examined at baseline but only 268 (67.5%) faecal samples were re-

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turned. Only the results from the 268 children with faecal samples were used for the analyses. The age of the child was determined from the birth documents of the child. The clinic records were checked for the age of the child if the birth document was unavailable. The weight was taken with the children naked or in underpants and without shoes using a Seca electronic weighing scale and was recorded to the nearest 0.1 kg. The height was measured to the nearest 0.1 cm using a measuring tape. The child was made to stand against a straight wall with a tape suspended 2 meters from the floor. For children less an 2 years, the recumbent length was measured using a locally made length board. The weight and height of the children were compared with the National Centre for Health Statistics (NCHS) reference values using the Anthro software (5). Children were classified as stunted, underweight or wasted if the z-score for height-for-age, weight-for-age and weight-for-height respectively was less than 2 standard deviation (SD) below the NCHS median.

Containers for faecal samples were given to each child and were collected on the following day. The consistency of the faeces was noted as either hard, soft, diarrhoeic or watery and was then preserved with 10% formalin. The stools were examined for the presence of *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm eggs. If positive, the worm load (eggs per gram of stool) was determined using a modified Stoll's technique, with a correction factor based on the consistency of the stools. The worm load was then categorised into the intensity of infection - negative, mild, moderate and heavy infection according to the WHO (1987) classification (6). Data entry and analysis were done using the Epi-Info Version 6 computer program (7). Statistical analyses of comparisons of proportions were tested with the Chi square-test. Probability less than 5% for null hypothesis was considered significant.

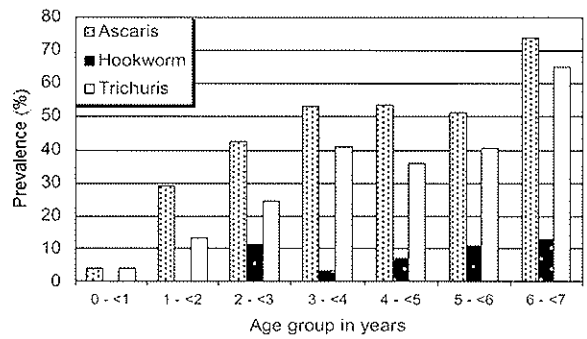

Fig. 1. Prevalence of helminth infections among pre-school children by age in Kuala Betis, Kelantan

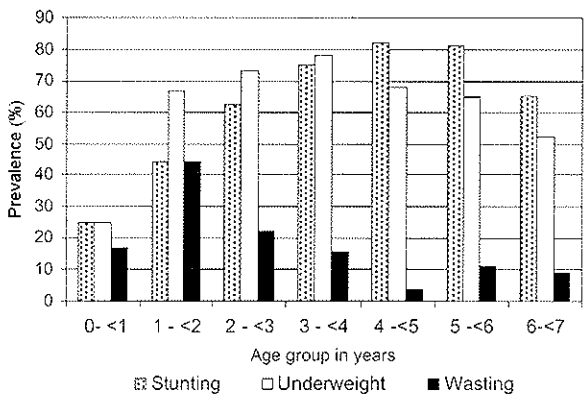

Fig. 2. Prevalence of stunting, underweight and wasting among pre-school scildren by age in Kuala Betis RPS, Kelantan

Results

The overall prevalence of helminth infections among the pre-school children in Kuala Betis was 47.4%. The most common helminth was *Ascaris lumbricoides* (43.9%), followed by *Trichuris trichiura* (29.7%) and hookworm (6.3%). The prevalence of *Ascaris lumbricoides* and *Trichuris trichiura* infections show an age dependent relationship, with the lowest prevalence in the age group 0-1 year and highest in the 6-7 years age group. However, hookworm infections appears not to be related with age, although the number of infections detected is too small to make any conclusion (Fig. 1).

The overall prevalence of stunting, underweight and wasting among the pre-school children in Kuala Betis, Kelantan were 61.7%, 60.4% and 17.5% respectively. The lowest prevalence of malnutrition was found in the 0-1 year age group while the highest prevalence of stunting and underweight were found in the 3-4 and 4-5 years age group. The prevalence of stunting and underweight increased rapidly in the older age groups, accounting for more than 50% of the children after 2 years of age. There also seem to be a decreasing trend in the prevalence of stunting and underweight after 4-5 years, although it is not certain whether this trend will continue during the school-age years. The prevalence of wasting, however was higher in the younger age group, with a peak in the 1-2 years age group (Fig. 2).

Table 1 show the comparison between the infected children, who were stool positive, and controls, who were stool negative for helminth ova. There were no significant differences between the gender and racial composition of the infected and control children. However, the mean age between the 2 groups was significantly different, with the infected children being much older than the control children. There were significantly more infected children from households with more than 5 persons. There were also significantly more infected children sourcing water from the river, as opposed to having pipe water among the control children. However, there was no difference between the father's occupation, either as rubber tapers, working with the government or doing small businesses.

Since there was a significant difference in age between the infected and control group, comparison of anthropometric indices was confined to height-for-age (HAZ), weight-for-height (WHZ), weight-for-age (WAZ) z scores and the mid upper arm circumference (MUAC). There were no significant difference in the mean HAZ, WHZ,WAZ z-scores and MUAC between the infected and control children. However, there were significant differences in the prevalence of stunting and underweight between the two groups. More infected children were stunted and underweight compared to the controls. However, there was no significant difference in the prevalence of wasting between the two groups.

An analysis between nutritional status and the intensity of the 3 helminthic infections was done (Table 2). Malnutrition was defined as positive if any of the z-scores for height-for-age, weight-for-age and weight-for-height is less than -2.0. The helminth infections were divided into two categories, uninfected/mild infections and moderate/heavy infections. However, there was no significant association between the intensity of infection and the prevalence of malnutrition found.

Discussion

There is a high overall prevalence of helminth infections (47.4%) among the pre-school children in Kuala Betis, with *Ascaris lumbricoides* as the most common helminth (43.9%), followed by *Trichuris trichiura* (29.7%) and hookworm (6.3%). The prevalence are comparable to those found in previous studies. Kan *et al* found the prevalence of *Ascari lumbricoides*, *Trichuris trichiura* and hookworm infections to be 24.3%, 26.2% and 3.4% respectively among pre-school children in the rural areas of Malaysia (8). In a study on pre-school Orang Asli children, the prevalence of *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm was 41.9%, 53.6% and 11.7% respectively (9) while a more recent study in a similar group, found a prevalence of 30.2%, 30.2% and 9.4% for *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm respectively (10). Orang asli children in resettlement villages are known to have a higher prevalence and intensity of helminth infections compared to those living in traditional villages, because the soil can become adequately contaminated due to the more permanent nature of the villages (11).

Helminth infections are common in disadvantaged communities, especially if there is poor water supply and sanitation facilities. In the Kuala Betis resettlement villages, the water supply was mainly from the river, and sanitation facilities were poor. This study found significant association between helminth infections with age, poor water supply and households with more than 5 members. Infected children were at an older age to the control children. The children start being infected at an age when they become mobile and move around the compound. The prevalence of *Ascaris lumbricoides* and *Trichuris trichiura* infections was noted to increase as the children grows older. School-age children are known to have the heaviest infections of *Ascaris lumbricoides* and *Trichuris trichiura* (12). Poor water supply and many family members are typical of the poor socio-economic status of the community. The high prevalence of hookworm in these children may be attributed to the lack of proper shoes and their behaviour of not wearing them in the villages. The situation is made worse by the improper defecation by these children, which is usually done near their houses.

Table 1. Selected characteristics of pre-school children in Kuala Betis, Kelantan

Variables	Worm positive (n=127)	Worm negative (n=141)
1. Gender - male	78	55
- female	71	64
2. Race - Malay	11	11
- Orang asli	138	108
3. Mean age in months (S.D)	56.1 (31.3)	32.9 (23.0) **
4. Water supply:		
- piped	21	37 *
- others (river, rain)	128	82
5. Father's occupation		
- government, business	33	38
- rubber tapers	107	78
6. Houseold size - <5	52	32
- >5	67	117 **
7. Anthropometric parameters – mean (S.D)		
- HAZ	- 2.0	-2.1
- WHZ	- 0.8	-1.0
- WAZ	- 1.9	-2.3
- MUAC	12.2	9.5
8. Nutrition - normal		
- stunting	94 (74.0%)	71 (50.4%) *
- underweight	91 (71.7%)	71 (50.4%) *
- wasting	22 (17.3%)	25 (17.7%)

Chi square value * $p<0.05$ ** $p < 0.01$

Table 2. Malnutrition and helminth infection among pre-school children in Kuala Betis, Kelantan.

Worm infection	Malnutrition (+)	(-)	p-value
Ascaris lumbricoides			
- Moderate / Heavy	34	14	n.s
- Nil / Mild	161	59	
Hookworm			
- Moderate / Heavy	8	2	n.s
- Nil / Mild	187	71	
Trichuris trichiura			
- Moderate / Heavy	25	12	n.s
- Nil / Mild	170	61	

There is also a high prevalence of malnutrition (stunting- 61.7%, underweight- 60.4%, wasting- 17.5%) found in these children. Zamaliah *et al* found the prevalence of stunting among rural pre-school children was 26%, while 31.5% were underweight and 3.8% wasted while Zawiah *et al* found the prevalence of stunting was 31.7%, underweight was 44.3% and wasting was 16.2% in a rural agriculture scheme (13, 14). Osman and Zaliha found the prevalence of stunting was higher in Orang Asli than in the Malays, where the prevalence was from 66.7% - 80% compared to 25.5% - 41.2% (10). The prevalence of underweight in these children was from 28.2% - 61.8%. The prevalence of malnutrition found in this study was high, comparable to those found by Osman and Zaliha (10). Stunting and underweight reflects the disadvantaged conditions, chronic or repeated infections, and inadequate food intake (15). The orang asli are among the disadvantaged communities in Malaysia. The change from a culture of 'hunting and gathering' to 'rubber planting and tapping' has taken a considerable toll on the health and nutrition status of these orang asli community (16). The low price of rubber and the diminishing food source from the jungle due to logging activities, have also contributed to the problem. The impoverished state of the Orang Asli communities during the period of resettling may have contributed to the high prevalence of wasting (17.5%) found. In contrast to stunting, wasting is of a more recent onset with relatively constant prevalence, usually less than 5% (17).

The prevalence of stunting and underweight were significantly more among the infected children. However, it is well established that the severity of disease is dependent on the intensity of the helminth infection. What is the extent to which the helminth infections contribute to malnutrition of these children? Univariate analysis between the intensity of infection and malnutrition found in this study did not show any association. Thus, helminth infections may be a covariate for socio-economic status, and by itself, may not be an important contributor to malnutrition in these pre-school children. Under these circumstances, the nature of the study design becomes crucial because detection of causation rather than association is required. The possibility of a causal association will be determined by prospective studies, where the change or improvement in growth following treatment of the helminth infections are measured, while not changing the other parameters of the relationship. It should also be noted that there are other effects of helminth infections, such as poorer cognitive function and learning ability, which may be of equal importance for economic and social development of the orang asli community. The World Summit for children in 1990 has set a target of achieving basic primary education for at least 80% of the children by the year 2000 (18). It was also recognised that providing access to schooling will only result in improved education if these children have the capacity to benefit from the schooling made available to them. For many children in the developing world, these few years of basic education may be the only formal education they will ever receive.

Thus, there is ample justification for the control of helminth infections among the pre-school children in these communities where both helminth infections and malnutrition are prevalent. The argument, that deworming is irrelevant to the control of helminth disease because children becomes re-infected is difficult to sustain in the face of remarkable catch-up growth achieved by children after a single treatment in a number of studies (19). The United Nations Subcommittee on Nutrition endorsed the recommendation that in areas where the prevalence of mild-moderate underweight in children is greater than 25%, and where intestinal helminths are known to be widespread, high priority should be given to deworming programs (20). The World Health Organisation has also recommended regular mass treatment for schoolchildren where the prevalence of helminth infections exceeds 50%, and in areas where the prevalence of underweight exceeds 25%, a high priority should be given (21). The same criteria can also be applied to pre-school children, since from a nutritional perspective, pre-school children may be more vulnerable to growth problems for the same worm burdens as compared to schoolchildren (22).

A child growing up in such disadvantaged communities, which cannot meet basic needs for food, housing, clean water supplies and good sanitary systems, such as the Orang Asli resettlement villages in Kuala Betis, Kelantan, will need to be given adequate support during the adjustment period in changing their traditional lifestyle. School going children have the advantage of having school-based health care, including supplementary feeding programs and periodic health monitoring by the health care team. The pre-school children have a more limited access to heath care, especially in the disadvantaged communities. It is important for the government to provide adequate resources to make the pre-school children in such communities healthier and more ready to learn when they start schooling (23). A comprehensive primary health care programme has been suggested for the Orang Asli, which include family planning, periodic deworming, vitamins and mineral supplements and food supplements to the Orang Asli children (16). Surveillance of the nutritional status will detect growth failure early, so that intervention, which include the provision of supplementary food, can be given. Such programs for the community control of malnutrition and helminth infections will require a coordinated effort, and contributions from the various sectors.

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INVESTIGATION OF A RECURRENT CASE OF SALMONELLOSIS DUE TO *SALMONELLA BOVISMORBIFICANS* AND *SALMONELLA MATOPENI* USING PULSED-FIELD GEL ELECTROPHORESIS ANALYSIS AND ANTIBIOGRAMS

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ABSTRACT: A restropective study on a case of recurent salmonellosis in a 3 month-old child due to *Salmonella bovismorbificans* and *S. matopeni* was carried out using pulsed field gel electrophoresis (PFGE) and anitbiotic susceptibility analysis. PFGE clearly distinguished the two serovars and that the recurrent infection was shown to associated with variant forms of *S. bovismorbificans*. The chromosomal changes detected among the seqential isolates of *S. bovismorbificans* appeared to be associated with varing antibiogram patterns. The study also showed that the recurrent infection in the patient could be related to prolonged antibiotic therapy. *(JUMMEC 1999; 2: 103-109)*

KEYWORDS: Recurrent salmonellosis, PFGE typing, Antibiograms, *Salmonella bovismorbificans*.

Introduction

Acute gastroenteritis caused by *Salmonella* spp. remains a major global public health problem affecting millions of children under 5 years of age. The most common agent of non-typhoidal salmonellosis is *S. enteritidis* (1). However, outbreaks of salmonellosis caused by *S. bovismorbificans* do occur although they are relatively rare (2,3,4). Koe *et al.* (4) (1991) in their study of 97 children with acute gastroenteritis showed that the most common bacteria isolated was food-poisoning *Salmonella* (25.8%). Among these 20 *Salmonella*, 5% was *S. bovismorbificans*. In another study by Jegathesan (1984), *S. bovismorbificans* accounted for 2 % of the serotypes isolated in Malaysia (3). A survey of *Salmonella spp.* isolated from stools of children admitted to the University Hospital Kuala Lumpur from 1994 to 1996 showed presence of *S. bovismorbificans* and *S. matopeni* in 19 (11%) and 9 (5%) out of 173 isolations respectively (1).

There has been great interest in the application of molecular subtyping techniques to examine multiple isolates obtained sequentially from an individual patient (5,6). This may help to differentiate between relapsing infection with the same strain or reinfection with a new strain. Thus, such studies are of value in the epidemiology of human salmonellosis. The objective of this study was to apply the technique of PFGE and antibiograms to investigate the genetic variability of sequential isolates of *S. bovismorbificans* and *S. matopeni* from a 3 month-old child admitted to the University Hospital Kuala Lumpur. In addition, this study also enabled us to assess any molecular changes in the genome occurring during relapsing infection.

Methods and materials

Case report. A retrospective study on thirteen sequential isolates obtained from a 3-month old female child between July, 22 to September 2, 1994 was carried out. The child was admitted to the University Hospital, Kuala Lumpur with fever, vomiting, diarrhoea, and, just an hour before admission, she had an episode of generalised fits. The first isolate was obtained on July, 22, followed by 12 subsequent isolates (Tables 1,2). The patient was treated with 5 different antibiotics. Antibiotic therapy was stopped on September 21 and subsequent stool samples became culture-negative. The patient was finally discharged on September 29 (Table 1).

Serotyping and identification of the *Salmonella* spp. were performed by using standard microbiological procedures in the Department of Medical Microbiology, Faculty of Medicine, University of Malaya. All isolates were tested for susceptibility to antibiotics by standard disk diffusion procedures for measuring resistance according to

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Table 1. Clinical data and antimicrobial therapy of a 3 month-old child with salmonellosis

Date	Clinical presentation	Antibiotics given (duration)	Stool culture (date of isolation; isolate no.)
Before admission	fever, vomiting, diarrhoea (watery), one epidode of generalised fits		
21.7.94 (admitted)	10% dehydration	ceftriaxone (9 days)	*S. bovismorbificans* (22/7;#151)
29.7.94 Discharged			
4.8.94 (admitted)	fever, diarrhoea, 5% dehydration	cefotaxime (10 days)	*S. matopeni* (5/8; #154)
6.8.94	diarrhoea, poor feeding, hepatomegaly	cefotaxime (10 days)	*S. matopeni* (6/8;#155) *Subsequent cultures taken on 11/8;#158, 12/8;#149, 16/8;#150) showed presence of S. bovismorbificans*
17.8.94		ceftriaxone (10 days)	*S. bovismorbificans* (18/8; #147; 22/8; #153; 25/8; #157)
26.8.94		ampicillin (14 days) 29/8;#148)	*S. bovismorbificans* (26/8; #146 and
30.8.94 Discharged			
6.9.94 (readmitted)	fever, diarrhoea, 5% dehydration	chloramphenicol (2 weeks)	*S. bovismorbificans* (7/9; #152 and 16/9;#156)
20.9.94		Amoxycillin-clavulanic acid	
21.9.94		antibiotic therapy stopped	stool and urine cultures all negative
29.9.94	Discharged well		

Table 2. Antibiograms and PFGE patterns of multiple isolates of *S. bovismorbificans* and *S. matopeni* from a single patient.

			Antibiogram											PFGE patterns			
Date	No	Species	C	Aug	Ctx	Amp	Cip	Gen	Tet	Kan	Cot	Cef	Stp	*Xbal*	*AvrII*	*SpeI*	*XhoI*
22/7	151	Sbm	S	S	S	S	S	S	S	S	S	S	S	X1	A1	S1	XH1
5/8	154	Sm	S	S	S	S	S	S	S	S	S	S	S	X6	A5	S2	XH2
6/8	155	Sm	S	S	S	S	S	S	S	S	S	S	S	X6	A5	S2	XH2
11/8	158	Sbm	S	S	R	R	S	S	S	R	R	S	R	X2	A2	S1	XH1
12/8	149	Sbm	S	S	R	R	S	S	S	R	R	S	R	X2	A2	S1	XH1
16/8	150	Sbm	S	S	R	R	S	S	S	R	R	S	R	X2	A2	S1	XH1
18/8	147	Sbm	S	S	R	R	S	S	S	R	R	S	R	X3	A2	S1	XH1
22/8	153	Sbm	S	S	R	R	S	S	S	R	R	R	R	X4	A2	S1	XH1
25/8	157	Sbm	S	S	R	R	S	S	S	R	S	R	S	X5	A3	S1	XH1
26/8	146	Sbm	S	S	R	R	S	S	S	R	S	R	S	X5	A3	S1	XH1
29/8	148	Sbm	S	S	R	R	S	S	S	R	R	R	R	X2	A4	S1	XH1
7/9	152	Sbm	S	S	R	R	S	S	S	R	R	S	R	X2	A2	S3	XH1
16/9	156	Sbm	S	S	R	R	S	S	S	R	R	S	R	X2	A2	S1	XH1
22/9		NEG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

C=chloramphenicol (25mg), Aug=amoxycillin-calvenic acid (30mg), Ctx= cefotaximine(25mg), Amp=ampicillin (10mg), Cot= cotrimoxazole (30mg),Cip = ciprofloxacin (5mg), Cef = ceftriaxone (30mg), Gen = gentamicin (10 mg), tet =tetracycline (25mg), Kan= kanamycin (30mg), Stp = streptomycin (10mg), *Sbm= S. bovismorbificans*, Sm= *S. matopeni*, Neg = negative isolation, S= sensitive, R = resistant

the National Committee for Clinical Laboratory Standards (1995).

PFGE. Chromosomal DNA was prepared for pulsed-field gel electrophoresis (PFGE) as previously described (7). DNA digestion was performed overnight at 37°C with 10 units each of *Xba*I, *Spe*I, *Avr*II and *Xho*I (New England BioLab, USA) in 100 ml of restriction buffer. PFGE of restricted genomic DNA was performed by using the contour clamped homogenous electric field on a CHEF DRII/III (Bio-Rad, Laboratories, Richmond, Calif.) in gels of 1% agarose (Sigma) in 0.5X Tris-Borate-EDTA buffer (0.1M Tris, 0.1M boric acid, 0.2mM EDTA) for 28 hours at 12∞C with ramped pulsed times varying according to the restriction enzymes used (2 –40 sec) and at 6V/cm. A molecular weight marker (Lambda DNA concatemer) was included in each run. The same procedure was performed with undigested DNA to identify extrachromosomal DNA on a separate gel. The gels were stained with ethidium bromide and photographed with a UV transilluminator (wavelength, 302 nm; Spectroline). In order to assess the stability and reproducibillity of the PFGE patterns, the strains were passaged three times *in-vitro* on the laboratory medium.

Plasmid extraction was carrried out according to the alkaline lysis method (8).

All isolates were analysed without prior knowledge of their identities and the results were then compared retrospectively with the clinical records.

Results

The first isolation on July 22 was *S. bovismorbificans* which was sensitive to all the antibiotics tested (Table 1). However, *S. matopeni* was isolated on two subsequent isolations and not *S. bovismorbificans* (Table 1). The subsequent ten isolates were all *S. bovismorbificans* which had acquired resistance to ampicillin, cefotaxime and kanamycin (Table 2). The isolates also showed changing resistance patterns to cotrimoxazole, streptomycin and ceftriaxone. For example, *S. bovismorbificans* isolates obtained on 8 occasions were resistant to cotrimoxazole and streptomycin but isolates obtained on two other occasions (August 25, 26) were sensitive to these antibiotics (Table 2). On the other hand, 7 isolates were sensitive to ceftriaxone and four isolates were resistant to it. (Table 2). Interestingly when all antibiotics were withdrawn, subsequent attempts at isolation from stool and urine were negative for *Salmonella* spp. (Tables 1,2).

Stable and reproducible PFGE patterns were obtained with four restriction endonucleases, *Xba*I, *Spe*I, *Avr*II and *Xho*I. These macrorestriction analysis clearly distinguished *S. boviSmorbificans* from *S. matopeni* (X6/A5/S2/Xh2 patterns) (Table 2, Fig 1, A-D). Eleven to eighteen DNA fragments ranging from about 40 to >480 kb were well-separated and the individual isolates were clearly differentiated. Among the *S. bovismorbificans* isolates, five *Xba*I patterns (X1 to X5) differing in 1-2 DNA bands were noted (Fig. 1A). *Avr*II digestion gave 5 PFGE patterns with 6-9 DNA fragments ranging in size from about 40 to 485 kbp.(Fig 1B). Four *Avr*II patterns, A1 to A4, differing in 1-2 bands were observed. All the *S. bovismorbificans* were indistinguishable by *Xho*I while *Spe*I digestion gave 2 patterns which differed by a single band (Fig.1 C,D).

When the isolates were regrouped according to the *Xba*I and *Avr*II patterns and the antibiograms, the variations observed in the antibiotic susceptibility appeared to correlate with the variations in the chromosomal restriction sites of *Xba*I and *Avr*II (Table 3). Isolate #151, which was sensitive to all antibiotics tested, had X1 and

Table 3. Association between antibiograms and the *Xba*I and *Avr*II PFGE patterns of *S. bovismorbificans* isolates from a single patient

Antibiogram grouping	Antibiograms	*Xba*I-PFGE grouping	*Xba*I-PFGE patterns	*Avr*II-PFGE grouping	*Avr*II-PFGE grouping
151	Sensitive	151	X1	151	A1
158,149,147, 150,152,156	Ctx^R,Amp^R, Kan^R, CotR, Stp^R	158, 148, 149, 150, 152, 156	X2	158, 149, 150, 147, 152, 156, 153	A2
146, 157	Ctx^R,Amp^R, Kan^R, Cef^R	146,157	X5	146, 157	A3
148,153	Ctx^R,Amp^R, Kan^R, Cot^R,Cef^R, Stp^R	153, 157	X4	148	A4
		147	X3		

Ctx=cefotaximine (25mg/ml), Amp=ampicillin (10mg/ml),Cot= cotrimoxazole (30mg/ml), Cef =ceftriaxone (30mg/ml), Kan= kanamycin (30mg/ml), Stp = streptomycin (10mg/ml), R = resistant

A1 PFGE patterns after digestion with *Xba*I and *Avr*II respectively (Table 3). Isolates #158, 149, 150, 152 and 156, all of which had similar antibiograms, also had similar PFGE patterns X2 and A2 (Table 3). Similarly, isolates 157 and 146 shared the same antibiogram and PFGE patterns (X5/A3). Isolate #148 and #153 which shared the same antibiogram had PFGE pattern X2/A4 and X4/A2 respectively. However, the detailed analysis of such variations, i.e. whether the property of antibiotic sensitivity or resistance was plasmid-mediated or chromosome-based has not been determined. PFGE of undigested genomic DNAs from these isolates clearly showed the existence of extrachromosomal elements in the *S. bovismorbificans* isolates except isolate 151 (sensitive strain) and both the *S. matopenic* isolates (data not shown). Plasmid extraction of the isolates by using the alkaline lysis method confirmed the presence of plasmids (data not shown). However, further characterization of these plasmids has not been carried out.

Discussion

In this study of a 3 month-old child, there are possible reasons for the presence of *S. matopeni*. The first possibility is coinfection. During the first isolation, *S. matopeni* could have been missed. Secondly, *S. bovismorbificans* could have been missed during the next two isolations. Thirdly, the patient could have been infected with a strain of *S. matopeni* during her readmission to the hospital as confirmed by serotyping and PFGE. However, reinfec-

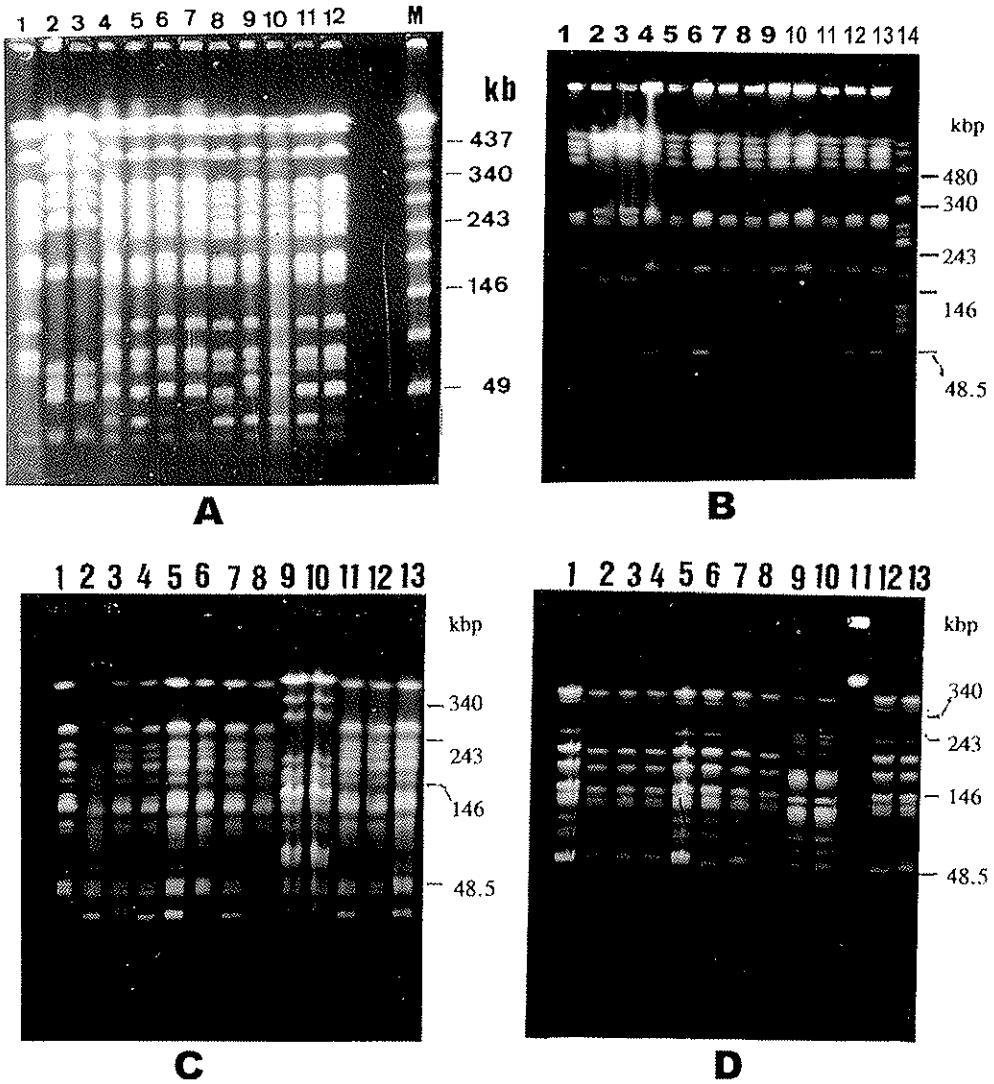

Fig 1. PFGE patterns of *S.bovismorbificans* and *S.matopeni* after digestion with *Xba*I (A), *Avr*II (B), *Spe*I (C) and *Xho*I (D). Pattern-types are designated in brackets.

A: lanes 1-12 (X1), 154 (X6), 155 (X6), 158 (X2), 149 (X2), 150 (X2), 147 (X3), 153 (X4), 157 (X5), 146 (X5), 152 (X2), 156 (X2)
B: lanes 1-14: 151(A1), 154(A5), 155(A5), 158(A2), 150(A2), 147(A2), 153(A2), 157 (A3), 146 (A3), 148 (A4), 152 (A2), 156 (A2), unrelated *S. typhi*

C & D: lanes 1-13: 151, 147, 148, 149, 150, 146, 152, 153, 154, 155, 156, 157, 158. C, lane 11: undigested DNA
Pulsed-conditions: A: 2-40sec, B: 5-50 sec. C: 1-40, D: 1-30 sec.

tion with the strain of *S. matopeni* is very unlikely because this is a rarely encountered serotype. Later, the strains of *S. bovismorbificans* which had acquired some resistance to cefotaxime, ampicillin, cotrimoxazole, kanamycin, and streptomycin were isolated. Subsequently 4 of the 11 isolates which showed resistance to ceftriaxone were isolated. How the *S. bovismorbificans* strain became multidrug resistant remains unclear. Since there were extrachromosomal DNA elements, could these be plasmids coding for the multidrug resistance? This extrachromosomal DNA was not present in the sensitive isolates. PFGE analysis of these isolates with REs (*Xba*I and *Avr*II) showed some correlation with these varying antibiotic susceptibility traits. The difference in the *Xba*I and *Avr*II patterns (1-2 bands shifts) may be the result of genomic rearrangements in the persisting strains (9,10). The significance of these genomic changes in relation to the antibiotic susceptibility trait is not clear. Future studies including conjugation and transposition experiments will be needed to further clarify this observation.

Another interesting observation from this case study was that *S. bovismorbificans* was no longer isolated when the patient was not given the antibiotic therapy for a week. This gives credibility to the notion that the multiple drugs given to the patient prolonged the infection caused by *S. bovismorbificans*. Both *S. bovismorbificans* and *S. matopeni* are not considered part of the normal flora of the human gut but carriage without diarrhoea is possible. In Malaysia, both these serotypes are not commonly isolated. For example, out of 163 *Salmonella* spp isolated in University Hospital Kuala Lumpur in 1994, of which 140 (48%) were from paediatric patients, only 12 (7.4%) were identified as *S. bovismorbificans* (1). The study showed that antibiotic therapy failed to eradicate faecal salmonella carriage. A number of other clinical studies have also shown that antibiotic treatment was associated with prolonged excretion (11). Antibiotics per se have not proven positively to influence the course of disease but are associated with increase in the duration and frequency of the carrier state without improving clinical symptoms. The frequency of drug resistance to particular antibiotics often reflects the indiscriminate use of such drugs by medical and veterinary practitioners. Antibiotic resistance poses therapeutic problems and enhances the epidemic potential of the strains. This is even more important because of the phenomena of transferable drug resistance among the enterobacteriaceae.

In other studies, PFGE has also been used to suggest the presence of two different strains among isolates from sequential cultures of *Mycobacterium avium*, and this may reflect an ongoing polyclonal infection in a single patient (12). It was thought that antimicrobial therapy was not a contributing factor in the development of the polyclonal infection (12). However, in another study in which Southern blot hybridization with a species-specific probe was used, Schroppel *et al.*, (1994) showed that pathogenic strains of *Candida albicans* were genetically unstable *in vivo* during recurrent vaginitis and that drug treatment can result in the selection of variants of the original infecting strain (13).

Corbett-Feeney and Riain (1998) and Wain *et al.* (1999) have also demonstrated the usefulness of PFGE to assess the extent of genetic variations among antibiotic-resistance strains of *S. typhimurium* and *S. typhi* respectively (14, 15). A good correlation between the antibiograms of *S. typhiumurium* and PFGE profiles was also noted (14).

In terms of its relevance to clinical practice, molecular techniques such as PFGE are of value in addressing the question of whether sequential isolates are the 'same' or 'different' in any recurrent infection, and has important applications in epidemiological studies, management of patients and in studies of the pathogenesis of bacterial infections. The present study reiterates the value of PFGE in conjunction with antibiograms in detecting a concurrent infection of *S. bovismorbificans* and *S. matopeni*, in documenting genetic changes and in showing the association between recurrent infection with *S. bovismorbificans* and the prolonged use of antibiotics.

Acknowledgement

The research described in this paper was funded by IRPA Grant No. 37295 from the Ministry of science , Technology and Environments, Malaysia.

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INTRAMUSCULAR VERSUS ORAL IRON SUPPLEMENTATION IN PATIENTS ON RENAL REPLACEMENT THERAPY RECEIVING ERYTHROPOIETIN

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ABSTRACT: Anaemia in patients on renal replacement therapy is a common problem and response to treatment with erythropoietin may be limited by functional iron deficiency. We recently studied prospectively for 22 weeks the effect of iron supplementation via intramuscular and oral vs intramuscular vs oral routes in 16 patients on chronic haemodialysis with renal anaemia treated with erythropoietin injections. The rise in haemoglobin was significant in all patients except those on intramuscular iron only. This study supports unconfirmed observations that oral iron supplementation may be effective in patients with renal anaemia associated with functional iron deficiency. *(JUMMEC 1999; 2: 110-112)*

KEYWORDS: Renal, Anaemia, Erythropoietin, Iron deficiency, Oral, Parenteral.

Introduction

Anaemia in patients on renal replacement therapy is a common problem (1). The causes of renal anaemia are multi-factorial, one of the most important of which is the relative deficiency of the hormone erythropoietin or reduced sensitivity to its actions (2). The introduction of erythropoietin in the 1980's have revolutionized the management of renal anaemia in these cases with the vast majority responding well to erythropoietin replacement therapy (3, 4). However, there still remains a small proportion of patients who fail to respond to erythropoietin, and iron deficiency whether absolute or functional, remains a major cause (3, 5). Patients started on erythropoietin may develop iron deficiency due to the increased demand by erythroid cells in the marrow outstripping supply. Studies on iron supplementation in these patients (6-8) suggest that parenteral iron may be superior to oral iron in maintaining iron stores (6, 7) but this has yet to be confirmed. In this study, we compared the effects of oral versus intramuscular iron in patients starting erythropoietin to determine the optimum route of iron replacement therapy.

Subjects and methods

All patients stable on renal replacement therapy for a period of at least 3 months with Hb < 10 g/dl and not on treatment with erythropoietin were eligible for this study. Patients with inadequate iron stores with serum ferritin < 100 mg/ml, elevated C reactive protein, upper gastrointestinal bleeding, iPTH >20 times normal and allergy to iron were excluded. Fifteen consecutive patients, 14 on Continuous Ambulatory Peritoneal Dialysis (CAPD), and one on haemodialysis were identified and enrolled into the study. There were no significant difference in haemoglobin, ferritin and transferin saturation levels among the three groups at entry into the study. Patient demographics are summarised in Table 1.

Patients were randomised to 3 groups to receive oral iron (Ferrous fumarate 200 mg TDS) and/or intramuscular iron (Ferrum 200 mg monthly, Housmann Laboratories Inc, Switzerland). Group A patients were given oral and and intramuscular iron, Group B patients were given intramuscular iron only, whilst Group C patients were given oral iron only. All patients were also started on erythropoietin 2000iu twice a week which was continued throughout the duration of the study. All three groups were followed-up for a period of 22 weeks. Haemoglobin levels were measured once every two weeks, whilst transferrin saturation and ferritin levels were measured once every four weeks. Results are expressed as mean ±SD. Statistical analysis was performed using the student's t test.

Results

All subjects tolerated intramuscular and oral iron well. There were no reported problems with local reactions

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Table 1. Patient demographics

	Group A	Group B	Group C
No of patients	5	6	4
Age (years)	43.2 ± 12.8	43.8 ± 12.0	36.5 ± 15.5
Transferin saturation (%)	37.6 ± 14.2	31.4 ± 12.1	36.8 ± 12.5
Serum ferittin (mg/ml)	338.0 ± 140.5	320.8 ± 312.3	489.2 ± 268.2
Haemoglobin (g/dl)	7.8 ± 1.2	8.0 ± 1.3	7.5 ± 1.0

Group A, oral + i.m. iron; Group B, i.m. iron only; Group C, oral iron only.

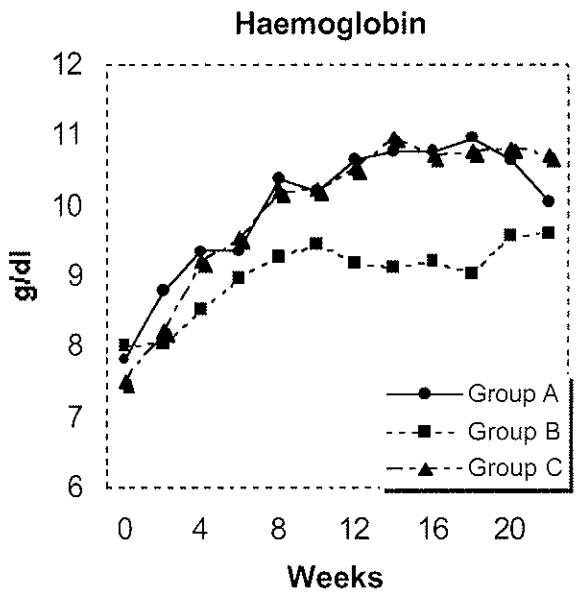

Fig. 1. Changes in haemoglobin concentration in patients receiving oral + i.m. iron (Group A), i.m. iron (Group B) and oral iron only (Group C). For Groups A and C, $p < 0.05$ compared to baseline.

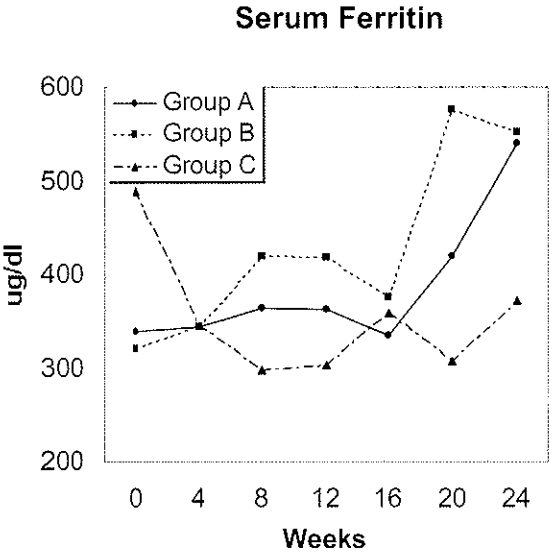

Fig. 2. Changes in serum ferritin concentration in patients receiving oral + i.m. iron (Group A), i.m. iron (Group B), oral iron only (Group C). There was no statistical significant changes in ferritin levels in all 3 groups.

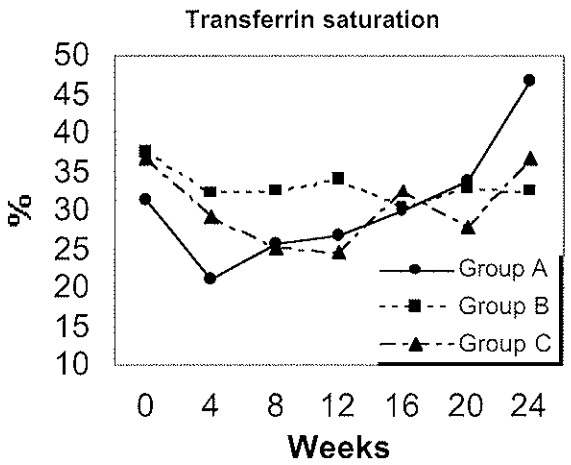

Fig. 3. Changes in percentage transferin saturation in patients reciving oral + i.m. iron (Group A), i.m. iron (Group B) and oral iron (Group C). There was no statistical significant changes in transferin saturation levels in all 3 groups.

after injection as has been previously described (9). The dosage of erythropoietin was unchanged in all patients except for one patient from Group A, where the dosage was reduced to 2000iu/week after two months. All three groups showed a rise in haemoglobin but it was significant only in Groups A and C (Fig 1). There was no significant drop in the ferritin and transferrin saturation levels in all three groups (Fig 2,3).

Discussion

Patients on renal replacement therapy are at increased risk of iron deficiency (9). This could be due to increased external iron losses in dialysis filters, bloodlines, frequent blood sampling or occult gastrointestinal blood loss. In addition, in end stage renal failure (ESRF) there is evidence for sequestration of iron in storage tissues with decreased availability to erythropoietic cells resulting in functional iron deficiency (5) Iron supplements are therefore frequently needed to maintain iron status in patients with ESRF especially those receiving erythropoietin. Intravenous iron has been reported to be superior to oral iron in maintenance of iron stores (7) and oral iron may indeed be no better than placebo in maintaining serum ferritin levels. This has yet to be confirmed and in our study we have demonstrated in our small series of patients that oral

iron can be used successfully to maintain iron status in patients on renal replacement therapy receiving erythropoietin. This was also demonstrated by Wingard *et al* (8) where hematocrit levels were found to be stable after 6 months of oral iron therapy. Surprisingly, the results with intramuscular compared to oral iron supplementation was poor. This observation has to be interpreted with caution due to the small number of patients involved and limited duration of follow-up. If true, it is possible that the poor response to intramuscular iron supplementation could be due to a combination of reasons including the dosage used in this study and variable absorption after injection. Finally, we have demonstrated in this study that oral iron is an effective route for iron replacement therapy in patients on chronic dialysis receiving erythropoietin. However the efficacy of oral iron supplementation compared to parenteral iron supplementation remains to be determined with larger scale studies with longer duration of follow-up.

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ANGIOEDEMA SECONDARY TO ANGIOTENSIN CONVERTING ENZYME INHIBITORS

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ABSTRACT: Angioedema due to whatever cause is potentially life threatening, especially if it involves the head and neck region. Patients at risk need to be identified and precautionary measures are necessary. The use of Angiotensin Converting Enzyme Inhibitors (ACEIs) has been associated with angioedema of the face and tongue. Its widespread use has resulted in an increased awareness of this rare but important complication. We report here a case of angioedema secondary to ACEIs developing a few months after initiation of therapy and discuss its clinical importance. *(JUMMEC 1999; 2: 113-114)*

KEYWORDS: Angioedema, Angiotensin Converting Enzyme Inhibitor.

Introduction

Angioedema is a nonpitting oedema of vascular origin, which can involve the floor of the mouth, tongue, larynx, lips and face. There are numerous causes of angioedema including idiopathic causes, C1 esterase deficiency, drugs, sunlight, cold, heat and allergic disorders. Angiotensin Converting Enzyme Inhibitors (ACEIs) was first reported to cause angioedema in 1984, subsequently a retrospective study in a tertiary referral center in United States showed it to be the number one cause of acute angioedema (1).

The use of ACEIs is now established in the treatment of patients with congestive cardiac failure, post myocardial infarction, diabetic microalbuminuria, hypertensive diabetic and non-diabetic chronic renal impairment, resulting in its widespread use in clinical medicine. It has become among the most frequently prescribed drugs in the past several years (1). Though it has a favorable side-effect profile, ACEIs induced angioedema is now more increasingly recognized (1,2,3). Angioedema occurs in 0.1-0.7% of patients on ACEIs and nearly always occurs in the head and neck region, frequently involving the mouth, tongue, pharynx and larynx (2). The onset can be early, however it may be considerably delayed in a significant number of cases.

Case report

A 71 year old man, a known hypertensive was started on Enalapril after coronary by pass surgery in 1996. Prior to this he had been on Aspirin, Atenolol and Isosorbite dinitrate for 3 years with no adverse-effects. About a month after starting Enalapril, he developed facial swelling affecting his cheeks, lips and tongue. It lasted for 24-48 hours before the swelling resolved spontaneously. Due to its mild nature he didn't think much of it and continued his medication. He developed a second episode 3 months later and subsequently an episode every 2-3 months. He didn't complain about it during his medical follow-up until recently when the swelling got worse. When he was seen at the clinic, there was swelling of the cheeks, lips and tongue resulting in dysarthria. However the was no signs of airway obstruction nor did he have any other cutaneous manifestations. A diagnosis of angioedema was made and Enalapril was replaced with Atenolol and the patient advised to come to clinic daily over the next few days. The angioedema resolved completely by the third day. He denied having a history of angioedema prior to starting Enalapril and there was also no family history of angioedema.

Discussion

Cases of ACEIs induced angioedema are likely to increase in the future, as treatment with this category of drugs becomes widespread. The mechanism of ACEIs induced angioedema is not fully understood. However, it is thought to be a biochemical rather than an immunological reaction for a number of reasons. Firstly, angioedema can occur within hours of the first dose, leaving insufficient time for an immunological response to occur; secondly, the effect can occur with any ACEIs, regardless of its structure (2). ACEIs influences a num-

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ber of biochemical pathways including bradykinin, substance P degradation and the renin angiotensin pathway. ACEIs induced angioedema is most likely to involve increased local levels of bradykinin, possibly with the additive effect of reduced angiotensin II (2,3).

Clinical features of ACEIs induced angioedema, include a predilection for the tongue and lips although oedema of the palms, soles, genitalia and visceral oedema have been rarely reported. Urticaria is seen only rarely with ACEIs induced angioedema (2). Captopril was associated with a significantly lower incidence of angioedema compared to long acting agents (1,3).

Episodes of angioedema due to ACEIs are known to resolve spontaneously, even though treatment is continued as seen in the above case. This phenomenon can be confusing to the physician who may attribute it to some other cause and persist in prescribing the drug. It is important to recognize this adverse-effect, as subsequent episodes may be more severe resulting in life threatening upper airway obstruction if treatment is continued (3). In the United States, a study conducted over a period from 1986 to 1992, revealed that physicians often failed to recognize the association between ACEIs and angioedema, despite the fact that angioedema has been included in the United States Food and Drug Administration-approved package inserts since the mid 1980s (2).

Treatment of ACEIs induced angioedema requires stopping the agent and replacing it with another suitable antihypertensive drug. Specific treatment of the angioedema would include antihistamines, steroids, adrenaline and in severe cases airway protection with tracheal intubation or emergency tracheostomy.

In summary, a high index of suspicion is necessary to diagnose ACEIs induced angioedema and necessary measures taken to prevent putting the patient at an increased risk of a life-threatening event.

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BLURRING OF VISION DUE TO VLM

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ABSTRACT: A thirty two year old taxi driver presented with complaints of headache, nausea, vomiting and blurring of vision of the left eye of two days duration. He was found to have an acute anterior uveities and secondary glaucoma. On further examination patient was also found to have a neuroretinitis and phlebitis in the same eye. A worm was found in the anterior chamber and it was removed via a limbal incision under local anaesthesia. The worm-like structure sent to the Department of Parasitology was identified as *Gnathostoma spinigerum*. The patient was treated with topical eye drops and oral steroids at the same time to reduce the inflammation. No neurological symptoms were seen. The patient was not available for further evaluation and followup. *(JUMMEC 1999; 2: 115 -116)*

KEYWORDS: Blurring of vision, Gnathostomiasis

Introduction

Gnathostoma spinigerum is a rare cause of ocular helminthiasis. This worm was originally identified in the stomach of a tiger by Owen in 1836. The first human case of orbital gnathostomiasis was reported by Rhithibaed and Daengsvang in Thailand in 1937. Several cases of intraocular involvement, primarily of the anterior segment have been described (1). This parasite is found in many countries of the orient, but the most important foci for human infections are Japan and Thailand. A person acquires infection by eating raw, marinated, or poorly cooked fish. Third-stage larvae have been reported to be found in pork (2). It is suspected that food prepared from poorly cooked meat of paratenic hosts, such as the hog or chicken, may be important sources of human infection. There is the possibility that infective larvae liberated from dead aquatic intermediate hosts can be ingested in drinking water. There are previous records of human gnathostomiasis in Malaysia (3) but this is the first ocular gnathostomiasis reported in Malaysia.

Material and methods

This paper presents a case of blurring of vision due to ocular gnathostomiasis. Patient is a 32 - year old Malay taxi driver who complained of headache associated with vomiting of one day duration and blurring of vision in the left eye of two days duration before admission. Patient showed no history of trauma, no history of eating raw meat or having travelled abroad recently. The ocular examination revealed vision of the right eye to be 6/6 and of the left eye, 6/36. The remainder of the right eye examination was normal. Cornea of the left eye was hazy and intraocular pressure was raised to 33 mmHg (normal 15 mmHg - 20 mmHg). Slit lamp examination of the left eye showed marked activity in the anterior chamber with fibrinous exudate covering the pupil. A worm like structure was seen covered with the exudate inferiorly in the anterior chamber. The left pupil was intensively dilated. On further examination, the fundus showed a swollen disc with surrounding oedema. There was a track, noted below the upper temporal arcade with retinal haemorrhages. Track was in the shape of a worm. A diagnosis of acute anterior uveitis with secondary glaucoma was made. The admitting laboratory studies demonstrated a marked eosinophilia (Eosinophils - 17%, Polymorphonuclear cells - 43%, Lymphocytes - 35%, Mononuclear leukocytes - 5%). Erythrocyte sedimentation rate was raised to 43 mm / hr. LFT was normal. Stool examination for ova and cyst was negative after repeated examination for 3 times. Chest x-ray and skull x-ray were normal.

The patient was treated with topical antiglaucoma therapy, topical steroids and antibiotics and oral prednisolone 60 mg daily for 3 days which was tapered subsequently as the vision improved after two days. The patient's vision improved to 6/18 and the inflammation in the anterior chamber reduced remarkably after 3 days of treatment. About one week later, the worm like structure was found to be alive on slit lamp exami-

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nation. An operation was performed under local anaesthesia. The worm like structure was removed in a limbal incision with a Mac Pherson's forceps. M.R.I. was done after removal of the worm from the eye. No intraocular or intracranial calcifications or foreign body seen. Patient was discharged home 2 days after operation with topical steroid eye drops to the left eye. Patient was last reviewed about 2 weeks after operation and vision had improved to 6/9. There was no more inflammation in the anterior chamber. The optic disc was normal with pigmentary changes in the retina. Patient defaulted further follow up. The worm like structure was preserved in formalin and sent to the Department of Parasitology, Faculty of Medicine, University of Malaya. It was taken out and clean with fine brush to remove debris. It was then mounted in Hoyer's media. The length of the larva is approximately 4mm (Fig. 1). The anterior end of the worm or head bulb had diagnostic features of the third larval stage of the *Gnathostoma*. These features were the 4 circular rows of spines surrounding the mouth and 4 glandular sacs lying on either side of the oesophagus. From the anterior row to the posterior row of the head bulb, the numbers of hooklets in each row were respectively : 34, 38, 40, 44 (Fig. 2). The morphologic characteristics of the larva are consistent with the third stage larva of *Gnathostoma spinigerum*.

Discussion

Gnasthostoma spinigerum is the most common species known to cause human gnathostomiasis. Human infection is more often acquired by eating raw or improperly cooked fish, either through carelessness or through choice. Third stage larva fails to mature in man and it migrates for years causing inflammation in multiple organ systems. Clinical finding of gnathostomiasis are variable and may include : larva migrans, respiratory disorders, gastrointestinal masses, and intraocular infection (4). CNS involvement have been reported (4). Currently diagnosis of human gnathostomiasis can be made only by removal and morphologic identification of the larvae. An eosinophilia or elevation of sedimentation rate is more often absent than present in gnathostomiasis. In our patient there was marked eosinophilia and ESR was raised. The uveitis was caused by a third stage larva of Gnathostoma spinigerum which had entered the globe by boring through the sclera, choroid and retina, traversing the vitreous, entering the anterior chamber after penetrating the ciliary body and iris. In the future, opthalmologists should be aware of *Gnathostoma spinigerum* for causing intraocular lesions because removal of the parasite may be life saving in view of the longevity of the worm in the human host and the potential for central nervous system involvement.

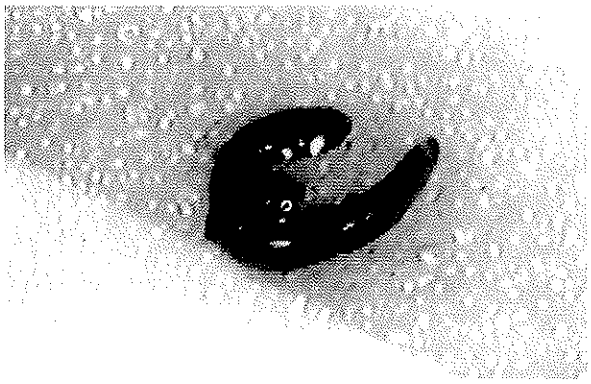

Fig. 1 The whole third stage larva recovered from the eye.

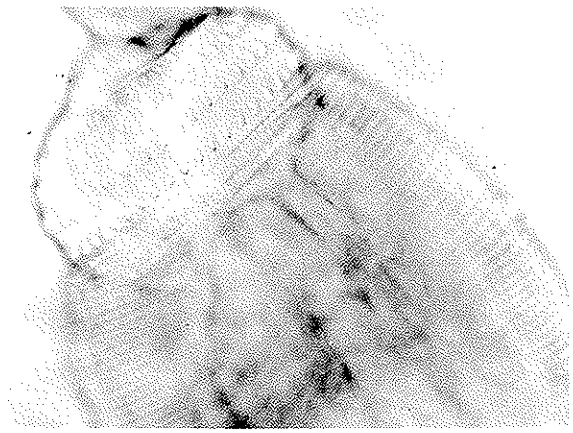

Fig 2. Anterior end of worm showing the head bulb, with the four circular rows of spines surrounding the mouth.

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PENETRATING CARDIAC INJURY

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ABSTRACT: **A case of penetrating cardiac injury is reported where cardiorrhaphy is done without cardiopulmonary bypass and via a right thoracotomy even though median stemotomy is the usual approach. It is also stressed that all precordial stabwounds must be carefully explored.** *(JUMMEC 1999; 2: 117-118)*

KEYWORDS: **Penetrating cardiac injury, Without cardiopulmonary bypass, Right posterolateral thoracotomy, Centrally placed chest injury.**

Introduction

Penetrating cardiac injury account for about 5% of penetrating chest injuries. The injuries are most commonly caused by stab injuries and gunshots. Gunshot injuries tends to be worse prognosis.

Up to 70% do not make it to the hospital and for those who made it to the hospital, overall mortality rate exceeds 10% (2).

We report a case of penetrating cardiac injury whom we repaired via a right thoracotomy without cardiopulmonary bypass.

Case

A 45 years old man was admitted to our hospital with multiple stab wounds over the chest. He was assaulted 7 hours earlier. Clinically he was pale with pulse rate of 120 beats per minutes and blood pressure of 85/56 mmHg. Four superficial stab wounds each measuring 0.5cm in diameter were noted over the precordium. Two deep penetrating stab wounds each measuring 0.5cm in diameter were noted over right sixth intercostal space just medial to the midclavicular line and another over the right tenth intercostal space along the mid axillary line. There were no engorged neck veins and auscultation reveals normal heart sounds with reduce air entry over right side with overlying subcutaneous emphysema. The abdomen was guarded. His haemoglobin was 5g/dl and chest radiograph showed a right haemothorax.

A right thoracostomy was inserted initially draining 1.0 litre of blood and subsequent drainage was minimal. In view the guarded abdomen and hypotension an exploratory laparotomy was performed and the right thoracostomy was monitored closely. No abdominal injury was detected. During the laparotomy, the right thoracostomy drained a further 900 mls of blood. With a continous thoracostomy drainage, two deep penetrating wound and with no intraabdominal injuries, the right thorax was explored. With no signs of cardiac tainponade from the four superficial praecordial stab wounds, we chose the right posterolateral approach over median sternotomy.

A 1 cm laceration of the right lower lobe which was not actively bleeding and a pericardial fat pad haematoma were found. As the lung injury could not account for the amount of bleeding, we decided to explore the intrapericardial structures. Minimal haemopericardium and two right ventricular stab wounds measuring 1 cm and 0.5 cm were found. The 1 cm wound penetrated into the right ventricular cavity, while the 0.5 cm wound only involved partial thickness of the right ventricle. The 1 cm wound was repaired with buttress horizontal mattress suture. No cardiopulmonary bypass support was needed.

Post operative two dimensional echocardiogram showed normal intracardiac structures. The patient was discharged well on seventh post-operative day.

Discussion

Penetrating cardiac injury should be suspected in all centrally placed penetrating chest injury (located between the midclavicular lines) (1). Beck's triad of hypotension, raised jugular veins pressure, muffled heart sounds are unreliable signs for pericardial tainponade. The triad is present in only a third of patients with cardiac tamponade.

Indications (1) for thoracotomy and/or cardiorrhaphy are:

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1. Mediastinal location of the entrance wound;
2. BP < 90 mmHg on admission;
3. Initial thoracostomy blood loss > 800 mls;
4. Radiographic evidence of retained haemothorax;
5. Evidence of cardiac tamponade.

Right ventricular laceration and wound size less than 1 cm tends to bleed slower. It has been postulated that ventricular injury has better prognosis because of its lower pressure and thick muscular wall that becomes occluded during systole (3). Cardiac tamponade was absent in our patient because blood escape out of the pericardial cavity into the capacious right pleural cavity.

The majority of major cardiac or great vessel injuries would die en route. Those that survive should be operated without delay, even if the centre is without cardiopulmonary bypass facility and always maintaining a high index of suspicion in centrally placed thoracic injuries as early thoracotomy as the primary treatment yields high survival rates (3). Attempts to transfer patient to specialize cardiac centres will only delay surgical treatment and will reduce survival.

Median sternotomy (2) is the recommended approach, however our case illustrates that cardiorrhaphy can also be performed through a posterolateral thoracotomy and without cardiopulmonary bypass (2,3) support which can be done in any non cardiothoracic centre.

Our case also illustrates that all praecordial penetrating wounds should not be taken lightly but should be explored carefully.

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LEGAL IMPLICATIONS IN ROUTINE CLINICAL PRACTICE

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Introduction

Medico-legal management forms an important part of the total patient care. With the rapid progress of medical science and technology, the law and ethics pertaining to clinical practice have become more complicated in order to meet the various complex issues that have arisen. Medical ethics is a code of behavior accepted voluntarily within the profession, as opposed to statutes and regulations that are imposed by official legislation. Much of medical ethics consists of good manners and civilised behavior in the general sense, but there are certain matters, which are particular to the practice of the profession of medicine. Matters of immediate concern in routine clinical practice are pertaining to consent, confidentiality and negligence.

Strictly ethical issues generally involves the respective professional bodies, medical council in the case of the doctors and the dental council in the case of dentists. This kind of self-regulation is essential in order to safe guard the interest of the public. On the other hand medical practitioners could be taken to task and may end up in litigation for failure to follow the fundamental principles involved in the day to day practice of medicine or dentistry. There are occasions where even criminal charges are being brought against doctors in the course of their routine duty. In the western countries, particularly in the United States of America, there is so much pressure on the medical practitioners owing to the high possibility of civil litigation, the practice of medicine has become quite challenging. What they call, "defensive medicine" is practiced in that part of the world with the main intention of safe guarding the interest of the doctor. Every doctor should compulsorily enroll himself with a medical protection society and the premium for indemnity goes on increasing owing to more and more litigation. There are law firms specialising in litigation cases, and looking for possible victims to be used on a fee-sharing basis. As a result health care becomes expensive and doctors are reluctant to undertake borderline cases for treatment due to fear of litigation in the event of failure. The high chance of developing residual impairment in certain specialties such as orthopaedic surgery and plastic surgery has made these specialties very expensive. The medical practitioners will develop a cautious attitude and always tend to safeguard themselves. They may carry out unnecessary investigations to safeguard themselves. Such a scenario is certainly a very unhealthy situation. It does not help the patient or the medical profession in any way. There is no doubt that the medical profession should have the freedom and right to pursue its professional duty without undue interference, but that professional freedom should have its limits, and the interest of the public must be paramount in the provision of services.

The present day medical practice, though scientifically very advanced has become more technically oriented. The concern and respect for human feelings and human values are slowly but steadily disappearing. There is a serious break down in communication between the doctors and the patients. In spite of increased efficiency in the system of health care delivery in the developed countries, the practice has become less intimate and less compassionate. The earlier period family practitioner system that maintained a very close personal relationship is fast disappearing. The traditional family practitioner had all the time for the patients and their families and he was more a family friend than a physician on whom public had great faith. In modern day medicine, with busy hospitals and so many specialisms, the patients are just part of the system, mere cases, who are moved from one place to another, similar to a factory production line. There is less and less personal communication and understanding and hence the public too has no reluctance in suing the doctors. In today's context proper and efficient health care delivery is broadly regarded as a right rather than a privilege in the developed world. So it is not surprising that the incidence of litigation against doctors will continue to rise.

Malaysia is basically an Asian country with its own culture, traditions and values. Over the last few decades there has been tremendous economic and social developments and naturally this will also have an influence on the traditional beliefs and values. Anything-untoward happening to patient was earlier accepted as fate, ill fucks, destiny or karma and rarely the doctors were blamed. The present urbanisation, modernisation and mass communication has created a better awareness and this has lead to less tolerance to accept any failures on the part of the doctors by the patients and their relatives. Already many practitioners have been taken to task.

The objective of this article is not to go into the intricacies of all aspects of unethical and unprofessional is-

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sues that are involved in medical practice. It is intended to high light some of the very fundamental principles involved in the day to day clinical practice, which is often the underlying cause for civil litigation.

Consent in medical practice

Touching some one without the authority may be an assault. An assault can take the form of a criminal or civil offense or both. It is obvious that in a doctor patient relationship there is almost always a physical contact. From a casual examination at the out patient department to an internal examination and other kinds of invasive and non-invasive treatment, involve physical contact. It is a person's right to decide what is to be done to his or her body. This right is protected by the criminal law by making unauthorised interference against the human body punishable as crimes with either fine or imprisonment or both (1). In civil law unauthorised interference with a person's body is considered as trespass, and action may result in awarding of damages. Therefore the primary objective of consent is to protect the interest of the doctor from unnecessary allegations and civil and criminal litigation. On the other hand it is also intended to protect the interest of the patient by making him or her fully aware of the steps that are taken by a clinician prior to agreeing on these medical procedures.

For routine history taking and basic clinical examination in an out patient department implied consent is generally applicable. By the patient's behavior the doctor is given to understand that the patient has no objection to such procedure and hence the consent is implied. But for more intimate examination and other procedures for investigative or therapeutic purposes, an express consent has to be obtained. This can take the form of verbal or written consent. Written consent has the advantage in the event of a contest.

In any situation consent has to be "informed consent", before it becomes valid. Taking the patient's signature on a consent form does not amount to a valid consent. Before obtaining consent, it is the doctor's responsibility to provide the patient sufficient details and information regarding the patient's condition, expected procedure, may be investigation or even treatment. The patient should be told in clear manner and in a language that the patient understands the various advantages and disadvantages of the proposed course of action and the possible expected results, and then it is the patient's responsibility to make the final decision. The patient who gives consent should be in a clear state of mind and have the intellectual capacity to understand all the implications and the doctor should satisfy himself about this point. Consent should always be for a specific procedure or a course of action. However, exception to this rule does exist under certain situations. Some time a doctor may have to obtain a "blanket consent", if he is not certain about the patient's medical condition, for example undertaking an explorative operation where no definite diagnosis has been made. Under such a situation a doctor should have the freedom and flexibility to decide what is best for the patient.

If the patient is unconscious or in a confused state of mind then a consent has to be obtained from the next of kin. Same principle is applicable to minors and mentally retarded patients. Age of consent for medical treatment is 18 years. For minors and mentally retarded generally parents or guardians could provide consent. This is referred to as "consent by proxy"(2). However, under life threatening or emergency situation a doctor can carry on with the necessary treatment if there is no way of immediately obtaining a valid informed consent. In such a situation the procedure should be very specific, pertaining to the emergency or life threatening condition. In the above event, however, all relevant details and circumstances have to be carefully and methodically documented in the patient's clinical notes. There are unusual situations where sometimes parents may refuse to give consent for blood transfusion or surgery on their children who are minors. Those who follow the faith of Jehovah's Witness are against blood transfusion. In an emergency situation if the parents refuse blood transfusion, a doctor in good faith can ignore the refusal of consent and go ahead with the necessary treatment. It is widely recognised in both criminal and civil law that there are certain circumstances in which acting out of necessity legitimates an otherwise wrongful act. However, in order to protect himself, the doctor should have another doctor to be a witness to his course of action and the entire details have to be carefully documented in the clinical notes. No junior doctor should resort to such a course of action. As an alternative, if time permits, it may be possible to obtain a court order to render the necessary treatment. In the case of adults who refuse consent the course of action to be taken could be different. In spite of explanation, if there is refusal then the patient should be made to sign a written declaration of his refusal(3).

Consent regarding donation of organs in the living is different. Various countries have various regulations pertaining to living donors and cadaver donors. In the case of minors, there are many safeguards introduced in spite of parental consent for donating an organ (4,5). In some countries such as in Canada, minors cannot be donors (6). Owing to various mal-practices many countries have brought in restrictions even for adult living donors (7). Cadaver donation is governed by the Human Tissue Donation Act and here too the regulations vary from country to country.

Medico-legal postmortem examination is covered under the Criminal Procedure Code. According to sec-

tion 329, 334 and 337 of the Malaysian CPC, sudden, unnatural and unexpected deaths could be subjected to a medico-legal postmortem for which no consent is necessary from the next of kin (8). On the other hand the next of kin has no right to object to such a procedure and if they object it will amount to contempt of court. The situation with clinical postmortem is different. Clinical postmortem does not come under the purview of the criminal procedure code and is conducted usually at the request of the clinician who has treated the patient. Clinician may be interested in knowing the exact nature and extent of the disease, efficacy of the treatment that was rendered, circumstances for failure and so on, in other word it is purely an academic exercise. In such a situation consent from the next of kin is essential.

Another situation is when police produce patients, victims and suspects to be examined in a medico-legal context. No medico-legal examination should be undertaken without a valid consent. The person should be told that he could object to the medical examination. Further more the findings will be divulged to the police and courts. In the case of minors and mentally handicapped, parental or guardian's consent is needed. If the law enforcement agency feels that a medical examination is essential but the person refuses consent, then an order may be obtained from court so that examination could be carried out without consent. There may be a situation when a person could be brought in for examination by the police who is heavily intoxicated and not in a fit state to give a valid consent. Usually such cases are admitted to ward. In such cases the doctor can carry on with the observation, examination and even undertake certain basic investigations such as blood alcohol estimation but should withhold all such information until the person had fully recovered and is in a fit state to make up his mind about consent. This is beside the immediate treatment that is rendered for his clinical state.

There is also exception to examination without consent under certain situations such as new admission to prisons, recruiting personnel into the armed forces, at the port of entry and so on.

Confidentiality

One of the most important principles of a doctor patient relationship is the maintenance of secrecy on the part of the doctor and this is referred to as confidentiality or professional secrecy (9). By virtue of the nature of the duty, the doctor gets knowledge of many personal and intimate details about a patient and the patient's family. For medical reasons the patient is often obliged to divulge all kinds of personal information to the doctor and from the doctor's point of view such information may be of relevance to advise and decide on the appropriate course of treatment and so on. Hence, one can understand the importance of confidentiality and the dangers of violating such a code of conduct. The original Hippocratic Oath and the subsequent International Code of Medical Ethics emphasise the importance of confidentiality(10). According to the international Code of Medical Ethics, "a doctor shall preserve absolute secrecy on all he knows about his patients because of the confidence entrusted in him". A breach of this confidence may lead to civil litigation. However, this principle at times gets the doctors involved in unnecessary conflict with the police and the lawyers. In the legal profession, whatever that is being conveyed by the client, the lawyer is not obliged to divulge, and no one can force him to do so. Such absolute immunity usually does not exist in the case of doctors with regards to cases pertaining to clinical practice. However, there are countries where there are laws preventing doctors from violating confidentiality.

In the day to day practice of a doctor there are instances where doctors may have to divulge certain confidential information about patients to third parties. This is done under certain circumstances and the information are always passed on to responsible persons who are in some way officially involved, or covered by statute or in the larger interest of the community. Divulging information under such special circumstances is termed as "privileged communication".

There are many instances where the doctor by virtue of various statutes is expected to divulge information. Statutory notification of deaths and births, infectious diseases, notification of poisoning, abortions are all such examples. Information can be released with the patient's consent. In insurance claims or compensation claims once the patient gives consent there is no difficulty in releasing the information. In the event of death, the next of kin or the lawyer who looks after the interest of the deceased can authorise the release of such report. Necessity may arise for the doctor to disclose certain information to immediate family members about the patient's illnesses in the larger interest of the patient. Certain sensitive and distressing issues may be better discussed with relatives rather than the patient. In the course of clinical management, information about patient can be shared among professional colleagues including dentist and nurses who are involved in the patient care. Information can also be shared in ethically approved research projects.

Courts of law can always request for confidential reports about patients and the doctor is obliged to abide. But the order should originate from the presiding judge. If the details are harmful to the patient, the doctor may politely appeal to the Judge about non-disclosure of such information and explain to him the harm it could cause to the patient. Some judges may agree with the doctor

and some may decide to take up such matters in the chambers rather than in open court. If the judge still persists then the doctor has no alternative but to comply. There are also certain special legal provisions where information has to be divulged. For example under the prevention of terrorism acts any person who has been injured in suspicious circumstances, it is the doctor's duty to notify the police. Failure to do so may lead to criminal charges being brought against the doctor. In Government medical institutions all traumatic cases are as a routine notified to the police. However, in the private sector the doctor will have to obtain consent before doing so. In certain suspicious cases, if the patient refuses consent in the private sector, the doctor can refuse to treat that patient altogether. The doctor is not obliged to take any one as his patient in the private sector even in a life threatening emergency. The situation in the government sector of course is different, and the doctor is under an agreement with the hospital to treat all cases and to abide by the hospital manual of procedure.

Another sensitive area where certain information has to be divulged are in the larger interest of the public. While providing respect for confidentiality it is important that the public interest too should be protected. For example there is no doubt that the public has to be protected from drivers who are colour blind or suffering from epilepsy particularly if they are driving public vehicles, or food handlers who are suffering from infectious diseases like typhoid. But there are certain protocols that have to be followed in handling such cases. Initially the doctor may advise a colour-blind driver to change his job and if he fails to do so then his employer should be notified. Similar cases have to be handled in a responsible manner and authorised officers should be informed about various medical conditions for necessary action, the objective of this exercise being to protect the interest of the public.

Negligence

There is nothing more disastrous in a doctor's professional career than an action for negligence against him. The concept of medical negligence is comparatively new. It did not come into prominence until the early 19th century. With the industrial revolution and urbanisation in the West, people gradually began to understand their rights and privileges. Surgeons, apothecaries and lawyers were the earliest to get involved in cases of negligence.

It is common law that for liability to occur in medical negligence there must be a duty of care owed by the doctor to the plaintiff, the defendant doctor must be in breach of that duty, and there must be damage to the plaintiff of a form recognized by the law as compensable, and which is caused by, and is not too remote a consequence of, the breach of duty (11). So first and foremost there should exist a doctor-patient relationship in a professional sense. In the private sector no doctor is compelled to take any one as his patient, but once he or she is under his care as a patient, immaterial whether it is for a fee or otherwise, the doctor-patient relationship is in force. From that moment the doctor will be compelled to treat him unless the patient on his own breaks that contract. As indicated earlier in government hospitals the situation is different and the doctors will have to treat all the patients who come to the hospital, owing to their agreement with the institution.

Basically most cases of medical negligence arise out of breach of duty. Here the test of a "reasonable man" is applied. A practitioner is expected to exhibit reasonable skill and care in the over all management of his patient. Accordingly, he should not do some thing that an average doctor would not have done and will do some thing that an average doctor would have done. What is expected out of a doctor is the reasonable skill and care. However, according to the seniority and specialisation the court may expect different degrees of skill.

In medical practice negligence can take the form of civil or criminal negligence. But the majority of cases are civil in nature. Civil negligence is a tort or civil wrong and the punishment will be in the form of compensation. To prove civil negligence the three elements namely, duty of care; breach of that duty; and a damage directly arising from it, should exist. Proof of guilt is the balance of probability, the usual civil test. Criminal negligence is very rare and the offence is so great as to be an offence against society. For example a doctor under the influence of alcohol operates on a patient and if some thing goes wrong, then the doctor could be charged for being criminally negligent. In such cases the state undertakes the prosecution unlike in civil cases and the proof is beyond reasonable doubt, the criminal test. If found guilty the doctor may end up in prison and may even have to pay compensation.

A doctor is not liable simply because of failure to cure or for bad results, provided that he has exercised reasonable skill and care. His reasonable skill, care and judgement should conform to the accepted medical practice(12). No procedure is free of risks. Even an ordinary, routine procedure can turn out to be a disaster. When some thing untoward happens, the doctor cannot be held liable, provided that he has followed the correct procedure and taken proper precautions. If the doctor has secured all necessary data on which he has made the judgement, then he is not liable even if there is an error of judgement. At this point it is very relevant to emphasise the importance of an informed consent. If something goes wrong which may be considered as unexpected or unusual could become negligent if there is no valid consent.

Often the doctors are sued for making very ordinary mistakes and failure to follow basic instructions and guide lines. Many cases are instances of carelessness or recklessness. Improper instructions over the phone, illegible writing, not carefully reading the notes, mixing up of specimens and drugs, not obtaining proper consent, poor communication with the patients and other para-medical staff are some common causes. Some time no proper clinical ward rounds are performed. Consultants, registrars and junior doctors may not do the rounds together and hence instructions may not have been properly passed down the line for necessary action. Negligence is rarely due to technical malfunction but much more often due to human errors in communications and understanding (13).

In civil negligent cases, the patient or the patient's relatives take the doctor to court. Usually the plaintiff has to prove that the defendant doctor had been negligent. But under the doctrine of "res ipsa loquitor", which means in Latin "the fact speaks for itself", the balance of proof may be shifted from the plaintiff to the defendant. Sometime the mistakes that are made by doctors are so obvious that the plaintiff will not have any difficulty in proving the case. For example amputating a wrong limb may come under this doctrine. Leaving behind swabs or instruments in body cavity is another instance. Under such circumstances the defendant doctor may have to fight his case and try to prove that he was not at fault. The doctor may take up the position that the patient's condition was so serious that he had to finish surgery as soon as possible. This time constraint could have inadvertently given rise to the above situation (14).

- Precaution against negligence:
- There should be a good doctor patient relationship
- Always obtain valid informed consent
- Keep accurate and complete medical records
- Do all relevant investigations
- Do not guarantee a cure
- You are responsible for the supervision of your subordinates
- Communicate well with the patient
- You must be sure about your limitation
- Never hesitate to consult other professional colleagues if in doubt
- Never undertake procedures in specialties in which you are not competent
- Keep reasonably informed of recent development in your specialty
- Be considerate about human life and human suffering

Conclusion

As already mentioned medical ethics has become more and more complicated and the medical profession is in a dilemma at times to take a correct and an acceptable course of action. But still, if the medical litigation cases are analysed, most of them have not originated from ethically complicated situations but from very basic fundamental principles of clinical practice. The objective of this article is to educate an average medical practitioner regarding the legal implications that he may be encountered in his day to day practice. It is always presumed that a doctor acts in good faith. But if he fails to follow the fundamentals of clinical practice especially pertaining to consent, confidentiality and negligence then he runs the risk of litigation. It is also important to remember that a practitioner in a hospital differ in many respects from that of a private practitioner. Medical doctors some time forget this difference and get involved in unnecessary embarrassment.

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Journal of the University of Malaya Medical Centre
JUMMEC
Volume 4❖Number 2 December 1999

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