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The 3rd Ministry of Health-Academy of Medicine Malaysia Scientific Meeting & International Congress of Medicine in the Tropics was held at the Shangri-La Hotel, Kuala Lumpur from 1st to 4th November 2000. Abstracts of papers presented follow:

PRE-CONFERENCE WORKSHOP ON GOOD CLINICAL PRACTICE

Health research in Malaysia

Ismail MERICAN

Deputy Director General of Health (Research & Technical Support), Malaysia

Research is a process of enquiry that produces knowledge to improve the diagnosis, treatment, control and prevention of disease. There are two interlinked categories of research: that which increases the understanding of health, ill health and the process of healthcare and that which enables assessment of interventions to promote health, prevent ill health or improve the process of healthcare. The setting up of the National Institutes of Health (NIH) in the Ministry of Health (MOH) will strengthen its research component and bring together under one umbrella five institutes, in order to create a seamless continuum from the identification of research priorities and research questions through carrying out the research to the utilization of the research results in health policy formulation, health management, health promotion and development of better tools for the diagnosis and treatment of nationally important diseases. The Institute for Medical Research (IMR) will focus on biomedical research and the Institute of Public Health (IPH) will be the national focal point for health systems research while the Institute of Health Management (IHM), the Institute of Health Promotion (IHP) and the Network of Clinical Research Centres (CRC) will focus on management research and training for professional staff, socio-behavioural research and clinical research, respectively. Other new institutes may be added in the future, depending on our needs and the progress made in particular areas of research e.g. environmental health research and traditional medicine research. The NIH will help prioritize research activities in health and allocate resources, promote institutional and research capacity strengthening, integration of different skills and greater interaction between researchers, fund managers and policy makers. It will also provide for linkages and networking with other centres of excellence, locally and abroad and help create and enhance the career development of our researchers and scientists. Funding is always a challenge and very competitive and new ways of procuring funds, other than using the Intensification of Research in Priority Areas (IRPA) mechanism, are being explored. Research priority areas for the 8MP (2001-2005) have been identified, with input from all stakeholders in health. Drug-related clinical research is on the increase and in 1999, there were 2 phase I, 5 phase II, 21 phase III and 8 phase IV clinical trials. Several initiatives have been taken over the last 2 years to facilitate quality research. 'These include the publication of various useful procedural manuals and the Malaysian guidelines for Good Clinical Practice (GCP). The Government has introduced several initiatives to encourage research and development in the private sector which can invest and capitalize on the "best buys" concept where indigenous technology is used to exploit the local market to offset the stiff competition from developed countries e.g. investing in product research and development in tropical diseases like malaria. Traditional medicine research is yet another area that has yet to be fully exploited and viable partnerships between MOH, other ministries, research institutions, the academia, the industry and others are necessary to co-ordinate and harness the expertise available in the country. The future of health research in this country is promising but a lot needs to be done to strengthen our research capacity and capability and establish linkages and forge strategic partnerships with other renowned research institutions worldwide, before Malaysia can be regarded as a major research player in the international arena.

Principles of good clinical practice (GCP)

NOR SHAHIDAH Khairullah

Malaysian Liver Foundation, Malaysia

Clinical trials are defined as a systemic administration of drugs which includes common drugs, radioactive drugs, natural and related remedies and some preparations for external application, or the use of a medical device for the purpose of discovering or confirming efficacy, patterns of adverse effects, pharmacokinetics, etc. These studies are required prior to registration of a new drug or a medical device to ensure the efficacy and safety of these drugs and treatment methods that may be administered to thousands of patients. A clinical investigator has the responsibility for both the patients' well being and that the treatment being offered is the most appropriate in any given case. In order to ensure this, the investigator is obligated to conduct clinical trials within the guidelines of Good Clinical Research (or "Trial"). The term "Good Clinical Practice" (GCP) is accepted internationally and is a term coined for labeling a collection of recommendations, rules and guidelines about how good clinical research ought to be performed. The Food And Drug Agency (FDA) in the United States was the first to issue these kinds of rules and guidelines in the 1960s. The European Union (EU) established guidelines applicable to the entire EU in May 1990. Japan has produced similar guidelines and the WHO has also released guidelines intended for use outside the USA, Europe and Japan. Work which began years ago to further harmonise the US, European and Japanese guidelines within the framework of a large international cooperative forum collectively called The International Conference of Harmonisation (ICH) has resulted in the formalisation in May 1996 of the ICH-6 GCP guidelines. These guidelines are applicable to all clinical trials carried out after January 1997 within the ICH's jurisdiction i.e. USA, EU and Japan. GCP has several purposes. The two principal ones are the protection of the patient's own self interest based on ethical principles originated in the Declaration of Helsinki, and to establish that clinical research be correctly carried out using high standards of quality and in such a manner that it may be verified later. The patient's own interest is primary, and their safety and integrity are protected, prevailing over interests of science and society. This is made possible by emphasizing the role of the ethics committee and making them strictly obligatory. The content and quality of information given to patients is of central significance. The principles also detail instructions about how adverse events are to be collected and reported. Both the quality and verification functions are ensured via instructions on how the study is to be set up, how data is gathered, verified regularly and then stored away for any later inspection. Systems with procedures that assure the quality of every aspect of the trial should be implemented and are emphasized within the principles of GCP.

Investigator's responsibilities

CC LANG

University of Malaya Medical Centre, Kuala Lumpur, Malaysia

The Malaysian Guidelines for Good Clinical Practice was launched last year in order to establish globally applicable standards in the conduct of biomedical research on human subjects in this country. This paper will discuss the functions, obligations and responsibilities of the investigator as defined in these guidelines.

Informed consent

LOKMAN HAKIM S

Institute for Medical Research, Kuala Lurnpur, Malaysia

Informed consent (IC) is a prerequisite for participating in a trial, especially in protocols planned for regulatory submission. Th principle of respect for the person (to treat a subject as an autonomous individual) requires that the subject give informed consent to participate in the research project. The

introduction of something new-unknown modifies the implicit contract between the patient and the care provider. Decisions related to care are made on the basis of a protocol that addresses the patients not only as an individual but also as part of a randomised (not personalised) decision process. Random allocation assigns unpredictably, the exposure to an experimental therapy and thus the chance to experience specific benefits and specific risks. Therefore, IC expresses the respect due to the patients who are in the position of choosing whether or not to enroll, and it protects those who propose the new-unknown. It is a process by which a subject voluntarily confirms his/her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. The essential elements (content) in the IC outline the required facts for the patient to make a reasonably informed decision. In legitimate clinical trials, consent procedures should focus on information and on communication and participation of the care provider/investigator and the patient. If the goal of the trial is not directly towards improving patient care, formal IC become more critical and emphasis should be focussed on the conditions of expression of consent.

Sponsor responsibilities

Erike DE **VERGA**

Sponsor responsibilities, as defied by ICIH GCP cannot be seen isolated from the responsibilities of the investigator and the IRB/IEC. Main categories of sponsor responsibilities are Quality Assurance and Quality Control; Medical Expertise; Trial Design, Trial Management, Data Handling, Record Keeping and Independent Data Monitoring Committee; Investigator Selection; Allocation of Duties and Functions; Compensation to Subjects and Investigators; Financing; Notification/Submission to Regulatory Authorities; Confirmation of review by ERB/IEC; Information of Investigational Products; Manufacturing, Labeling and Coding Investigational Products; Supplying and Handling Investigational Products; Record Access; Safety Information; Adverse Drug Reaction Reporting; Monitoring; Audit; Noncompliance; Premature Termination or Suspension of a Trial; Clinical Study reports and Multicenter Trials. A sponsor may transfer any or all responsibilities to a CRO, however the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The sponsor is responsible for selecting investigators/institutions. Each investigator should be qualified by training and experience and should have adequate resources to properly conduct the trial for which the investigator is selected. The monitor is the main communication link between the sponsor and the investigator. Monitors are appointed by the sponsor and should be qualified by training, and should have the scientific and/or clinical knowledge to monitor the trial adequately. Monitor's detailed responsibilities are defined by ICH GCP. The monitor visits the site regularly and provides a written monitoring report to the sponsor. The sponsor is responsible for implementing quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

Adverse event reporting

ABIDA Syed **Haq**

National Pharmaceutical Control Bureau, Ministry of Health Malaysia

With the use of any medication comes the possibility of unintended consequences. If the safety of a product is to be assessed and monitored properly, then clearly the registration holder, regulatory authorities, practitioners and consumers must have confidence in the quality and accuracy of the data used to analyze the risk-benefit assessment of a product both before and after it is marketed. During clinical trials, all adverse events (AE), which are defined as any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment, must be reported by the investigator to the sponsor and ultimately to the regulators. By definition, a serious adverse event or reaction is any untoward

medical occurrence that at any dose may result in death, is life-threatening, requires/prolongs hospitalisation causes significant disability/incapacity or congenital abnormalities. Investigators must notify sponsors of serious, unexpected events or death while on the study or within 30 days of treatment, within 2 days of the event and followed-up by a detailed written report within 7 calendar days. Within 7 days, the sponsor should notify all concerned investigators and regulators of findings that could affect adversely the safety of subjects, impact the conduct of the trial or alter the ethics committee's approval/opinion to continue the trial. For marketed products, all adverse reactions, which can be simply defined as an AE where a causal relationship with the drug is suspected, must be reported based on the timelines defined in the protocol s/regulations. It cannot be too strongly emphasized that a reporter is not required to judge whether an event was drug induced though he may usefully express an opinion. For serious AE encountered during preregistration clinical trials, an assessment of causality should be made based on follow-up information which has been evaluated by the investigator. Drug research does not stop when a drug is marketed. Industry and practitioners need to understand that drug safety is a continuum throughout the life of a product and they have a moral obligation to inform regulators on any reactions encountered.

Malaysian GCP guidelines

NOR SHAHIDAH Khairullah

Malaysian Liver Foundation, Malaysia

Throughout the world, thousands of drug trials are performed each year for efficacy and sfety confirmation of new strengths or indications for either existing drugs, generic preparations or completely new substances. In Malaysia, there has been an increasing demand for such drug related research by pharmaceutical companies in recent years as they begin to appreciate the value of collaboration with our local clinicians. The evolution of the Malaysian GCP guidelines started off sometime in 1997 when some researchers in the Malaysian Liver Foundation realising the generall lack of awareness and adherence to GCP of many of our clinical trialists decided to organize the first GCP workshop in collaboration with the Ministry of Health as a precongress activity of a regional Hepatobiliary Meeting "The Liver Update". A spinoff from this precongress workshop were a series of other GCP workshops conducted in the country. In 1999, during the 3rd Liver Update, another precongress workshop was organised to deliberate over a consensus guidelines to cater for our local requirements. This special meeting was chaired by the subcommittee charged to develop the document by the Ministry of Health's Steering Committee for Clinical Research which was later deliberated, discussed, voted on and passed by representatives from the local universities, pharmaceutical industries, drug control authority, pharmaceutical associations as well as consumer associations during the 33rd Malaysia-Singapore Congress of Academy of Medicine in August 1999. The Malaysian GCP guidelines was officially launched in November 1999 by the Director General of Health and has since been used for the conduct of GCP workshops and training throughout Malaysia. The Malaysian guidelines for GCP is adapted from the ICH Harmonised Tripartite Guideline E6 GCP guidelines with local requirements added in to reflect local legislations and practices.

Clinical trial protocol, essential documents for the conduct of a clinical trial

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The protocol describes the objective(s), design, methodology, statistical considerations and organization of the trial. The contents of the protocol should generally include all topics described in the ICH GCP guidelines. Since the protocol and the clinical trial/study report are closely related, the ICH guidelines for Structure and Content of Clinical Study Reports may need to be considered when writing a protocol. Essential Documents individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents serve to demonstrate the

compliance of the investigator, sponsor and monitor with the standards of GCP and with the applicable regulatory requirements. Essential documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones that are usually audited by the sponsor's independent audit function, and inspected by the regulatory authorities as part of the process to confirm the validity of the trial conduct and the integrity of the data collected. ICH GCP specifies which documents should be filed either at the investigator/institution or sponsor files, or both. The essential documents are grouped in 3 sections: before, during and after the trial, according to the stage of the trial in which they are typically generated.

PLENARY LECTURES

100 years **of** medical research in Malaysia.

M JEGATHESAN, * Sew Keoh TEN and • Munn Sann LYE

*Sistem Hospital Awasan Taraf, Kuala Lumpur and *Institute for Medical Research, Kuala Lumpur, Malaysia*

The hundred years story of health research in Malaysia parallels that of the history of the Institute for Medical Research (founded 1900) for the first seven decades. After that the medical faculties of our universities incrementally make their presence felt as key players on the national scene. The story is perhaps best told in terms of three eras: 1900-1963, the IMR era (both pre- and post independence); 1963-1986, the era of the advent of the universities and from 1986 onwards, the era of IRPA (the Intensification of Research in Priority Areas). It is a story earmarked by pioneers, personalities, partnerships and breakthroughs. Personalities like Hamilton Wright, Ungku Omar, Danaraj, Khalid Sahan, Omar Abdul Rahman and Abu Bakar Suleiman. Partners like the United States Army Medical research Unit, the Hooper Foundation, the WHO, SEAMEO-TROPMED, IDRC and JICA, universities in Europe, North America and Japan. Breakthroughs like the discovery of the cause of beriberi, the field stain, in vitro culture of filarial larvae, commercialiable diagnostic kits, and various findings that led to significant policy change and/or program implementation in areas such as applied nutrition, diarrheal disease, acute respiratory infection, antibiotic and disinfectant usage and vector borne diseases. It is a story of gradual build up of research capacity and institutional strengthening and funding sources albeit with occasional land marking spurts. Timely stocktaking at the turn of the century will reveal how health research has fared in this country, not only in comparison with the community of nations at large but also with other sectors within the country and with its overall socioeconomic development. We leave the century with a good national research infrastructure and mechanism in place but with clear gaps and shortfalls, particularly in the area of human resources and appropriate research mix. The lessons learnt will serve as a backdrop and help forge new visions and action plans for the coming decades. Proposed strategies should include profile enhancement of research and researchers, debureaucratisation of procedures and mechanisms, internalization and internationalization of research as well as the emplacement of a seamless research continuum.

Prion disease

Janice R ANDERSON

Department of Histopathology Addenbrooke's Hospital Cambridge United Kingdom

Bovine spongiform encephalopathy (BSE), a previously unknown disease of cattle, became a focus of world attention as it reached almost epidemic proportions in the UK in the 1980's. Predictions that it would be transmissable to man appeared to have been confirmed when a new variant of Creutzfeldt-Jakob Disease (CJD), a hitherto obscure dementing disorder, was detected in 1996. Histological similarities between the brains of sheep suffering from scrapie and of humans dying of kuru and Creutzfeldt-Jakob Disease led to discovery of transmissable human neurodegenerative

diseases with an apparently unique pathogenesis. The only identifiable source of infectivity in scrapie-infected animal brain was a protein designated PRION protein (PrP) by Prusiner, (from PROteinaceous INfectious particle). It was shown to be homologous with a larger, normal, membrane-bound protein encoded by a highly conserved host cell gene but a different tertiary structure of PrP conveyed resistance to proteolysis and ability to polymerise into amyloid fibrils. The relevance of PrP was strengthened by discovery of rare familial human neurodegenerative diseases, including familial CJD, linked to mutations in the PRP genome. The majority of cases of CJD are sporadic and lack PrP gene mutation but both forms have been transmitted to laboratory animals. Iatrogenic human disease has also been transferred via cornea1 and dural grafts and pituitary-derived growth hormone. The enigma of PRION infectivity is explained by catalytic conversion of the normal to the abnormal protein via dimerisation. Separation of heterodimers initiates a chain reaction and progressive accumulation of prions ultimately leads to spongiform encephalopathy and widespread neuronal death. Certain human PrP isoforms may have a greater susceptibility to dimerisation and conformational transformation. If PrP is the seed, theoretically CJD may arise through germ-line mutation, accidental inoculation, or somatic mutation. Conformation and glycosylation distinguish different PrP strains. Whereas there are multiple PrP strains of scrapie only three are identified in sporadic CJD. In 1986 another prion disease BSE emerged in cattle in the UK. BSE is widely believed to have been transmitted through the food chain and in 1996 a new variant of human CJD with the same strain characteristics appeared in young persons. Whilst it is postulated that new variant CJD was transmitted to man through consumption of contaminated beef there are many uncertainties. The real human risk is unknown and even the 'prion only'hypothesis is still challenged.

Vector-borne diseases and human development

Harold TOWNSON

Liverpool School of Tropical Medicine, United Kingdom

This plenary paper discusses the influence of vector-borne disease on human development. Estimates are provided of the economic impact of the most important vector-borne diseases, as well as their contributions to disability and overall mortality. The risk from emergent vector-borne diseases and their possible globalisation will be evaluated. Attention will also be given to ways in which development may lead to new problems with vector-borne disease. The paper will conclude with a consideration of the needs for both surveillance and responsive public health units. The costs of emergency interventions where new outbreaks occur can be high. Furthermore, on a global basis, declining human capacity within the field of vector-borne disease epidemiology and control is reducing our capacity to deal with the threats these diseases pose to human health and development.

HIV management and treatment strategies

Praphan PHANUPHAK

Faculty of Medicine, Chulalongkorn University and the Thai Red Cross AIDS Research Centre, Bangkok, Thailand

HIV-infected individuals require both psychosocial and medical care, starting from the first day of known seroconversion. Regular medical and immunologic (CD4+ cells) follow-up is essential to prevent rapid progression of disease. Prophylaxis of certain opportunistic infections (OI) and antiretrovirals (ARV) can be initiated, whenever possible, according to set clinical and immunologic criteria before the individuals become sick. For countries with high incidence of tuberculosis and cryptococcal meningitis, primary prophylaxis of these 2 conditions is considered cost-effective, even with limited resources. However, it is not routinely practiced in Thailand. Diagnosis and treatment of certain OI's such as MAC and CMV in developing countries are limited by the cost of investigations and treatment as well as by physician's attitude to the performance of invasive investigations. Antiretrovirals are expensive, therefore, often regarded as impossible therapeutic approach for developing countries. However, efforts should be made both at the governmental,

physician, patient, private and community levels to seek strategies that will enhance access to ARV to as many patients as possible. Concerted efforts and commitment from all key players in Thailand, including the pharmaceutical industry, are good examples for countries with similar economic levels to learn. Although drug price eventually has to come down, highly active antiretroviral therapy (HAART) is still far from real most developing countries. Less than ideal but readily affordable regimens such as double or triple nucleosides, hydroxyurea and structured treatment interruption (STI) must be seriously evaluated in each local setting. Although the benefit may not last long, these regimens may prove cost-effective if they are given at the critical timing which may be much later than that recommended in the West.

SPONSORED SYMPOSIA

Extended-spectrum beta-lactamases (ESBLs) - Are we the culprits?

David L PATERSON

University of Pittsburgh Medical Center, Pittsburgh, USA

Extended-spectrum beta-lactamase (ESBL) producing organisms are predominantly found in hospitalised patients, especially those residing in Intensive Care Units. Prolonged hospitalisation and greater severity of illness are clearly risk factors for acquisition of ESBL producers. Patients undergoing haemodialysis and those with severe bums are also at increased risk. Although published reports of outbreaks of ESBL producers in nursing home mainly emanate from North America, unpublished experience suggests that nursing home outbreaks occur worldwide. True community-acquired cases of infection have been infrequently reported, although increasing use of orally administered third generation cephalosporin may lead to more cases in the future. It is clear that in both hospitals and nursing homes, asymptomatic carriers of ESBL producers substantially outnumber those with clinical disease. Outbreaks of infection frequently occur with organisms of the same clone, indicating failure of adequate infection control measures. Additionally, prior use of third generation cephalosporins such as ceftriaxone (usually as empiric therapy) is a major risk factor for development of ESBL producers. Control of outbreaks of ESBL producing organisms has been achieved with restriction of use of cephalosporins and enhanced infection control procedures. Patients with serious infectious due to ESBL producers most commonly present with hospital-acquired pneumonia, intra-abdominal abscesses related to previous abdominal surgery, bacteremia related to use of intravascular or urinary catheters and bum wound infections. A number of cases of nosocomial meningitis complicating neurosurgical procedures have been described. Successful clinical outcome has most frequently been associated with use of imipenem. Quinolones should be regarded as second-line therapy. Increasing chromosomally mediated quinolone resistance and now the advent of plasmid-mediated quinolone resistance limit the usefulness of this class against organisms like cephalosporin-resistant Klebsiella. Cefepime, ticarcillin/clavulanate and piperacillin/tazobactam have not been extensively tested in treatment of serious infections with ESBL producers; clinical failure may be related to rising MICs for these antibiotics as inoculum of organisms rises. These antibodies should not be used for serious infectious with ESBL producers if imipenem is available. Challenges to the control and treatment of ESBL producers in the future will include the advent of strains with multiple resistance mechanisms (that is, emergence of "panresistant" ESBL producers) and detection of ESBLs in increased frequency in bacteria other than K. pneumoniae.

NSAIDs and the GI tract: past perspectives and future promises

Richard H HUNT

Division of Gastroenterology, McMaster University Medical Center, Canada

The gastroscopic demonstration of gastrotoxicity of aspirin was first demonstrated century ago and the gastrointestinal adverse events of non-steroidal anti-inflammatory drugs (NSAIDs) have been increasingly reported in the literature ever since. Despite their undoubted efficacy for the treatment

of joint inflammation and musculoskeletal injury, a significant proportion of patients taking NSAIDs may experience gastrointestinal symptoms usually dyspepsia, and endoscopic abnormalities, which range from petechial hemorrhages to fatal' complications of peptic ulcer. The risk of developing a severe GI adverse event varies from patient to patients and from NSAID to NSAID. Numerous epidemiological studies have shown that the use of NSAIDs increases the overall risk of peptic ulcer bleeding (OR 3.09-4.5) adverse events-related hospitalisations (OR 3.9-5.5), GI surgery (OR 7.75), and GI adverse events-related death (OR 4.79-7.62). Certain factors may predispose NSAID users to a greater risk of developing a severe GI event including: patients older than 60 years (OR 2.86), previous ulcer history or ulcer bleeding (OR 4.76-9.5), high dose or multiple NSAIDs (OR 4.0-23.3), concomitant corticosteroid therapy (1.83-4.4), and concomitant anticoagulant therapy (OR 2.1-16). Many agents have been developed to minimize these side effects with varying degree of success and acceptance. Currently, seven classes of FDA approved NSAIDs are available in the USA. These are proprionic acids, anthranilic acids, salicylic acids, acetic acids, oxicams, naphthylalkanones and cyclo-oxygenase-2 (COX-2) specific inhibitors. Results from the ARAMIS database of adverse events and meta-analysis have shown that, among the conventional NSAIDs, ibuprofen and salsalate are the least toxic NSAID, whereas tolmetin, fenoprofen, indomethacin, piroxicam, ketoprofen and azapropazone are among the most toxic to the GI tract. More recent analyses have suggested that some newer NSAIDs including nabumetone, meloxicam and etodolac have a significantly lower incidence of severe GI side effects, expressed as PUBs than comparator NSAIDs. This is believed, at least in part, to be due to a preferential inhibition of COX-2 by these NSAIDs. Subsequently, it was suggested that there is a correlation between the risk of GI complications and the potency of selective inhibition of COX-2/COX- 1. The more selective inhibition of COX-2 over COX- 1, the less the risk of GI complications. However, the assay methods used with the conventional NSAIDs have been widely variable and these ratios are controversial. Nevertheless, with the-recent development of highly specific COX-2 inhibitors such as celecoxib (Celebrex) and rofecoxib (Vioxx), GI toxicity appears to be minimised. Data on GI safety with these two agents have shown significantly lower gastric mucosal damage as assessed in short term endoscopic studies compared to naproxen or ibuprofen, and virtually no difference compared to placebo. Even at doses 2-4 times higher than those known to be effective for treating osteoarthritis, rofecoxib has been shown to be as safe as placebo and does not increase fecal blood (^{51}Cr labelled red blood cells) loss. Furthermore, macromolecular permeability of the small intestine is not increased by rofecoxib, in contrast to that seen with indomethacin. Endoscopic studies in OA patients, including those considered at high risk (prior ulcer history, age etc.) taking rofecoxib over six months have shown no significant increase in ulcers over placebo and significantly less than ibuprofen. Moreover, patients taking the COX-2 specific inhibitor had fewer dyspeptic symptoms, required less GI medications and underwent fewer clinically driven GI investigations than those taking non-specific NSAIDs. Analysis of the adverse events in clinical trials of celecoxib and rofecoxib indicates an approximately 50% risk reduction for perforations, ulcers and bleeds and the recent VIGOR study confirms reductions of > 50% in clinical upper GI events (54%), complicated upper GI events (57%) and any GI bleeding (62%) in a prospective outcome study of more than 8000 RA patients taking rofecoxib as compared to naproxen. There was a slight but significantly lower rate of myocardial infarction in those taking naproxen (0.1%) compared with those taking rofecoxib (0.4%), which is considered due to a protective effect of naproxen which effects an –95% inhibition of thromboxane across the whole dosing interval, and this is likely to provide a protective effect similar to that of aspirin. The introduction of COX-2 specific agents offers the opportunity for safe and effective treatment for patients who are at high risk for developing GI complications. Large, long-term, randomised and controlled studies are needed in the future to access the overall safety of COX-2 specific inhibitors, especially in organs outside the GI tract.

MIXED SYMPOSIUM 1 : MALARIA UPDATE

Malaria vaccines

FEG COX

Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, UK

Despite vast expenditure of time and money, progress towards a vaccine against malaria has been slow and disappointing but the future is more promising. There are currently five approaches to the development of a vaccine: (1) pre-erythrocytic vaccines directed against the sporozoite and the early liver stages, (2) erythrocytic vaccines directed against the asexual blood stages and, in particular, the merozoite as it invades the red cell, **(3)** combination (cocktail) multi-stage vaccines incorporatiing the genes for antigens representing different stages in the life-cycle, (4) transmission-blocking vaccines directed against the sexual stages in the blood and in the mosquito and (5j anti-disease vaccines directed towards neutralising parasite products or by-products involved in pathology. Vaccines based on the repeat region of the circumsporozoite protein (CSP) have not been successful but newer recombinant vaccines based on molecules from the non-repeat CSP regions are currently being assessed. The emphasis is also switching from antibody inhibition of sporozoite activity to possible cytotoxic responses directed against the early liver stages. Experimental vaccines based on the erythrocytic stages have used a large number of different antigens associated with merozoites and schizonts but attention is gradually being focused on a few relevant ones such as the merozoite surface protein (MSP- 1). So far, the only widely tested erythrocytic vaccine is a synthetic one, SPf66 based on three asexual stages proteins. Preliminary studies in South America indicated that SPf66 reduced the number of episodes of malaria but it was less successful when used to immunise children in sub-Saharan Africa. Experimental studies suggest that it should be possible to develop a vaccine against malaria and, drawing on the potential of molecular biology, attention is now centering on the construction of multi-stage vaccines incorporating the genes for up to 21 antigens and trials of these are currently being planned. There have been no trials using transmission-blocking or anti-disease vaccines but the genes for the molecules involved may be incorporated into combination vaccines in future. However, there are major hurdles to be overcome and a widely available commercial vaccine will be many years away.

Research on antimalarial drugs at the Bangkok Hospital for Tropical Diseases, Thailand

Sornchai LOOAREESUWAN

Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

With the emergence of multidrug resistant falciparum malaria in Thailand, new drugs and drugs in combination are urgently needed. New antimalarial drugs have been investigated at the Hospital for Tropical Diseases in the recent years. Atovaquone, a hydroxynaphthoquinone, was evaluated and found that Atovaquone alone proved safe and effective. All patients treated had clinical cure, however, one third of patients had late recrudescence (RI). When it was combined with proguanil, the cure rate increased to 100%. This combination is now developed as a fixed drug named Malarone®. Artemisinine derivatives such as artesunate, arteniether, arteether, dihydroartemisinin are also tested at the Bangkok Hospital for Tropical Diseases. Artesunate and artemether alone with a total dose of 600 to 750 mg. given over 5-7 days produced cure rates of 80 to 95%. Artesunate or dihydroartemisinin suppositories with the dose of 10 mg/kg/day have been proved successful for the treatment of severe malaria. The artemisinin derivatives when used in combination with mefloquine given over 3 days improved cure rates to 95-100%. Dihydroartemisinin alone with a total dose of 480 mg given over 5 days gave a cure rate of 90%. Arteether, a WHO/TDR supported drug, has been evaluated in the hospital and now has been registered for use in severe malaria under the name artemotil®. Other combinations (artemisinin derivatives combined with lumefantrine or doxycycline and mefloquine combined with tetracycline or doxycycline) have also been evaluated with improvement in cure rates. Recently, a fixed drug (artemether plus lumefantrine) named Coartem® (six doses

given over 72 hours) proved safe and effective for treatment of falciparum malaria and has been registered for used in many western countries. At present, studies with the combination of artemisinin derivatives plus mefloquine (in various doses and duration of treatment) are being investigated. In general, artemisinin derivatives (12 mg/kg given over 2-3 days) combined with mefloquine (25 mg/kg total dose) has been a standard regimen for treatment of multidrug resistant falciparum malaria in Thailand. Until proven otherwise, the drug combinations are still recommended for all adult patients suffering from acute uncomplicated falciparum malaria contracted in multidrug resistant areas. In severe malaria, the choice of antimalarial chemotherapy depends on the clinical severity, the drug sensitivity of the parasites and the availability and preparation of the drug. Chloroquine is still the drug of choice for chloroquine-sensitive parasites occurring in some areas in Africa. Quinine and quinidine are the only widely available drugs which are effective against chloroquine-resistant strains. Two new synthetic antimalarial drugs, mefloquine and halofantrine are also effective against chloroquine resistant strains, but they have no parenteral formulation and cases of resistance to these drugs have already been reported. Qinghaosu (artemisinin and ancient Chinese herbal medicine) and its derivatives have been used successfully in treating both uncomplicated and severe falciparum malaria. Their effectiveness in eliminating the parasites have been extensively documented, however, the recrudescent rate is rather high (10-30%). The recrudescent rate depends upon the dose, duration of artemisinin derivatives used and severity of disease: the more severe the higher the recrudescent rate. Intravenous artesunate (2 mg/kg/day, with a loading dose, total dose of 480 mg) is effective but not available in some countries. Recently, intramuscular arteether (Artemotil®) developed by a Dutch company under support by WHO/TDR has proved safe and effective for the treatment of severe malaria. It is useful in remote areas where intravenous facilities are not available. In remote areas, artesunate suppositories is preferable as it can be applied by unskilled personnel (e.g. mothers, health staff). The early treatment before reaching hospital might reduce mortality and morbidity of malaria. In summary, in Thailand drugs for treatment of uncomplicated malaria is the combination of artesunate (10 mg/kg/day) plus mefloquine (8 mg/kg/day) given for 3 days or Coartem® (six doses in 2 days) or quinine 10 mg/kg 8 hourly plus tetracycline 250 mg 6 hourly for 7 days, in patients aged 8 years and over. In treating severe malaria, early diagnosis and early treatment are vital and the aim is to save the patient's life. Prompt administration of an adequate and effective antimalarial drug is needed once the diagnosis is made. The antimalarial drugs of choice are intravenous quinine, or artemisinin derivatives. Other symptomatic and supportive treatment include careful monitoring of fluid input and urine output, frequent observations for complications with appropriate treatnient and good nursing care. In spite of these efforts, the mortality of severe malaria is still high.

Roll back Malaria

Ah Suan *TEE*

Malaysia

There are at least 300 million cases of acute malaria in the world each year with many of them causing severe illness associated with time away from work or studies. Each year, at least a million people die of malaria in tropical and subtropical regions of all continents, particularly in Africa. Among the most vulnerable populations are children under five and pregnant women. The disease is a particular burden for the poorest countries. In several regions - particularly Asia and Latin America - mortality levels have declined. However, progress is now threatened as a result of the emergence of drug resistant forms of the parasite and new epidemics, which reflect climate change, population movements or breakdown in control measures. A range of interventions has been shown to be effective in reducing the malaria burden but many of these have been used inefficiently or under-exploited. To counter the malaria scourge, the Roll Back Malaria (RBM) initiative was announced in July 1998 by Dr. G.H. Brundtland, the Director General of WHO, and officially launched with the World Bank, UNDP and UNICEF in October 1998 with the aim of halving deaths due to malaria by 2010. The six elements of the RBM strategy build on the WHO global malaria control strategy which was endorsed in Amsterdam in 1992. RBM is also supporting malaria eradication where feasible (e.g. the European and Eastern Mediterranean Regions). Monitoring and evaluation of programme impact is a cross-cutting feature of all interventions.

MIXED SYMPOSIUM 2: SEPSIS SYNDROME

Resistance patterns of nosocomial pathogens in intensive care units in Malaysia

N PARASAKTHI

Department of Medical Microbiology, University of Malaya Medical Centre, Kuala Lumpur, Malaysia

Management of critically ill patients with infections in intensive care units poses many challenges. The use of broad-spectrum antibiotics in such settings is high and may predispose to the development of resistant organisms that may then become disseminated by nosocomial transmission. Infections with methicillin-resistant staphylococci and Gram-negative bacilli are common in intensive care units. Extended-spectrum b-lactamase (ESBL) producing *Klebsiella,* inducible-Enterobacteriaceae and carbapenem-resistant *P. aeruginosa* and *Acinetobacters* are of particular concern as nosocomial pathogens in Malaysia. Between 1997 and 1998, a multi-centre study was carried out to determine the species prevalence and antimicrobial susceptibility pattern among Gram negative bacilli in four adult ICUs in Malaysia. Four hundred and ninety-nine isolates of which 411 were nonduplicates and 86 were repeats, were obtained from 288 patients. The most common isolates in order of frequency were *Acinetobacters* (34%), *P. aeruginosa* (24%), *Klebsiella* (22%), inducible Enterobacteriaceae (7%) and E. *coli* (6%).Seventy of the isolates were from blood; *Acinetobacters* were the predominant isolate from bacteremic infections followed by *Klebsiella* species and *P. aeruginosa.* Inducibles accounted for a small proportion (7%) of bacteremic infections. The species prevalence of isolates from CVL and respiratory tract was also reflective of the overall distribution of the isolates from all body sites.

Sepsis - pathogenesis and pathophysiology

David L PATERSON

University of Pittsburgh Medical Center, Pittsburgh, ***USA***

Sepsis and its sequelae represent a continuum of clinical and pathophysiological severity. The following clinically recognizable stages can be seen: (I) sepsis - the systemic response to infection manifested by two or more of (a) temperature of>38°C or <36°C, (b) tachycardia (>90 beats/minute), (c) tachypnoea (>20 breaths/minute) or $PaCO_2$<32 mm Hg, (d) white blood cell count >12 x 10^9/L, or <4x 10^9/L, or >10% immature (band) forms; (2) severe sepsis - this is sepsis associated with organ dysfunction or hypoperfusion, as manifest by alteration in mental state, hypoxaemia, elevated plasma lactate level or oliguria (urine output <30 mL for at least one hour); (3) septic shock - this is sepsis induced hypotension (i.e. a systolic blood pressure <90 mmHg or a reduction of >40 mm Hg from baseline) despite adequate tluid resuscitation; and finally (4) multiple organ dysfunction syndrome (MODS) which can be broadly defined as the presence of altered organ function in an acutely ill patient such that homeostasis can not be maintained without intervention. Both Gram positive and Gram negative bacteria induce a variety of pro-inflammatory mediators, particularly cytokines (interleukins and tumor necrosis factor). Such cytokines play a pivotal role in initiating sepsis and shock. Of particular relevance for the induction of cytokines are three types of bacterial cell wall components - endotoxin (lipopolysaccharide - present only in Gram negative bacteria), peptidoglycan (present in Gram positive and Gram negative bacteria) and lipoteichoic acid (present only in Gram positive bacteria). Some bacteria also secrete powerful exotoxins that are not a part of the cell wall. A complex, cascading interaction occurs between tumor necrosis factor, interleukins 1, 6 and X, complement, the intrinsic coagulation pathway, nitric oxide, neutrophils and lipid mediators. These mediators have effects on every organ system in the body and result in the clinical manifestations of sepsis described above.

Sepsis - treatment strategies

David L PATERSON

University of Pittsburgh Medical Center, Pittsburgh, USA

Treatment of sepsis entails a rapid, but thorough, early evaluation and urgent resuscitative efforts carried on in parallel with efforts to determine the source of sepsis and properly directed empirical antimicrobial therapy. When initial resuscitation has been accomplished and diagnosis established, definitive medical and surgical management of the infectious problem follows with continued careful attention to organ system dysfunctions. Numerous authors have found that the most important predictive factor of outcome in sepsis was the adequacy of early antimicrobial therapy. The majority of episodes of sepsis are due to Gram negative bacterial infection. Unfortunately, empiric antibiotic choice is made difficult by multiple antibiotic resistance mechanisms exhibited by these organisms. Foremost of these is beta-lactamase production. *Klebsiella pneumoniae* and *Escherichia coli* may produce extended-spectrum beta-lactamases (ESBLs) which can inactivate third generation cephalosporins, aztreonam and penicillins such as piperacillin or ticarcillin. An association exists between ESBL production and ciprofloxacin resistance further limiting antibiotic options for this type of infection. Imipenem remains active against ESBL producing organisms and in clinical trials has been associated with the lowest mortality rate for this type of infection. Gram negative organisms such as *Enterobacter, Serratia* and *Citrobacter* may produce a different type of beta-lactamase (termed ampC) which also inactivates third generation cephalosporins, aztreonam and penicillins such as piperacillin or ticarcillin. Imipenem, quinolones and aminoglycosides remain active against such organisms. *Pseudomonas aeruginosa* is probably the most difficult organism to treat in sepsis. Antibiotic options are limited by an impermeable outer membrane plus a wide variety of beta-lactamase enzymes. Combinations of active drugs are often used to treat sepsis due to *P. aeruginosa*.

MIXED SYMPOSIUM **3:** *HEMOSTASIS AND THROMBOSIS*

The missing growth factor - thrombopoietin

Beng Hock CHONG

The Centre for Thrombosis and Vascular Research, University of New South Wales and Haematology Department , Prince of Wales Hospital, Sydney, NSW, Australia

It is known for many years that there are megakaryocyte (MK) -specific growth factors but these factors were not isolated nor characterized. Studies in 1980s and early 1990s suggested the existence of two factors: Megakaryocyte-Colony Stimulating Factor (MK-CSF) which stimulates megakaryocyte proliferation and Thrombopoietin (TPO) which induces megakaryocyte differentiation. It was not until 1994, when four groups independently cloned and characterized this elusive growth factor. This factor in fact has the activity of both MK-CSF and TPO, and for simplicity, it is now called TPO. The main sources of TPO are liver, kidney and bone marrow but it is also expressed at very low levels in many tissues. Gene knock-out studies showed that it is the major regulator of platelet production. The liver and kidney TPO production is constant but bone marrow stromal cell TPO production varies inversely with the circulating platelet level. This indicates that there is a local feed back control in the marrow where platelets are produced. We found that the local regulation is mediated by MK and platelet a-granular proteins such as platelet factor 4 (PF4) and thrombospondin. TPO regulates megakaryocyte proliferation and differentiation by binding to its receptor, c-mpl on MK cells, and activates specific intracellular signal transduction pathways (e.g. Jak2/Stat3 and 5) and transcription factors (e.g. GATA 1 & 2 and FOG). These processes lead to activation or repression of genes that control megakaryocyte development and consequently platelet production.

Management of ITP in pregnancy

Muhammad Abdul JAMIL

Department of Obstetrics and Gynecology, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Idiopathic thrombocytopenic purpura (ITP) occurs more commonly in young women and is one of the commonest immune mediated disorders in pregnancy. Four clinical situations are recognized. 1. Gestational thrombocytopaenia. A condition in pregnancy invariably associated with a platelet count of greater than 100 x 10^9/L and is associated with a very low incidence of fetal thrombocytopenia. 2. Thrombocytopaenia due to maternal disease.e.g. SLE, antiphospholipid syndromes, HIV infection and drugs such as heparin. Serious obstetrical disorders like abruptio and IUD is also associated with thrombocytopenia. 3. Autoimmune thrombocytopenia. Commonly associated with low platelet counts in the fetus at an estimated incidence of 20-40% (recent papers indicate a lower estimate). The management of ITP in pregnancy is complicated by the fact that fetal thrombocytopenia is difficult to diagnose and carries substantial risks during the delivery process with rare cases of fetal hemorrhage. 4. Alloimmune thrombocytopenia. A serious fetal disorder with no maternal significance occurring in 1 in 2000 pregnancies. It is caused by the passage of maternal IgG antibodies against fetal alloantigens on the fetal platelets. Unfortunately there are no laboratory studies that can be precisely performed in the mother that may predict the occurrence of fetal thrombocytopenia. Maternal management is usually directed towards treatment of maternal symptoms. Maternal treatment is inconsistently associated with changes in the fetal platelet count. Obstetric management is aimed at reducing the risks of life threatening fetal hemorrhage occurring at the time of delivery and is directed towards the obtaining of fetal platelet samples in order to plan an appropriate strategy for delivery. Fetal blood samples are obtained either by a scalp vein puncture at the time of delivery or earlier in gestation by the use of percutaneous umbilical blood sampling (PUBS). Fetuses with platelet counts of less then 50 x 10^9/L are generally delivered by cesarean section whereas those with counts greater than 50 x 10^9/L are allowed to proceed with vaginal delivery. The use of IV IgG therapy during pregnancy has theoretical implications on improving platelet counts in the mother at risk of severe hemorrhage. It however cannot be considered to be appropriate treatment for the prevention of fetal thrombocytopenia, since the exogenous transport of IV IgG across the placenta appears to be inconsistent and unpredictable. Conclusion: ITP in pregnant women carries a small morbidity risk to the fetus. In contrast alloimmune ITP results in platelet destruction in the fetus with risk of bleeding in the fetus and effort should be made to identify high risk fetus and to consider intrauterine intervention to prevent intracranial bleeding.

Heparin-induced thrornbocytopenia

Rudy Seok Ching YEOH

Faculty of Medicine & Health Sciences, University Putra Malaysia, Selangor, Malaysia

Heparin is widely used in medicine for the prevention and treatment of thromboembolic disease. One potentially fatal side effect of heparin that is increasing being recognized is heparin-induced thrombocytopenia (HIT). This condition is associated with potentially fatal thromboembolism involving both the venous and arterial systems. In addition to this, a new syndrome of warfarin-induced acral tissue necrosis in patients with HIT and deep venous thrombosis was recently described. Two clinically distinct types of HIT have been described: type I and type II HIT. Type I HIT is characterized by an early onset (usually within 48 hrs of commencing heparin), mild thrombocytopenia (platelet count rarely dropping below 100 x 10^9/L) and occasionally platelet count returning to normal even with continuation of heparin therapy. The underlying cause is non-immune in nature and this type is of no known clinical significance. HIT type I1 is an immune-mediated reaction caused by an immunoglobulin (usually IgG) that occurs 5-14 days after commencement of heparin. It has been clearly demonstrated that the target antigen recognized by the HIT-IgG is a heparin/platelet factor 4 complex. The 2 most commonly used laboratory methods are the serotonin

release assay (SRA) and the platelet aggregation test (PAT). Both are functional assays. Recently antigenic tests have come into use, using enzyme-linked immunosorbent assay (ELISA), whereby the patient immunoglobulin (antibody) recognizes the heparin/platelet factor 4 complex (antigen). Treatment includes stopping heparin. The 2 currently favoured drug treatment options are danaparoid and hirudin. Argatroban is another promising agent.

MIXED SYMPOSIUM 4: CHRONIC BACK PAIN

Multidisciplinary approach to the management of chronic back pain

MS CARDOSA

Anaesthesia Unit, Hospital Selayang, Selangor, Malaysia

Approaches to the management of chronic back pain range from administration of various types of analgesics to surgery and nerve blocks to physiotherapy and manipulation, either singly or in combination. Multidisciplinary management of chronic pain is based on the biopsychosocial model of chronic pain, which recognizes that nociception and pain are interlinked with suffering and pain behaviour which in turn is linked with the environment of the patient. Multidisciplinary management of chronic back pain addresses three aspects of the problem: medical, physical and psychological, beginning with the multidisciplinary assessment of the patient. The members of the team include a pain specialist (an anaesthetist, physician or surgeon), who assesses the patient from the medical viewpoint, a physical therapist who assesses the patient's musculoskeletal system and physical function and a clinical psychologist or psychiatrist who assesses psychological factors. Pain Management Programs employ a combination of education, rationalisation of medication, a graded physical therapy program and cognitive behaviour therapy, with the overall aim of helping patients learn to manage their pain, to lessen distress and suffering, to improve mood, to increase function and accelerate return to a normal life. Meta-analyses of studies that evaluated the efficacy of multidisciplinary treatments for chronic back pain revealed that multidisciplinary treatments are superior to no treatment, waiting list, and single-discipline treatments like medical treatment or physical therapy. There were also additional benefits of earlier return to work and decreased use of the health care system. In Malaysia, although there are pain clinics where multidisciplinary assessment of patients with chronic pain are carried out, to date there are no multidisciplinary Pain Management Programs available. The challenge facing Pain Management practitioners in Malaysia is how to carry out a Pain Management Program in a multiethnic, multicultural society.

Surgery for a 'failed back'

ABDUL MALIK Hussein

Malaysia

It is estimated that good outcome from spinal surgery ranges from 50% - 80% depending on the skill of the surgeon and complexity of the case. We discuss the causes, investigation and treatment of a 'failed back'.

Review of non-surgical treatment modalities

TL LEE

Department of Anaesthesia, National University of Singapore, Singapore

Low back pain (LBP) is a major health problem and a major cause of medical expenses, work absenteeism and disablement. Although LBP usually is a self-limiting and benign disease that tends to improve spontaneously over time, a large variety of therapeutic interventions are available for its management. However, the effectiveness claimed for most of these interventions have not been

convincingly demonstrated and consequently, the therapeutic management of LBP varies widely. Ongoing literature searches and analyses have identified four alternative treatment categories as having at least some evidence to support clinical efficacy for the treatment for back pain: acupuncture; homeopathic therapies; manual/manipulative therapies; and mind-body therapies. Modern acupuncturists use not only traditional acupuncture points (APs) but also non-meridian APs and trigger points. Acupuncture commonly includes manual stimulation of the needles, but various adjuncts often are used in modem forms of the therapy including electrical acupuncture, injection acupuncture and acupuncture with moxibustion. It has been suggested that acupuncture might act according to principles enunciated by the gate control theory of pain. There also is some evidence that acupuncture may stimulate the production of endorphins, serotonin and acetylcholine in the central nervous system, enhancing analgesia.

MIXED SYMPOSIUM 5: PAEDIATRIC INTENSIVE CARE

The use of albumin in the ICU

Lucy Chai See LUM

Division of Paediatric Critical Care, Department of Paediatrics, University of Malaya Medical Centre, Kuala Lumpur, Malaysia

In this era of cost-conscious health care, the rational use of albumin should be reviewed carefully. Albumin is the main product of protein synthesis in the liver. It has a molecular weight of 69,000 Daltons. Albumin is an active molecule that not only facilitates fluid retention in the intravascular space by its oncotic pressure but also binds to calcium, bilirubin and most drugs to alter their 'free' and active concentrations. Albumin binds exogenous toxins and is a scavenger of oxygen derived free radicals. Hypoalbuminaemia is a widely accepted biologic marker of metabolic stress. Its presence has been suggested as an indicator of risk of mortality and morbidity in acutely ill patients. A rather simplistic response from this association is the use of exogenous albumin transfusion in increase serum albumin concentration in hypoalbuminaemia. Human albumin solutions are also used in the management of shock and other conditions in which restoration of blood volume is urgent. The Cochrane injuries Group's meta-analysis of 32 randomized controlled trials in critically ill patients with hypovolaemia from trauma, surgery or bums showed that the risk for death in the albumin treated group was higher than in the comparison group. This could be explained that in disease states where increased permeability of vessels is a main feature, administration of albumin is less effective in maintaining the plasma volume than in healthy individuals who have normal vessel permeability. Low serum albumin should not be an indication for albumin supplementation. When seen in the complexity of the patient's problems, the serum albumin is an insignificant parameter for determining therapy aimed at improving the survival chances of severely ill patients.

Role of nitric oxide in ARDS

Swee Fong TANG

Department of Paediatrics, Faculty of Medicine, National University of Malaysia, Malaysia

Despite advances in intensive care and ventilator management, the diffuse lung injury process, known as acute respiratory distress syndrome, or ARDS, continues to be associated with significant morbidity and mortality in children. The main pathophysiological processes in ARDS are pulmonary arterial hypertension and intrapulmonary shunting leading to severe hypoxaemia. Conventional management has included the use of high fractional inspired oxygen, inotropic support and intravenous vasodilators. However, the use of intravenous vasodilators is limited by systemic hypotension and worsening of ventilation-perfusion matching. The role of inhaled nitric oxide in ARDS include lowering of pulmonary arterial pressures and pulmonary vascular resistance, improving the distribution of pulmonary blood flow to improve ventilation-perfusion matching and reducing lung oxidant stress and inflammation. Various studies have demonstrated the acute physiologic

effects of inhaled nitric oxide in improving oxygenation and lowering pulmonary vascular resistance. The optimal doses of inhaled nitric oxide required to improve oxygenation is not well defined hut doses as low as 1 ppm has been shown to be efficacious. Overall inhaled nitric oxide therapy have not been associated with significant toxicities. It, however, remains uncertain whether these improvements in oxygenation and pulmonary haemodynamics actually translate to significant benefits in long-term outcomes, as recent studies have not shown a reduction in mortality or morbidity. This may be related to the heterogeneous patient populations with ARDS with multiple complicating factors. Further studies are required toward developing a greater understanding of the determinants of nitric oxide responsiveness and its relative role in the complex management of acute respiratory failure.

The critically ill child: how much analgesia, how much sedation?

FADHILAH Taib

Department of Anaesthesia and Intensive care, Hospital Kuala Lumpur, Malaysia

Sedation and analgesia in the paediatric intensive care unit are essential parts of the management of the critically ill child. It facilitates both therapeutic and diagnostic procedures, ensures patient comfort especially those receiving assisted ventilation, reduces distress in the child and as a result reduces parental anxiety. Analgesia means relief from pain. Pain has very undesirable consequences in the critically ill and can lead to significant physiologic responses e.g. tachycardia, hypertension, increased generalised and myocardial oxygen consumption, immunosuppression, catabolism and hypercoagulability. Children in ICU experience pain for various reasons: a) Pathology e.g. trauma, fractures, operations; b) Diagnostic procedures e.g. insertion of monitoring lines; c) Therapeutic procedures e.g. presence of endotracheal tubes, physiotherapy; d) Prolonged stay in one position (usually supine) can itself give rise to pain and discomfort. Most ICU patients need to be sedated in order to tolerate the endotracheal tube as well as comply with the ventilator. Asynchrony with the ventilator may cause hypoxaemia, hypercarbia and trauma to the respiratory system. Respiratory depression as well as the antitussive effect of certain drugs is helpful in achieving patients' compliance. Most ICUs are noisy places, brightly lit with ongoing activity often round the clock. This not only precludes any sleep and/or rest for the patients but also gives rise to anxiety and agitation. Older children may be anxious because of anticipation of real or imagined catastrophic events or may consider themselves in danger of death. Agitation can cause harm to the child e.g. child falling out of bed. displacement of drips, invasive monitoring lines, endotracheal tube and increase oxygen consumption. Sedation helps to relief discomfort and agitation, blunting of autonomic responses to pain and facilitation of nursing care. Sedation may also be required to reduce raised intracranial pressure, to sedate patients in whom neuromuscular paralysis is indicated and to facilitate long term ventilation and other organ support in patients with multiple organ dysfunction syndrome. Agitation may be caused by hypoxia, hypercarbia or carinal irritation, thirst, itching, stiff joints, plaster casts, sticking plaster or tight dressing, full bladder and rectum, too much suctioning of the airway and aggressive physiotherapy. The problems are less obvious and do not necessarily need to resort to pharmacological means for their resolution. Adequate nurse staffing of the ICU is important which allows for proper nurse/patient ratio. This allows the nursing staff to be able to respond to various situations that cause discomfort to the critically ill. Passive joint movements, regular turns and positioning may be useful adjuncts for patient comfort. It is important to remember, however, that even in the high-technology PTCU environment, verbal and physical reassurance remains a powerful tool for providing comfort and anxiolysis to the critically ill child. There is no pharmacologic equivalent of human compassion. 1. Appropriate analgesia and sedation in the critically ill child can be a complex process. The patients have specific requirements and altered physiology and pharmacology. Listed below are Some of the problems faced in achieving ideal conditions of sedation and analgesia in the critically ill child and their practical issues will be discussed: Pharmacology in the critically ill. 2. Ideal agents for analgesia and sedation - Benzodiazepines (Midazolam, Diazepam). Opiates (Morphine), Propofol, Keamine, Chloral hydrate, Promethazine, regional analgesia and local anaesthetics. 3. Scoring sedation and analgesia in the critically ill child. As a conclusion it is futile to believe that one drug will achieve optimal goals of sedation and

analgesia in all our patients. A "cookbook" approach is impossible because of the diversity of patients and clinical scenarios. The best practical approach should be based on multiple target setting, teamwork and communication.

MIXED SYMPOSIUM 6: EMERGING AND RE-EMERGING DISEASES

New diagnostic tools

Jane CARDOSA

Malaysia

Abstract not available

Re-emerging diseases: tuberculosis

I KUPPUSAMY

Institute of Respiratory Medicine, Hospital Kuala Lumpur

Tuberculosis is as old as humankind. It never really disappeared from the surface of this earth. Following the epidemics that occurred in Europe during the 18th century there was a steady decline in tuberculosis cases and mortality. This was even before effective chemotherapy became available in the middle of the last century. However, this decline was accelerated with the widespread implementation of effective chemotherapy. Further innovative approaches to chemotherapy such as ambulatory treatment approaches and short course directly observed treatment gave rise to optimism with regards to possibility of elimination if not eradication of the disease. However this optimism was short-lived. From the mid 80's of the last century case notifications, the world over, began to rise. Although this increase was first perceived in the developed and industrialized countries, it quickly also involved most developing third world countries. Although the major factor identified for causing this resurgence is the HIV/AIDS pandemic, other factors such as complacency and neglect of the disease by the medical fraternity, lack of political will and commitment, war, famine and poverty were also contributory. The WHO has taken the unprecedented step in 1993 of declaring tuberculosis as a global emergency and has increased its assistance and funding to poorer nations to strengthen tuberculosis control activities. It has also adopted the DOTS strategy, which has been shown to achieve high completion and cure rates and is aggressively promoting it worldwide. We are now faced with another emerging spectre; that of multi-drug resistant tuberculosis (MDR-TB). The WHO has also acknowledged the need for a special programme of care for these cases with the 'DOTS-plus' concept in areas with substantial levels of resistance. Strategies and targets have been revised with the aim of elimination of the disease in the next two to three decades.

Outbreak of Nipah virus encephalitis among humans, Malaysia, 1998-1999.

MS LYE[1], UD PARASHAR[2], GL ONG[5], AW MOUNTS[2], P KITSUTANI[3], M TAHA[4], AS TEE[4], AB SULEIMAN[4], TG KSIAZEK[3], BL ONG[6] and Aziz JAMALUDDIN[7]

Institute of Medical Research, Kuala Lumpur, Malaysia,[1] Centres for Disease Control and Prevention (CDC),Atlanta, GA, USA,[2] CDC,[3] Ministry of Health, Kuala Lumpur, Malaysia,[?] Sarawak Health Department: Department of Veterinary Services,[6] and Veterinary Research Institute.'

From September 1998 through April 1999, 265 human cases of febrile encephalitis (105 [39.6%] fatal) were reported to the Malaysian Ministry of Health. Four clusters of cases were identified. The first cluster was in Perak state; the second cluster occurred in Sikamat in Negeri Sembilan; the third and largest cluster was in Bukit Pelandok in Negeri Sembilan State and the fourth cluster occurred in a region of Selangor state adjacent to the affected area near Bukit Pelandok. Among the Nipah

cases, the mean age was 38 years (range, 2 to 75 years); 80.6% were male. 69.4% were Chinese; 16.4% were Indian, 4 (2%) and the rest belonged to other ethnic groups. The apparent source of infection among most cases appeared to be exposure to sick pigs. A case-control study showed that most patients were pig farmers. Clinically undetected Nipah infection was noted in 10(6%) of 166 community-farm controls (persons from farms without reported encephalitis patients) and 20(11%) of 178 case-farm controls (persons from farms with encephalitis patients). Case patients (persons with Nipah infection) were more likely than community-farm controls to report increased sick/dying pigs on the farm (59% versus 24%, p=0.001) and were more likely than case-farm controls to perform activities requiring direct contact with pigs (86% versus 50%, p=0.005). Only (8%) cases reported no contact with pigs. The outbreak stopped after pigs in the affected areas were culled. Direct, close contact with pigs was the primary source of human Nipah infection but other sources (e.g., infected dogs and cats) cannot be excluded.

MIXED SYMPOSIUM 7: SYSTEMIC FUNGAL INFECTION

Systemic fungal infections

Kee Peng NG

Department of Medical Microbiology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

Candida is recognized as one of the most important pathogen of systemic fungal infections. There are 196 species in the genus *Candida,* however, only a few *Candida* species are important human pathogens. The *Candida* species commonly isolated from blood stream are *C. albicans, C. parapsilosis, C. tropicalis, C. guilliermondii, C. glabrata, C. krusei* and *C. lusitaniae. C. albicans* was the most frequently isolated species from blood of patient with systemic *Candida* infection. However, during the past 2 decades, a substantial shift in the epidemiology of systemic candidiasis occurred due to different *Candida* species. Globally there was an increase in the isolation of non-albicans *Candida* like C. *parapsilosis, C. krusei, C. tropicalis* and *C. glabrata* from blood of patients with systemic candidemia. *C. dubliniensis,* a recently identified species closely related to *C. albicans,* has been implicated as a pathogen in systemic fungal infection among immunocompromised patients. Nine *Candida* species were isolated in blood cultures in University Hospital, these included *C.albicans, C.tropicalis, C.parapsilosis, C.famata, C. glabrata, C.guilliermondii, C.krusei, C.rugosa and C.zeylanoides.* The frequency of isolation of *C.albicans* was 14.2% in 1997, the rate dropped to 13.9% in 1998 and to 6.5% in 1999. *C.parapsilosis* was the most common isolate, in 1997, 57.2% in 1977, 58.3% in 1998 and 35.5% in 1999. In 1997, *C. tropicalis* constituted 17.2% of the *Candida* species isolated; the figure in 1998 was 16.6% but in 1999, the rate increased to 45.2%. No C.*dubliniensis* was identified among the *Candida* isolates. Recurrent systemic candidiasis was noted among the patients. These recurrent infections may be due to breakthrough infection; the *Candida* species isolated were predominately non-*C.albicans.* Systemic candidiasis caused by more than one species of *Candida* was also noted in critically ill patients. In such instance, two *Candida* species e.g.: *C.rugosa* and *C. glabrata, C.albicans and C. tropicalis* were isolated from a single blood culture. Molds were the second most common fungal pathogens isolated from blood of patients with systemic fungal infections. These included *Apergillus* species especially *Asp.niger, Asp.fumigatus, Asp. oryzae.* and *Asp. utus, Penicillium marneffei, Paecilomyces* species. *Chrysopsorium* species and *Fusarium* species. *Norcardia asteroides,* an Actinimycetes, was also a fungal pathogen identified among the isolates. ***Conclusions:*** It is important to continue monitoring the shift in fungal pathogens. The emergence of non-albicans *Candida* as the most important causative agent of systemic fungal infection is an important finding. With the availability of new antifungal agents with enhanced activity and less toxicity, more frequent use of antifungal prophylaxis is likely to occur, the risk for the emergence of drug resistant *Candida s*pecies are eminent.

Epidemiology, diagnosis and treatment of systemic candidiasis

Deborah MARRIOTT

St. Vincent's Hospital. Sydney, Australia

There are three important questions to be answered in relation to serious *Candida* infection in the immunocompromised host. First, are *Candida* species significant pathogens in this patient group; second, what is the epidemiologic pattern of the various *Candida* species; and third, how is systemic *Candida* infection best managed in the year 2000. There is now considerable evidence that *Candida spp.* are important nosocomial pathogens with a number of studies confirming that they are in the top five species of microorganisms isolated from blood regardless of the patient type or hospital location within the hospital. The attributable mortality of approximately 40%, the highest of any nosocomial pathogen, highlights the significance of candidaemia and the importance of early recognition and institution of therapy. This represents a major shift of paradigm in the management of patients from whom *Candida species* have been isolated from blood cultures. Previously these organisms were thought to be inconsequential isolates and were ignored. However the recognition of secondary complications such as endophthalmitis or osteomyelitis and the high attributable mortality has led to earlier, more aggressive therapeutic intervention. Laboratory speciation of Candida isolates from sterile sites is essential as the species is an important predictor of antifungal susceptibility. Currently the choice of treatment for systemic candidiasis is amphotericin B or fluconazole. These agents which have been shown to be equivalent in both neutropenic and nonneutropenic patients in several randomised, controlled studies. A number of new antifungal agents, including the extended spectrum azole drugs voriconazole, posiconazole and ravuconazole and the echinocandin caspofungin are undergoing phase II/III clinical trials and will enhance the repertoire available to treat serious Candida infection, particularly with species resistant to the current azole agents.

MIXED SYMPOSIUM 8: GLUCOSE-6 PHOSPHATE DEHYDROGENASE DEFICIENCY

Spectrum of G6PD mutations

AINOON Othman

Department of Pathology, Faculty of Medicine. Universiti Kebangsaan Malaysia

G6PD deficiency is the commonest enzymopathy in human estimated to affect 400 million individuals. The haemolysis in G6PD deficiency is thought to be produced by oxidative damage to red cell proteins. Since G6PD is the only source of NADPH in red cells the deficient cells are more susceptible than the normal red cells to oxidative damage. Haemolytic anaemia induced by certain drugs, chemical substances, fava beans and infections and the association with severe neonatal jaundice and risk of kemicterus has made G6PD deficiency a public health problem in many countries. Some G6PD-deficient individuals suffer from chronic haemolytic anaemia. Indeed it has now been established that G6PD deficiency is a heterogeneous disorder. Biochemical characterization has led to the description of no less than 442 G6PD-deficient variants with at least 229 variants characterised by methods agreed upon by WHO expert group. The cloning of the X-linked cDNA by Persico et al (1986) and the gene encoding for G6PD by Martini et al (1986) allowed the primary sequence of G6PD gene to be deduced. With the 'advent of the PCR technique, sequencing the mutant genes became easier and more rapid. To date, at least 100 different G6PD mutations have been discovered. The majority of the variants are polymorphic, occurring in area endemic for malaria with variant alleles (WHO class I & II variants) reaching high frequencies of 1 - 50 percent in various parts of the world and deficient individuals, though essentially asymptomatic in the steady state, have a risk of acute haemolytic attacks. The sporadic G6PD-deficient variants (WHO Class I) occur at low frequencies anywhere in the world and they usually present with severe phenotype, namely chronic nonspherocytic haemolytic anaemia (CNSHA). In both polymorphic and sporadic variants there is always some residual enzyme activity and this is invariably lower in RBCs than in other cells suggesting that instability of mutant G6PD molecules is probably the commonest cause of G6PD deficiency. Molecular analysis has proved to be valuable for diagnosis and to define which mutations

account for G6PD deficiency in various populations. However, with the construction of a 3-d model of the tertiary structure of human G6PD based on the structure of a bacterial G6PD by Naylor et al (1996) attempts have been made to use these mutations to identify the role of the different domains of the G6PD enzyme and individual amino acid residues in the stability of the protein and explain the clinical heterogeneity. This paper will discuss the frequency of mutations in various populations including some data on Malaysian G6PD deficiency, the distribution and nature of the mutations in a model of a 3-d structure of human G6PD that has enabled researchers to speculate some of the possible mechanisms underlying G6PD deficiency.

G6PD Deficiency and Public Health Practice

NARIMAH Awin

Family Health Development Programme, Ministry of Health Malaysia

Public health is a specialty in medicine and is based upon a defined scientific body of knowledge. Public health specialists use the natural, biological (including medical) and behavioral sciences. The extent of each of these varies, but much use is made of the discipline of epidemiology. Public health practice aims to reduce ill health in populations and for this, it uses a variety of methods, and these can be summarised as:- (i) ensuring a safe environment, (ii) enhancing immunity, (iii) behaving sensibly including good nutrition and diet, (iv) having well-born children and (v) providing appropriate and prudent health care. In preventing disease, public health practice uses different levels of prevention. Health promotion refers to the overall activities that maintain a state of good health, and depend to a large extent on the non-health sector. Primary prevention is the avoidance or elimination of the causes or determinants of disease, if they are known and something can be done about them. Secondary prevention is early detection of departures from health, so that they can be corrected, and often this takes the form of screening. Tertiary prevention is the diminution of ill effects of disease that has occurred including rehabilitation and avoiding recurrence. In deciding to screen for any disorder certain criteria must be followed, and these relate to (a) the disorder to be screened, (b) the screening test available and (c) the health delivery system. G6PD deficiency as a genetic disorder manifests generally in mild forms, mostly as haemolytic anaemia when the deficient person is challenged with certain drugs (the most well known is primaquine) and the fava bean. The anemia is often self-limiting. However, the disorder is a common cause of neonatal jaundice (NNJ) in many countries. NNJ which affects about half of new-born infants and up to a third of these are of sufficient severity to make it a public health problem of importance; indeed a few infants progress to kemicterus, a very severe complication. Therefore as far as the disease is concerned, there is adequate justification to have a nation-wide screening for any known cause of NNJ, such as G6PD Deficiency. There is a simple. easy, reliable and cheap screening test to detect this genetic disorder in newborns and parents of those affected are then appropriately counseled about the drugs and foods to be avoided to prevent haemolytic anaemia. The availability of the test further justifies nation-wide screening for this disorder. The Ministry of Health through the Family Health Development Programme has implemented this screening strategy for several years and there is evidence to show its effectiveness, efficiency and impact.

Glucose-6-phosphate dehydrogenase deficiency and kernicterus

Nem-Yun BOO

Neonatal Intensive Care Unit, Faculty of Medicine, Universiti Kebangsaan Malaysia

Severe neonatal hyperbilimbinemia associated with glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common problem in many parts of the world. Common factors identified to be associated with increased risk of hyperbilimbinemia are infection, and exposure to chemicals and fava beans. When treated late, severe hyperbilirubinemia causes kemicterus with resultant brain damage. Exposure to oxidant agents with acute onset hemolysis has been identified as an important cause of severe neonatal hyperbilimbinemia, even in the absence of haematological evidence.

Measurement of endogenous production of carbon monoxide by determining the serum level of carboxyhaemoglobin has helped identified cases due to hemolysis in the absence of haematological indices. However, numerous studies have shown that not all cases of severe hyperbilirubinemia are due to hemolysis. With the development of a simple method of measuring total serum conjugated bilirubin, bilirubin monglucuronide and diglucuronide, deficient conjugation of bilirubin is now identified as a second important cause of severe neonatal hyperbilirubinemia. No consistent correlation has been found between the level of G6PD enzyme activities and the degree of hemolysis and bilirubin production. It is not sure at this juncture whether the different genetic variants of G6PD deficiency plays any role in the degree of hemolysis, bilirubin excretion, and severity of neonatal hyperbilirubinemia. The most effective treatment of hyperbilirubinemia is still phototherapy and, when severe, exchange transfusion.

MIXED SYMPOSIUM 9: OLD DRUGS NEW USES

Arsenic trioxide in acute promyelocytic ieukemia

Min Hong **SAW**

Lam Wah Ee Hospital, Penang, Malaysia

90% of Acute Promyelocytic Leukemia (APML) is characterized by translocation between chromosome 15 and 17. The breakpoint on chromosome 15 involves an oncogene known as PML (Promyelocytic Leukemia gene) and the breakpoint on chromosome 17 involves a gene encoding for retinoid acid alpha- receptor (RAR- alpha). The hybrid produced a fusion protein of PML- RAR-alpha. It would appear that retinoid acid receptor is important for the maturation and differentiation process of myeloid cells. Disruption of the RAR gene causes the myeloid cells to be arrested at the promyelocvtic stage. Recent studies indicate that the molecular process involved the acetylated status of the histone protein. The diagnosis of APML is achieved microscopically by the presence of abnormal promyelocytes. These cells normally have heavy granulation in the cytoplasm except in the variant form. The cytochemistry stains very heavily for myeloperoxidase. Immunophenotyping showed the leukemic cells to be CD34, HLA-DR and CD56 negative, CD13 and CD33 positive. Clinically, dangerous coagulopathy and susceptibility to sepsis characterize the illness. The risk of bleeding is particularly high at the onset of induction chemotherapy. This complication has been substantially reduced when All trans- retinoic acid (ATRA) was introduced. The use of ATRA to treat APML epitomized the ideal form of cancer treatment. The drug induces differentiation instead of cell lysis in the immature leukemic cells. The coagulopathy is avoided when there is no sudden release of abnormal amount of the enzymes from the cells. However, ATRA does not cure the APML, and combination with chemotherapy is necessary. Despite this encouraging development 35-45% of the patients will still relapse. Treatment of these relapsed cases is difficult and often results only in a short period of remission. New therapeutic agents have been tried, the most promising of them all is Arsenic Trioxide (As_2O_3). Arsenic Trioxide appears to have biphasic action against the APML cells. At low dose it seems to induce differentiation and at higher dose it causes apoptosis in the leukemic cells. More importantly this compound appears to be effective both in the ATRA sensitive and resistant APML cells. Therefore the drug can be used up front to treat both the newly diagnosed as well as the relapsed cases. The availability of this drug further improved the outlook of APML and made this an eminently curable disease.

Newer uses of aspirin

A AZIZ BABA

Department of Medicine, Universiti Sains Malaysia, Kubang Kerian, Kelantan

Aspirin was first used as an analgesic, antipyretic and an anti-inflammatory agent. Subsequently, many clinical studies including prospective randomised trials, have definitively established the beneficial role of aspirin in secondary and to a lesser extent primary prevention of thromboembolic

problems. In recent years, efforts have focused on defining possible new uses of aspirin including chemo prevention of cancers and neurodegenerative diseases. There have been several observational studies of the effects of exposure to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDS) and the subsequent development of colorectal cancer. Collectively, these studies demonstrate that continuous use of aspirin and other NSAIDS results in a 40-50 % reduction in the relative risk of colorectal cancer. NSAIDS inhibit both isoforms of COX, COX-1 and COX-2. Because COX-2 levels are increased in a number of solid tumors, it may serve as a molecular target for cancer prevention. COX-2 expression may also be upregulated in patients with Alzheimer's disease; observational studies have also shown a reduced incidence of Alzheimer's disease in regular users of aspirin. Current research efforts have been focused on understanding the molecular basis for the chemoprotective effects of aspirin and other NSAIDS. It is likely, however, that emphasis will shift from aspirin and other non selective COX inhibitors to the selective COX-2 inhibitors to avoid side-effects associated with COX- 1 inhibition.

Biochemical modulation of drug resistance in chemotherapy

Gerard Chin Chye *LIM*

Department of Radiotherapy and Oncology, Hospital Kuala Lumpur, Malaysia

Resistance to chemotherapy arises through several mechanisms, such as suboptimal delivery of the drug to tumour cells, inherent resistance of the tumour cell to the drug, as well as acquired resistance. Biochemical modulation represents one of the mechanisms by which synergism occurs between two or more drags in combination, whereby bioavailabilitv and/or intracellular exposure of the drug on the target molecules are enhanced. Ensuring an optimal tumour cell kill from the beginning of chemotherapy will help to reduce the likelihood of development of drug resistance. ***Improving drug delivery to tumour cells:*** Taking the example of 5-fluorouracil (5-FU), strategies at maximising the clinical efficacy of the drug have included administration by prolonged dosing via the oral route. The absorption of oral 5-FU may be more consistent if its metabolism by dihydropyrimidine dehydrogenase (DPD) in the gastrointestinal tract is avoided. This is attempted either through the administration of oral 5-FU precursors (eg capecitabine, tegafur), or by inactivating DPD with drugs combined with oral 5-FU, eg uracil. Other agents used with 5-FU precursors which decrease the associated gastrointestinal toxicity, eg through selective inhibition of 5FU phosphorylation in the gastrointestinal tract by potassium oxonate, will improve the therapeutic ratio of 5-FU. ***Modifying metabolic pathway of cytotoxic drugs inside target cells:*** The cytotoxic effect of 5-FU is enhanced by folinic acid (calcium leucovorin) which leads to stabilisation of the ternary complex between fluorodeoxyuridylate (FdUMP), thvmidylate synthase, and 5, 10-methylenetetrahydrofolate within the target cells. 5-FU may also be biochemically modulated by other cytotoxic drugs, eg methotrexate, which is an inhibitor of dihydrofolate reductase. Other agents which have been used to augment the cytotoxic activity of 5-fluorouracil through biochemical modulation include cisplatinum, N-phosphonacetyl-L.-aspartic acid (PALA), recombinant interferon alfa-2a (IFNalpha-2a) and levamisole. Biochemical modulation of cytosine arabinoside (AraC) with inhibitors of ribonucleotide reductase aims to improve the cvtotoxicity against leukaemia bv raising intracellular levels of AraC triphosphate. ***Summary:*** Biochemical modulation is a clinically useful strategy through which the development of chemotherapy regimes with better therapeutic ratios is possible.

MIXED SYMPOSIUM 10: MANAGING SEVERE PRE-ECLAMPSIA

Managing severe pre-eclampsia - physiological and pharmacological considerations

YK CHAN

Department of Anaesthesiology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

Pre-eclampsia describes the development of hypertension with proteinuria and or oedema in parturients after the twentieth week of gestation. This is a multiple organ system disease, the

aetiology of which has not been thoroughly elucidated. There is a suggestion of it being due to failure of the second wave of trophoblastic migration resulting in the retention of the muscular structure of the maternal spiral arteries which fails to adapt to become low-resistance vessels. This failed trophoblastic migration also encourages the production of increased free radicals and lipid peroxides. These enhance the production of potent vasoconstrictors which is reflected in the impaired blood supply to various organs including the maternal supply to the fetus. The severity is measured by the degree of impairment in the performance of these organs. There is increased blood pressure with elevated systemic vascular resistance, with a suggestion of reduced blood volume that is not totally substantiated in other studies. The oncotic pressure is reduced and with increased vascular permeability may predispose these parturients to pulmonary oedema. They have increased hypercoagulability with activation of the fibrinolytic system and platelet activation. Renal ischaemia impairs glomerular function with associated proteinuria. Distension of the liver capsule by oedema or subcapsular or parenchyma1 bleeding underlies the epigastric or subcostal pain complained of by those with severe pre-eclampsia. Cerebral manifestations of impaired blood supply include severe headache, visual disturbances and hyperreflexia which could be due to vasospasm, microinfarctions, thrombosis, punctate hemorrhages or cerebral oedema. Studies show aspirin prophylaxis may have some role in reducing the incidence. Magnesium sulphate has been used for seizure prophylaxis and this has been shown to be more effective than phenytoin. Various antihypertensives have been used with hydralazine, labetolol and sodium nitroprusside being the commonest agents used.

The management of pre-eclampsia

Alex MATHEWS

Hospital Kuala Lumpur, Malaysia

Pre-eclampsia affects 2-8% of all pregnancies. Eclampsia is not uncommon and mortality associated with eclampsia is a matter of concern. In the 1995-1996 report of the Confidential Enquiries into Maternal Deaths in Malaysia several deaths were attributable to hypertensive disorders especially eclampsia. Management of this condition revolves around: (i) control of hypertension to reduce the risk of maternal cerebral hemorrhage and also to allow prolongation of pregnancy. (ii) Control of fits and prevention of recurrence of fits. (iii) Delivery of the fetus. All other measures are supportive of systems that can fail, namely, renal, coagulation, hepatic and cardiopulmonary or management of complications like intracerebral hemorrhage. Early intervention to treat or deliver reduces morbidity and mortality of both mother and baby. Recent improvements in understanding of the management of the condition include the use of magnesium sulphate in prevention of recurrent fits, the role of calcium supplementation, antioxidants and aspirin in prevention. The choice of anti-hypertensives has been studied (mainly between hydrallazine, labetolol, nifedipine and methyldopa) and there appear to be inadequate data for reliable conclusions.

Severe pre-eclampsia: managing the neonate

Nyok Ling LIM

Department of Paediatrics Hospital Selayang, Malaysia

The major concern for hypertensive diseases of pregnancy rests with the patient who has severe preeclampsia/eclampsia. Surveillance for foetal compromise is necessary besides controlling blood pressure and preventing seizures in the mother with preeclampsia. It's being found that pharmacologic treatment of women with hypertension reduces perinatal deaths but does not affect intrauterine growth retardation. Severe reductions in blood pressure however, and seizures are especially hazardous to the foetus. Risk of foetal death is 10-37% in eclampsia. Optimum time and route for delivery must be planned if mother's condition does not improve and or foetal compromise is significant. It is to be remembered that well-being of the mother does not always equate to well-being of the foetus. In the likely presence of foetal pulmonary immaturity (<34 weeks or as documented in the amniotic fluid) antenatal corticosteroid must be considered. A paediatric doctor must be

available at delivery of the baby who may have immediate complications of prematurity and asphyxia. Specifically risks of abruption and effects of antihypertensive drugs must be anticipated. Ventilatory and cardiovascular support are often necessary especially in the presence of maternal magnesium sulphate infusion or other drug therapy. Other essential aspects of neonatal intensive care for the small and ill infant include surfactant therapy, cardiorespiratory monitoring, prevention of infection, and 'aggressive' nutrition which is particularly important in the light of nutritional programming in foetal and early postnatal life for subsequent long term adult-onset diseases. Immediate neonatal outcome however is largely dependent on the weight and gestation and 'asphyxia status' of each child.

MIXED SYMPOSIUM 11: ORANG ASLI HEALTH

Health development for Orang Asli: future perspectives

Mohd SUHAIMI B A Majid

Department of Aborigines Affairs, Malaysia

The community of indigenious ethnics in Peninsular Malaysia are estimated at 120,000 as in year 2000 with 18 different subethnics with distinct cultural-linguistic and anthropological origins. Prior to the1950s, there was no access to modern medicine and the aborigines were depending solely on their own traditional health practices. The concept of illness was also a misfit. They believed that they were not sick as long as they can go out working and taking their food well. To date, considerable improvement of their health status have been observed, in particular their life expectancy rate, perinatal and maternal mortality rates but certain ailments such as malaria, tuberculosis, leprosy, intestinal infestations, fungal skin infestations and chronic forms of protein-energy malnutrition are beyond acceptable norms.

Understand Orang Asli reproductive health from an anthropological and gender sensitive perspective

Shanthi THAMBIAH

Gender Studies Programme, Faculty of Arts and Social Sciences, University of Malaya, Malaysia

An analysis of Orang Asli reproductive health must be contextualised within their belief systems, gender ideologies and the indigenous medical systems which are all interrelated and connected. The process of understanding Orang Asli reproductive health and childbirth practices must include an investigation into sex roles and the status of local childbirth attendants within the context of present-day realities. An investigation of gender ideology and behaviour provides insights into symbolic systems and their relation to empirical reality. This kind of analysis shows a decline in their reproductive health as their egalitarian gender ideologies are being subverted by hierarchical gender ideologies. Their belief system relating to a notion of shared pregnancy between men and women is being eroded by greater interaction with their sexually segregated neighbours and with the introduction of the modem sexually segregated notion of pregnancy as an all female experience. This decline in the notion of shared pregnancy between the sexes has contributed to a rise in childbirth complications and a decline in the overall reproductive health of Orang Asli women.

Medical anthropology

AYOB B Bah Los

Malaysia

Abstract not available

Current nutritional status of Orang Asli

Geok Lin KHOR

Universiti Putra Malaysia

A comprehensive insight into the various medical and health issues, including nutrition, that affect the Orang Asli is provided in a recent biomedical bibliography by Baer (1999). Besides this, nutrition studies undertaken in the 1990s will be included in this presentation, which will focus on children and women. Childhood malnutrition in Orang Asli has persisted since the colonial era often at levels of severity that are higher than that in other poor rural communities in Malaysia. Prevalence of underweight and stunting are reported in one-third to three-quarters of the children studied. Such serious levels of malnutrition are found in a wide spectrum of habitats from interior to periurban villages. The low nutritional status of Orang Asli children can be attributed directly to poor diet and high helminthic infestation. The latter is widespread in young children ranging from one-third with hookworm to over three-quarters with ascaris and trichuris. Anaemia is a common finding in children and also among the females especially in the reproductive age. Dietary intake of calories and most nutrients particularly iron is inadequate in all age groups. Nonetheless, overweight problem has emerged as documented in some periurban villages particularly among the women. While this overweight problem needs to be addressed, greater efforts are needed to alleviate the severity of under-nutrition problems as they continue to beset the Orang Asli.

MIXED SYMPOSIUM 12: MANAGING AN OUTBREAK

Principles of managing an outbreak

Hitoshi OSHITANI

World Health Organization, Regional Office for the Western Pacific

Outbreaks of communicable diseases continue to occur throughout the world. Early detection and rapid response are essential to minimize the impact of an outbreak. Public health officials recognize outbreaks through various sources, including notification from clinicians, routine surveillance, and mass media. However public health response to such information is often delayed due to late reporting. Therefore it is necessary to strengthen the mechanism to detect and report outbreaks effectively and rapidly. Once outbreak is recognized, outbreak investigation is carried out. Outbreak investigation provides useful information such as transmission route and source .of infection to control the outbreak. Proper epidemiological skills are essential to conduct epidemiological outbreak investigations. The field epidemiology training programme (FETP) have been established in many countries to train public health officials on such skills. To respond to outbreaks effectively, complete preparedness plan should be developed. It is also important to improve outbreak response capacities at district, state and national level. Coordination is another important component to respond to outbreak, coordination include those among different programmes in the Ministry of Health and also with other ministries. International collaboration is sometimes required to respond to major or unknown disease outbreaks. World Health Organization (WHO) is establishing a Global Outbreak Alert and Response Network to coordinate such international collaboration.

Responses to a newly emerging disease outbreak

MOHAMAD TAHA Arif

Ministry of Health, Malaysia

The purpose of the presentation is to describe the responses to a newly infectious disease outbreak as exemplified by the response to the Nipah Virus Outbreak of 1999. The law requires that the occurrence of 27 specific diseases and conditions be notified to the Medical Officer of Health. In the response, one has to look at various issues at clinical, epidemiological and public health levels. These

should include outbreak verification, case definition, laboratory, support, clinical diagnosis and management. The outbreak investigation would require the identification of the causative agent, the predisposing factors, source of infection, mode of transmission, the incubation period, risk factors and others. These knowledge would be useful in strengthening surveillance and the institution of specific control measures. The latter would include the elimination of the source of infection, cutting the transmission, self-protection, immunization, quarantine, environmental control, law enforcement and others. In this process one has to look at human resources from within the country and outside, rapid response team, intelligence team, food organization, financial needs and appropriate risk communication. Information gathered from the clinical, laboratory and epidemiological investigations need to be made known to all parties involved in the outbreak response. This will strengthen further the surveillance, control and inventive actions. Post-outbreak management and documentation are equally important.

Management of Enterovirus Outbreak in Sarawak 1997

Andrew KIYU, Flora ONG, KAMALIAH Moh Noh, MOHD TAHA Arif, Lye Munn SANN, JAMILAH Hashim, Sik King YAO, JAMAIL Muhi, Choo Huck 001, ZULKIFLI Jantan, Fauziah Z EHSAN and KUMARAJOTHY Supramaniam

Sarawak Health Department, Malaysia

Between 15 April and 30 June 1997, 29 previously healthy infants and young children died in Sarawak as a result of cardiovascular collapse after a short febrile illness. Those 29 fatalities occurred during an outbreak of hand, foot and mouth disease in the community. The cause of the outbreak of sudden deaths was initially unknown. So the management and control measures were based on a working hypothesis of it being due mainly to enteroviruses. The measures taken were focused on: (1) setting up of surveillance mechanisms for hand, foot and mouth disease (HFMD) and related diseases, namely (a) HFMD, (b) acute flaccid paralysis, (c) aseptic meningitis and encephalitis, (c) other very ill children; (2) field investigations, namely (a) investigation of fatal cases, (b) investigation of contacts of fatal cases, (c) case-control study, (d) toxicologic investigation, (e) serologic case control study, and (f) micronutrient surveys; (3) institution of specific control measures which were aimed at reduction of disease transmission and prevention of infection, namely (a) closure of pre-schools and kindergartens, and swimming pools, (b) setting up isolation and observations wards, (c) mandatory notifications, (d) mandatory post-mortems, (e) health education, (f) staff protection, and (g) vector control measures.

Public Health and infection control of the Bird Flu outbreak - the Hong Kong experience.

WH SETO

Queen Mary Hospital, The Hospital Authority, Hong Kong and University of Hong Kong.

A brief historic account of the outbreak leading to the slaughter of the chickens will be described. The theoretical basis for this endeavor will be presented with results of the post-slaughter monitoring programme. At that time, 44 public hospitals in Hong Kong are administered by a single organization, the Hospital Authority and clinical cases were managed in these hospitals. Over 2960 patients were admitted for investigations of H5N1. A multidisciplinary task force of hospital specialists prepared a guideline for hospital procedures, which was implemented under its supervision. Key measures taken wiil be described. These include measures taken in informing the public, the provision of rapid viral diagnosis, and the guidelines for infection control and treatment. Data will be presented to show success in managing public fear and how the presence of an infection control infrastructure was critical in the handling of the outbreak throughout the temtory.

MIXED SYMPOSIUM 13: CRITICAL CARE MEDICINE

Acute respiratory distress syndrome

Patrick SK TAN

University Malaya Medical Centre, Kuala Lumpur, Malaysia

Acute lung injury results from different types of cellular injury to the lungs and different systemic conditions are also associated with acute lung injury (ALI). Acute lung injury has been graded in its severity of manifestations by a lung injury score, the most extreme form being synonymous with acute respiratory distress syndrome (ARDS). This concept was adopted by the 1994 Consensus Conference of American and European Investigators who agreed that the diagnostic criteria for ALI should include acute onset, bilateral chest radiographic infiltrates, a pulmonary artery occlusion pressure below 18 mm Hg or absence of evidence of left artrial hypertension, impaired oxygenation regardless of the positive end-expiratory pressure (PEEP) with a Pa02/FI02 ratio < 300 torr (<40 kPa) for ALI and < 200 torr (<40 kPa) for ARDS. Severe hypoxemia occurs as a result of intrapulmunary shunt, aggravated by edema and atelectasis. In the early stages of ALI, neutrophils and mesenchymal cells aggregate in the interstitium. The squamous epithelium is severely damaged and alveolar Type I cells are replaced with proliferating Type II .cells. Pulmonary capillary endothelium is well preserved initially but endothelial damage results in increased permeability to water and protein, causing oedema to accumulate in the interstitium and alveoli. At a later stage, obliteration of capillaries by endothelial damage, cellular aggregation and microthombi may account for pulmonary hypertension in ARDS patients. The aetiologic role of bacterial or other infection occumng after the onset of ALI and ARDS is uncertain. The histological changes of ARDS are believed to be uniformly diffuse; however, Gattinoni, et al. have demonstrated that the progressive bullous changes of late ARDS are preferentially distributed in dependent lung regions. ALI and ARDS may represent the pulmonary manifestation of an inflammatory response to tissue injury occumng in different organs, accounting for their respective dysfunction or failure. Neutrophils have been shown to be present in large quantities in bronchoalveolar lavage fluid of ARDS patients, together with proinflammatory cytokines such as TNF, IL-1. Evidence from clinical and experimental investigations has led to the hypothesis that the lung and other organs are damaged as part of a neutrophil-dependent response, involving the release of antioxidants, catalase, and markers of endothelial injury such as endothelin-1 and von Willebrand factor. Other possible mediators of inflammation in ARDS, such as platelet activating factor, prostaglandins and products of disseminated intravascular coagulation are being studied. Procollagen peptides present in bonchoalveolar lavage fluid represent another group of factors which possibly influence pulmonary fibrosis in late ARDS. In numerous experimental studies, mechanical ventilation using large tidal volumes and high peak inspiratory pressures with low or no PEEP has been shown to induce hyaline membrane disease histologically similar to that seen in ARDS. Mechanical ventilation with PEEP has been shown in numerous studies to improve oxygenation in patients with acute hypoxemic respiratory failure due to ALI and ARDS. PEEP increases alveolar plateau pressures, aids alveolar recruitment, and improves functional residual capacity and arterial oxygenation. Recruitment of alveolar lung units is maximal when PEEP is around 15 to 20 cm H_2O. PEEP may also reverse hydrostatic mechanisms which allow accumulation of extravascular lung water. An 'open lung approach', based on ventilating using small tidal volume (6 to 8 ml/kg body weight), PEEP at a level above the measured lower inflection point on the pressure-volume curve for that patient (commonly 15-18 cm H_2O in adults), pressure-limited ventilation (< 30 cm H_2O) and permissive hypercapnia was shown by Amato, et al, to improve oxygenation in ARDS although there was no impact on mortality because of the study's small sample size. The disparity of subsequent ARDS randomized trials of pressure limited ventilation resulted in confusion until subsequent analysis showed that negative results in three of these trials could have arisen because of insufficient differences in plateau pressure, a surrogate for end-inspiratory alveolar pressure, between the two treatment groups. Results from the Acute Respiratory Distress Syndrome Network showed that small tidal volumes (6 ml/kg) reduced mortality by 22 percent, are in keeping with the findings of Amato, et al, and have closed an era in research on the Acute Respiratory Distress Syndrome. ***References:*** (1) Gattinoni L, Bombino M, Pelosi P et al. Lung structure and function in different stages of severe adult respiratory distress syndrome. JAMA 1994; 271:1772-9. (2) Amato

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Disseminated intravascular coagulation (DIC)

BH CHONG

Centre for Thrombosis and Vascular Research, University of New South Wales and Haematology Department, Prince of Wales Hospital, Sydney, NSW, Australia.

DIC is an acquired clinical syndrome characterized by the widespread intravascular activation of blood coagulation, generation of thrombin and fibrin thrombi, consumption of blood clotting factors and platelets. It can be caused by a variety of conditions including severe infection, trauma, malignancy, obstetrical calamities (e.g. amniotic fluid embolism), severe hepatic failure, snake bites and transfusion reactions. These causes may induce a massive inflammatory response with release of proteases, cytokines and hormones from inflammatory and vascular cells leading to extensive microvascular endothelium damage. Depending on the severity of the condition, it may result in bleeding and/or end organ damage. Diagnosis of DIC is based on clinical ,features (the presence of one of the causes listed above, evidence of bleeding and/or end organ failure) and coagulation abnormalities (prolonged clotting times, reduced plasma fibrinogen, increased fibrin monomers, fibrin degradation products or d-dimers and thrombocytopenia). The Subcommmittee on DIC of the International Society on Thrombosis and Haemostasis has recently put forward the concept of "overt DIC" and "nonovert DIC" and has devised a scoring system for their diagnosis. It is believed that the detection of nonovert DIC will result in earlier diagnosis and treatment of the condition. Hopefully this could lead to a better outcome. The most important step in the management of DIC is treatment of the cause. Infusion of plasma, cryoprecipitate, clotting factors and platelets may help to correct the coagulopathy and hence may prevent or stop the bleeding in DIC. The use of heparin is controversial as it may cause bleeding. It may be helpful in the treatment of patients with extensive thrombosis and multiple end organ damage. New treatments e.g. antithrombin III infusion have yielded only variable results.

Acute renal failure in the critically ill

ZAKI MORAD Mohd Zaher

Hospital Kuala Lumpur, Malaysia

In the critically ill, acute renal failure (ARF) which usually takes the form of acute tubular necrosis (ATN) is a common complication, which is associated with a high mortality. While the prognosis of ARF due to medical and obstetric causes has improved tremendously, that associated with ATN has remained relatively unchanged. Since the early 1980's mortality in patients with ATN in the intensive therapy units has been around 40-60%. In part this is due to changing patient demographics. More elderly patients undergo complex surgery such as cardiac surgery. Patients in intensive therapy units often have severe sepsis, are hemodynamically unstable, on multiple drugs including vasopressors and are sometimes subjected to imaging studies involving radiocontrasts. These factors promote continuing renal ischemia thus delaying recovery of ATN. Multiorgan failure (MOF) states are frequent in these patients and mortality rates increase in proportion to the number of organs that fail.

The management of severely ill patients with ATN has seen a number of changes in recent years particularly in renal replacement therapy. Nonetheless the major thrusts in the management continues to be prevention and treatment of sepsis and maintenance of adequate effective blood volume. Infection continues to be the major cause of death. Nutritional support in the form of enteral and parenteral is important. Critically ill patients with ATN are hypercatabolic and thus choice of renal replacement therapy is important. While peritoneal dialysis can be performed in some patients most would require a more efficient dialysis technic to remove excess wastes and fluids. Thus daily hemodialysis has been advocated by some and there is some evidence that this improves patient survival. The choice of the dialysis membranes is of interest. It has been shown, though not conclusively, that the use of biocompatible synthetic dialysis membranes improves patient survival and reduces the need for frequent dialysis and length of stay in ICU. Lastly, there has been a major shift towards using a form of continuous renal replacement therapy (CRRT) in the treatment of ATN in the critically ill patients. A major advantage of a continuous treatment apart from constant removal of wastes and immunomodulatory vasoactive substances found in sepsis is that there are fewer tendencies to hypotension compared to daily or intermittent hemodialysis.

MIXED SYMPOSIUM 14: ONCOLOGY

Tumour markers

Leslie C LAI

Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, Malaysia.

The term 'tumour markers' embraces a broad spectrum of molecules of widely divergent characteristics. These molecules share an association with malignancy that allows their application in one or more of the following: diagnosis, screening, monitoring and prognosis in cancer patients. Due to the lack of sensitivity and specificity most tumour markers are not helpful in screening or diagnosis of a specific cancer. With few exceptions, tumour markers are also not of much use in determining prognosis of cancer patients. The main use of tumour markers is in monitoring of response to treatment and early detection of relapse. In the USA the National Academy of Clinical Biochemistry (NACB) has introduced a process known as Standard of Laboratory Practice (SOLP), designed to recommend guidelines in focused areas of clinical laboratory medicine. One such SOLP considered the utilisation of tumour markers in the management of patients with cancer. Moreover, in the USA the Food and Drug Administration (FDA) tightly regulates the measurement of tumour markers. The European Group on Tumour Markers published their guidelines on utilisation of tumour markers in 1999 and these closely reflect the recommendations of the NACB. The SOLP on tumour marker utilisation made specific recommendations which include the use of prostate specific antigen (PSA) in screening and monitoring prostate cancer, CA15-3 in monitoring advanced breast cancer, CA125 in monitoring ovarian cancer under specific clinical conditions, calcitonin as a diagnostic indicator of medullary thyroid carcinoma, alphafoetoprotein (AFP), human chorionic gonadotrophin (hCG) and lactate dehydrogenase (LDH) in evaluating and staging germ cell tumours and immunofixation and quantification of immunoglobulins and light chains in evaluating monoclonal gammopathies. These tumour marker guidelines should be adopted on an international basis.

Viruses and cancer

R PATHMANATHAN

Subang Jaya Medical Centre, Kuala Lumpur, Malaysia

Viruses are now accepted as *bone fide* aetiological agents of human cancer; these include the Epstein-Barr virus, the hepatitis B and C viruses, human papillomaviruses, and the human T-cell leukemia virus type 1, plus several candidate human cancer viruses. It is estimated that 15% of all human cancers worldwide are caused by viruses. Typically, such viruses exist in latent form or as persistent infections in the human host. One possible scenario correlates oncogenesis with enhanced viral

activation against a background of compromised immune control or viral overload. Generally, virus-associated cancers tend to occur early to mid-life and are an important cause of morbidity and mortality. It is becoming increasingly recognized that these malignancies may also occur as "opportunistic malignancies", especially in HIV-infected persons. In all these cases, infection alone is unlikely to be the sole causative factor, and the importance of multiple factors modulating oncogenesis cannot be overemphasized. Future directions for tumour virus studies are discussed.

New treatment modalities

KC SOO

Singapore

Cancer is an increasing important cause of death. In Singapore, one in four deaths is due to the disease. Survival to a large extent is determined by the stage of the disease, though in some instances the quality of therapy may also have a significant impact. Multi-disciplinary care has been the cornerstone of cancer management, and has involved local control with surgery or radiation and chemotherapy in an adjuvant and more recently in a neo-adjuvant setting. New modalities in treatment have developed with better understanding of fundamental biological processes and emerging technologies. These would involve immune modulation strategies, gene and viral therapies, alteration of expression of major histocompatibility molecules, etc. Other novel therapies would involve refinements of current standard therapies e.g. 3D conformal radiotherapy, photodynamic therapy and viral enhancement of chemotherapy to be discussed will be some of these new therapies undergoing trials at the National Cancer Centre, Singapore.

MIXED SYMPOSIUM 15: STEM CELL TRANSPLANTATION

Stem cell transplantation: detection of engraftment by molecular methods

Rahman JAMAL

Paediatric Haematology and Oncology Unit, Department of Paediatrics, Hospital Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia

Allogeneic bone marrow and allogeneic stem cell transplantation have become standard therapies for patients with haemopoietic disorders, including leukaemias, lymphomas and aplastic anaemias. It is the aim of the haematologist to achieve total engraftment of the donor marrow in a state of stable immune tolerance and a stable haemopoietic chimerism. Crude tests of engraftment include the recovery of counts and the testing of the blood groups in the post-transplant period, but these approaches have their own limitations. The advent of molecular methods have superseded these crude approaches and have offered a more rapid and more accurate assessment of engraftment and the chimeric state and at a much earlier post-transplant stage. Within this molecular approach, several methods have been devised. Amongst them is the use of restriction fragment length polymorphisms (RFLPs), use of microsatelites and variable number tandem repeats (VNTR) (Sreenan et al., 1997). The use of an even more elegant method has also been tried i.e. the use of short tandem repeats (STR) (Frankel et al., 1996). The rationale is simple. In the genetic sequence of an individual there are short repeats of DNA sequences and this phenomenon varies from one person to another in terms of the number of repeats for each particular sequence. Hence, this polymorphism for the STR and VNTR in each individual offers a molecular pattern, which is unique for every individual. Using the polymerase chain reaction method to amplify the VNTR or STR, one can then identify the presence of small numbers of donor cells in the peripheral blood of the recipient in a very sensitive manner. The theoretical advantages of VNTR and STR analysis include increased sensitivity, the use of smaller quantities of DNA, easier preparation of the DNA, faster turnaround time, the elimination of restriction enzymes and radioisotopes. This state-of-the-art approach for the analysis of engraftment and chimerism in post bone marrow transplant patients allows for the earlier detection of engraftment, prediction of disease relapse and graft rejection.

Stem cell transplant

Min Hong *SAW*

Hospital Lam Wah Ee, Penang, Malaysia

Haematopoietic stem cells (SC) belong to a heterogeneous group of cells that are pluripotent, capable of self-renewal, and able to reconstitute an ablated marrow. Small numbers of the stem cells may contribute to fairly large part of the mature haematopoietic cells, or different clones may take turns to produce blood cells at different time frames. There are also differences between the clones in terms of the "primitiveness", and some are more totipotent than others. SC transplantation involves a process where the preserved and frozen stem cells which have been spared "conditioning", are returned to the recipient for re-engraftment of the marrow. The conditioning treatment is aimed at eradicating malignant cells and at making the host immune system more receptive to allogeneic cells. This is achieved by high dose chemotherapy +/- radiotherapy. The same concept has also been applied to autologous transplant except in this case no immune reaction happened. This concept of using overwhelming cytotoxin to overcome the resistant residual tumour cells has been modified recently. It is now widely accepted that transplantation is a form of immunotherapy. The high dose treatment will only cure a small proportion of patients, the great majority depends on the immune system to eradicate the residual tumour cells. The immune cells can be potent in killing the cancer cells. This is done either through the release of granzymes from the reactive immune cells, or by the activation of FAS receptor which induces apoptosis in the target cells. Currently there are three different sources of SC in allogeneic transplantation whether related or unrelated. These are the bone marrow, the peripheral blood (PBSC) and the cord blood. It is possible that bone marrow may become less important as a source of SC for transplantation. The rapid engrafting ability of the PBSC has been demonstrated over eight years ago. This rapid recovery of blood counts has been translated into lesser procedure-related morbidity and mortality in SC transplantation. As such it has been shown to give better overall results in the setting of transplantation for CML. SC from cord blood have several advantages. Cord blood SC have certain proliferative advantage, moreover the immune system is much more tolerant and less reactive leading to a less stringent criterion for HLA matching between the donor and recipient. However, the low numbers of nucleated cells during repletion lead to a very delayed engraftment in some cases. Slow recovery of cell counts increases the complication rate of the transplant. Future use of ex-vivo expansion of the cord blood SC may overcome this problem, and cord blood could become a valuable and important source of SC for transplantation.

Allogeneic minitransplant: who would benefit?

SK CHEONG

Department of Haematology & Transplantation, MAKNA-HUKM Cancer Institute, Hospital Universiti Kebangsaan, Kuala Lumpur, Malaysia

Allogeneic bone marrow or peripheral blood stem cell transplantation traditionally uses myeloablative regimen for conditioning to enable grafting of donor's stem cells. Animal experiments have shown that a milder non-myeloablative conditioning regimen does allow engraftment to occur. This procedure is known as minitransplant. Non-myeloablative conditioning regimens are low-intensity immunosuppressive treatment given to the recipient before infusion of donor's stem cells. It was reported to have decreased immediate procedural mortality, in particular secondary to acute graft versus host reaction. However, it did give rise to higher risks of graft rejection, tumour tolerance and disease progression. Fortunately, appropriately administered donor lymphocyte infusion has been shown to establish full donor chimerism (complete donor stem cell grafting in the recipient's bone marrow) and potentiate anti-tumour effect (graft versus tumour reaction). The reduction of immediate transplant mortality allows the procedure to be carried out in older age groups, patients with concomitant disease such as invasive mycosis that otherwise would have made the patients unfit for the procedure, patients with non-malignant disorders such as congenital immune deficiencies, autoimmune disorders or thalassaemia majors. The regimen also allows transplantation of genetically manipulated haemopoietic stem cells (gene therapy) to be carried out more readily in the immediate future.

MIXED SYMPOSIUM 16: DRUG DEVELOPMENT IN TROPICAL DISEASES

Natural drug products – HIV/AIDS drug development

Tuah JENTA

Sarawak MediChem Pharmaceuticals. Inc.

The calanolides are naturally occurring pyranocoumarins that exhibit a range of anti-viral and anti-microbial activities. ***Calophyllum lanigerum*** and ***Calophyllum teysmannii*** (rainforest trees more commonly known as bintangor trees) are natural sources of calanolide A and calanolide B respectively. Both compounds exhibit anti-HIV and anti-tuberculosis activities. Dihydrocostatolide and oxocalanolide are semi-synthetic derivatives of the naturally occurring calanolides, and also exhibit anti-HIV activity. Oxocalanolide is also active towards human cytomegalovirus (HCMV). Sarawak MediChem Pharmaceuticals, Inc is coordinating pre-clinical and clinical drug development programmes with the naturally occurring and semi-synthetic calanolides. Our company is based in Chicago and represents a Joint Venture between the Sarawak Government and Advanced Life Sciences, Inc. Calanolide A is currently in Phase I/II clinical development and has already demonstrated anti-HIV activity in HIV-infected patients. A separate pre-clinical programme, supported by the U.S. National Institute of Allergy & Infectious Diseases (NIAID), is investigating the anti-tuberculosis properties of calanolide A. Unlike calanolide B, calanolide A exists in only very small quantities in its natural form. Therefore, for the purposes of clinical study, quantities of calanolide A are manufactured using proprietary chemical processes that are owned and patented by Sarawak MediChem. Pre-clinical programmes for calanolide B and dihydrocostatolide (to develop their anti-HIV activities) are supported through the Developmental Therapeutics Program of the U.S. National Cancer Institute (NCI). A pre-clinical programme to evaluate the anti-HCMV activity of oxocalanolide is supported by the U.S. NIAID.

Clinical trial development

P OLLIARO

Switzerland

Abstract not available

IMR SYMPOSIUM I : NUTRITION UPDATE

Nutrition for diabetes

Paulo POZZILLI

University Campus Biomedico, Rome, Italy and Department of Diabetes and Metabolism, St Bartholomew's Hospital, London, UK.

Optimum dietary approaches in Type I and Type II are similar in both disease conditions. The goal of dietary therapy for management of diabetes, as outlined by the American Diabetes Association, include normalization of blood glucose levels, optimization of blood lipoprotein levels, provision of adequate energy for attaining a desirable body-weight and prevention of acute and chronic complications, in addition to improvement of overall health. Specifically, for patients with Type II diabetes mellitus, there are two major considerations for achieving these goals: (a) diet composition and (b) reduction in total energy intake to achieve desirable body-weight. Reduction of body fat is the cornerstone for management of Type II diabetes; however, long-term weight management remains a challenge for patients and health-care professionals. Implementation of an optimal diet is a complex process encompassing the elements of diet composition but extending into lifestyle changes necessary to overcome barriers to dietary compliance. Owing to its complicated nature, this

challenge requires many different tools and techniques to meet the individual patient's needs. Barrier to successful weight loss in patients with Type II diabetes include:-Physical inactivity: Physical limitations secondary to illness or injury, Sedentary occupation and leisure-time activities; - Medications: Stimulate appetite and/or lead to increased food intake, Decrease metabolic rate; - Education: Poor understanding of diet/disease relationship, Misinformation, Lack of referral for dietary counseling/follow-up; -Psychologicalfactors: Sense of isolation, Feelings of deprivation, Negativeemotions, Denial of condition; -*Lifestyle/environment:* Time pressures/competing priorities, Lack of support from family/friends, Social events. Follow-up educational sessions with the dietician is important and focus on various topics such as food composition, food labeling, shopping, recipe adaptations, and eating in restaurants. Dietitians teach patients to use food records in conjunction with blood glucose records to observe patterns in blood glucose control. A problem-solving approach is used to analyze individual blood glucose response to food, activity and drugs. Patients are then able to make adjustments in food intake and/or insulin dosage to maintain target blood glucose levels. Algorithms for food, medication and activity can be developed to help manage diabetes on a daily basis. Small careful steps over weeks or months help move the patients toward nutrition goals. Follow-up sessions by the dietician can be accomplished via clinic visits and telephone conversations to facilitate problem solving. Family members should be involved in the nutrition education process and are encouraged to follow the same life-style recommendations as the person with diabetes.

Changes in dietary patterns and chronic diseases: where are we heading?

E-Siong **TEE**

Division of Human Nutrition, Institute for Medical Research, Kuala Lumpur, Malaysia

Rapid and marked socioeconomic advancements in Malaysia for the past two decades have brought about significant changes in the lifestyles of communities. These include significant changes in the dietary patterns of Malaysians e.g the increase in consumption of fats and oils and refined carbohydrates and a decreased intake of complex carbohydrates. This resulted in a decline in the proportion of energy from carbohydrates, while an increase in the percentage contribution of fat has been observed. Changes in meal patterns are also evident: more families eat out, busy executives skip meals, the younger generation miss breakfasts and rely too much on fast foods. Many Malaysians have the mistaken belief that the taking of vitamin and mineral supplements can make up for the lack of these nutrients in their daily diets. In addition, communities have become generally more sedentary. All these changes have brought about undesirable effects with significant proportions of the affluent segments of the population'being afflicted with various non-communicable diseases associated with overnutrition, namely obesity, hypertension, coronary heart disease and cancers. Nutrition activities and programmes are now being directed to tackle this increasing trend, whilst still attempting to eliminate the undernutrition problems. The ultimate strategy towards achieving a healthy nation is the promotion of a healthy lifestyle, including inculcating a culture of healthy eating. Comprehensive long tenn programmes, including a series of Healthy Lifestyle (HLS) Programmes have been carried out by the government. The implementation of these programmes is, however, a challenge to health and nutrition workers. There is a need to examine the strategies for nutrition education to ensure more effective dissemination of information. The challenge is to determine how best to promote healthy eating within the present scenario of rapid urbanisation, "western" dietary pattern influence, a whole barrage of convenience and "health" foods and nutrition misinformation.. Malaysia continues to march ahead with its development plans to elevate the nation and its people to an even higher level of socio-economic status. The crucial question is: are we able to arrest the increase in these diet-related chronic diseases? Or are we heading towards further deterioration in dietary pattern and increase in these diseases? It will be a difficult and challenging journey ahead, requiring the concerted effort of all in the country.

Current trends and controversies in parenteral nutrition

TM RAMANUJAM

Department of Surgery, University of Malaya Medical Centre, Kuala Lumpur, Malaysia

Parenteral nutrition was successfully applied as a basic and clinical technique 30 years ago. Despite many unanswered questions, parenteral nutrition represents a major breakthrough in the long periods of survival of patients who cannot take adequate enteral intake. Although its efficacy is well proven in certain areas, such as short bowel syndrome and tropical inflammatory bowel disease, its use in other areas remains controversial. Critical evaluation of the patients receiving parenteral nutrition has lead to better understanding of the need for nutritional support and its timing of administration especially in critically ill patients. Indirect calorimetric studies in these patients have confirmed that the previous estimated requirement (3000-4000 calorieslday) is very high and the actual measured resting expenditure is around 1400 calorieslday in adults. A similar downward trend has been proven in paediatric patients as well. The role of early. "aggressive" nutritional support has been questioned. The major danger of aggressive nutritional support in malnourished patients - the "Re-feeding" syndrome has been identified. Newer techniques of administration, newer and refined nutrition formulations for infants and adults, and those with specific organ dysfunction are being developed and used. Newer indications for TPN are being evaluated. Cholestasis remains as the major unresolved problem and sepsis still is the most dangerous problem. The effect of selenium and carnitine deficiency on the myocardium has led to appropriate supplementation of these in patients on long term TPN. Aluminium toxicity is emerging as a major cause for concern in long term TPN. The role of routine addition of heparin was questioned earlier, but the recent recognition of the problem of chronic pulmonary thromboembolic disease in long term TPN has justified the need for routine addition of heparin in TPN. The rote of streptokinase, ethanol and 0.1N HCL in unblocking the catheters due to blood clots, fat and mineral deposits has been well documented. Although the current trend is to use enteral nutrition whenever feasible, parenteral nutrition has its specific role and judicious use of both parenteral and enteral nutrition will benefit the patients. 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, arginine, branched chain amino acids, growth factors, 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. However, there is no doubt that in the near future this art and science of nutritional support of the whole organism and of the key organ system will lead to the cellular level of nutritional support and provide optimal nutrition for all patients.

IMR SYMPOSIUM 2: MOLECULAR BIOLOGY IN TROPICAL DISEASES

Molecular approaches to the diagnosis of tropical diseases

FEG COX

Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, United Kingdom

The requirements of a diagnostic test are specificity, sensitivity, ease of performance and cost and most current techniques suffer from deficiencies in one or more of these areas. The gold standard is the direct identification of the causative organism and, if appropriate its isolation in culture or in cell lines. Such methods are useful, if not essential, for the diagnosis of an infection in an individual but are too expensive and time consuming for epidemiological surveys. The most widely used alternatives, immunodiagnostic techniques, can be used for the identification of antibodies in the serum or indirectly for the identification of protein or carbohydrate antigens in the circulation or in tissues. Although easy to perform and suitable for large scale application, most immunodiagnostic techniques suffer from problems of false positives and false negatives, cross reactivity, difficulties in distinguishing between patent and past infections and being expensive. There is an obvious need for improvement and the future of diagnosis lies in the development and use of molecular techniques particularly those

based on the detection of nucleic acids that can be isolated and amplified using the polymerase chain reaction (PCR). In essence, molecular techniques involve the use of primers that bind to, and can thus be used to identify, specific fragments of pathogen nucleic acids. The primers can be designed for specific purposes such as the identification of a species, strain or variant. Such techniques permit the identification of minute amounts of material and are unlikely to give false positives. Molecular techniques also have the potential for automation and high-speed turnover. Currently, these techniques are in the developmental phase and tend to be expensive and to suffer from problems of reproducibility. Nevertheless molecular techniques have been used with encouraging results some of which will be discussed with special reference to parasitic infections. In addition, some of the problems inherent in developing and using molecular techniques for the diagnosis of tropical diseases will also be discussed.

Molecular approaches to tropical diseases research

Carlos M MOREL

Director, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) World Health Organization, Switzerland

Tropical diseases research has undergone a profound change as molecular approaches have, increasingly, been incorporated into basic and applied laboratory, diagnostic, clinical and epidemiological investigations. Seen by many some years ago as ***"too sophisticated*** and therefore ***"not suitable for use in disease endemic countries",*** the science and technology of molecular biology have quickly become indispensable companions of the tropical diseases researcher. Although at first only the most advanced centres in the North were indeed privileged to use molecular biology approaches, these approaches have progressively found space in disease endemic countries - first in a few centres of excellence and now in a number of institutions where they are routinely used in basic and applied laboratory or field projects, as described in the presentation. The path from the first cloning of a parasite gene in the 80's to the imminent complete sequencing of several parasite genomes has taken less than 20 years - and as a result tropical diseases research will never be the same. But the so-called "molecular biology revolution" is far from completed: new information and knowledge accumulate at an ever increasing rate and will continue to profoundly impact on the way we think, interpret and do research in tropical diseases. Coping with this continuing revolution represents a real challenge for disease endemic countries but, as learned in the past, harnessing its power may open new avenues for the control of tropical diseases.

Human genetic factor in parasitic disease

Kenji HIRAYAMA

Department of Medical Zoology, Saitama Medical School, Moroyama, Japan

To clarify host genetic factors determining susceptibility to parasitic diseases, DNA polymorphism within human major histocompatibility complex (HLA) region was analyzed in the patients with Chagas disease (Trypanosoma cruzi infection), with Schistosomiasis japonica, and with cerebral malaria. In Guatemala, the frequencies of HLA-B35 and MICA-AS were significantly increased in the seropositives (Chagasic patients). The effects of two genes were synergistic on the susceptibility. In China, severity of hepatic fibrosis due to repeated Schistosoma japonicum infections was estimated by the pattern of ultra-sonography as grade 0 (n=44), grade I (n=81), grade II (n=99), or grade III (n=6). HLA-DRB I*1101 (Pc < 0.02) and HLA-DRB 1*1501 (Pc < 0.02) were associated with protection and susceptibility to fibrosis. HLA-class II molecules might play a role in preventing or promoting fibrotic liver change after deposition with Schistosome eggs. In Myanmar, polyrnorphism of TNF-a promoter region was analyzed in the patients with cerebral malaria. TNF-a flanking region showed biallelic polymorphic sites at -238, - 308, -857, -863, -1031, and there were 7 alleles (TNFP-A, B, C, D, M1, M4, M7). TNFP-D allele was significantly associated with cerebral malaria.

IMR SYMPOSIUM 3: ADVANCES IN THE CONTROL OF VECTOR-BORNE DISEASES

The global programme to eliminate lymphatic filariasis

EA OTTESEN

World Health Organization, Geneva, Switzerland

Ten years ago, no one foresaw that in the year **2000** there would be a global programme to eliminate lymphatic filariasis (LF) that is already **2** years old, active in **>20** of the **80** endemic countries and operating under a wholly new paradigm in public health - a paradigm affirming that public/private sector partnerships are essential in sharing both responsibilities and responses to global health problems. Principally responsible for this initiative have been: 1) ***the development of tools*** capable of effecting **LF** elimination (simple intervention regimens to eliminate blood microfilariae; simple, effective regimens for managing disease; simple, accurate diagnostic tools to define the presence of infection and to monitor programme success), 2) a new ***understanding of the patbogenesis*** of LF (including recognition that infection is acquired during *childhood,* first causing subclinical and then overt disease by parasite damage to the lymphatics and subsequent bacterial superinfection); and 3) ***international commitment*** that includes the largest-ever private sector drug donations (of albendazole from **SmithKline Beecham** and Mectizan [ivermectin] from Merck & Co., Inc.) as well as a political mandate from the World Health Assembly and appreciable humanitarian support from more than **20** governmental and non-governmental aid organizations working together in a partnership termed the Global Alliance to Eliminate Lymphatic Filariasis.

Recent research on Dengue vectors

Han Lim LEE

*Division of Medical Entomology, Institute for Medical Research, **Kuala** Lumpur.*

Dengue today still remains a public health problem in many tropical and subtropical countries. In the absence of any specific treatment and an effective vaccine to date, the control of dengue depends primarily on the interruption of disease transmission by the vectors, *Aedes aegypti* and *Ae albopictus.* Major advances in the control, surveillance and bionomics of these vectors in the past 5 years are reviewed. In the development of vector control technologies, studies were conducted to search for more effective control agents. Microbial control agent such as *Bacillus thuringiensis* H-14 (Bti) has been shown to be highly and specifically effective against dengue vectors and effective mass application techniques such as ultra-low-volume spraying of these agents have been developed and used. Simultaneous spraying of chemical insecticides especially the pyrethroids and Bti has further enhanced the control of vectors since both adulticiding and larviciding can now be combined into a single operation. The effectiveness and extended activities (larvicidal activity, wall residual activity) of new insecticides continued to be tested for their suitability in dengue control. Techniques for the rapid detection of possible emergence of vector resistance to chemical insecticides have been developed. A kit is now available for field use. In vector surveillance, ovitrap has been found to be an efficient tool in detection and monitoring the *Aedes* populations. Based on ovitrap data, a mathematical model incorporating entomological and epidemiological data was first developed and used in outbreak prediction. Molecular and immunological techniques were developed for the detection and monitoring of viral infection in the vectors. The most important finding in bionomic studies of dengue vectors was the discovery of the transovarian transmission of dengue virus from infected adults to the larvae. In other fields of study, a more recent study involved testing the anti-dengue activity of anti-viral drug, ribavirin and other drug on the development of dengue virus in *Aedes aegypti* adults. These voluminous research findings and data are now gradually incorporated into dengue control programme in order to effect a more favourable outcome against these vectors and the diseases.

Japanese encephalitis

N RAMAN

Malaysia

Abstract not available

PATHOLOGY SYMPOSIUM I : LABORATORY INSTRUMENTATION

Testing at the point of care: issues and concerns

SF YAP

Department of Pathology, Faculty of Medicine, University of Malaya, Malaysia

Testing at the point of care, as an extension of the laboratory service, has been practised in various forms. The main objective of performing testing close to the patient is rapid turn around time (TAT) and immediate availability of test results. However, the practice of point of care testing (POCT) was relatively limited until the past decade or so. The increasing use of POCT in the 1990's was the result of two developments - (i) decentralisation of the healthcare service and (ii) major advances in technology. Point of care testing, as it is practised today, generally refers to the use of portable devices to perform biological testing at patient care locations. Operators of the service are largely clinical staff directly responsible for patient care. Superficially, POCT is a major improvement over traditional testing in central laboratories. It provides for patient and physician convenience, and improved patient care in the ambulatory setting. In hospitals, the use of POCT allows immediate therapeutic decisions, particularly in critical care areas. However, the fact that POCT is not widely used as an alternative to laboratory testing is indicative of the problems inherent in the service. The main issues are related to (i) problems in the maintenance of the quality of the service, (ii) difficulties in management of POCT and (iii) economics. The presentation will focus on these issues and the strategies that have been suggested to tackle these difficulties. The role of the laboratory in POC testing will also be addressed.

Static telepathology: an experience in a private laboratory setting

Kai Soon CHAN

Malaysia

Static telepathology is defined as the electronic transmission of digitized ("static") gross or microscopic images for remote consultation, research or education. This paper describes the experience in using static telepathology in a private laboratory over a two-year period. The equipment, method, results and problems are described. The advantages and circumstances in which static telepathology would be useful are also discussed.

Microminiaturisation of laboratory analysers: "labs-on-chips"

Leslie C LAI

Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Malaysia

Microminiature devices are being developed for many applications including drug discovery, pharmacogenomics, forensic science, genetic testing, clinical chemistry diagnostic panels, point of care testing and separation science. The size of the chips varies but is typically 1 to 2 cm^2. They contain micrometer-sized structures within microlitre to nanolitre volume reaction chambers. Microminiaturisation has developed along several paths. Firstly, the demands of drug discovery programmes have stimulated the development of high throughput analysis using high density arrays

of microreaction wells on plastic plates. The volume of these wells may be as little as 50 nl for 6,500 well microplates. Secondly, surface microarrays have been been developed comprising tens of thousands of 10-100 mm^2 reaction zones onto which individual oligonucleotides or cDNAs have been deposited or synthesized *in situ*. These biochip microarrays are proving to be invaluable tools, especially for the detection of genetic disease, infectious agents and expression analysis. A third type of chip exploits micromachined channels, chambers, filters, and other structures for defined analytical purposes, e.g. micrometer-sized channels etched in glass are effective for capillary electrophoresis, glass-capped silicon chambers can be used for polymerase chain reaction, and silicon filters are effective for isolation of white cells from whole blood. The integration of different structures on the same chip provides a combination of analytical functions. Biochip array technology was developed by Randox to enable simultaneous multi-analyte detection of a wide range of diagnostic parameters on a single patient sample, e.g. cardiac markers, tumour markers and drugs of abuse. The Randox biochip assays are based on immunoassay principles with chemiluminescence as the means of detection, using either competitive or sandwiched assay formats. These biochip assays are run on the Randox analyzer EVIDENCE. The applications of the multianalyte biochips coupled to the automated handling system (EVIDENCE) provide high sample throughput and may enable more rapid diagnosis. The ultimate goal of any microchip development effort is a fully integrated analytical system, incorporating sample preparation, biochemical reactions and detection as well as result analysis – "lab-on-a chip".

PATHOLOGY SYMPOSIUM 2: THALASSAEMIAS

Phenotypic diversity of a monogenic disease

Swee Lay THEIN

GKT School of Medicine, Department of Molecular Haematology, King's Denmark Hill Campus, London, United Kingdom

A major challenge in medical research is to relate genotype to phenotype. Since the early descriptions of sickle cell disease, the simplest of monogenic diseases it has become apparent that genotype at a single locus rarely predicts phenotype, the clinical phenotype can vary between families and even within families, affecting a different sub-set of organs with different ages of onset. I will focus on the inherited disorders of haemoglobin the commonest monogenic diseases, to illustrate the complexity of the contributing molecular mechanisms and to assess the problems one may encounter in relating genotype to phenotype in other common monogenic diseases such as cystic fibrosis. Understanding of the genetic interactions that determine phenotype in apparently monogenic diseases should help towards dissecting the complex interactions between the different genes that are involved in polygenic diseases. Such observations will be of major importance not only in predictive genetics and genetic counseling, but also in providing prognostic information for decision-making in novel and gene therapy programmes as they become available.

Rapid diagnosis of Thalassaemias using molecular techniques

Jin Ai Mary Anne TAN

Department of Allied Health Sciences, Faculty of Medicine, University of Malaya, Malaysia

The inherited disorders of haemoglobin are the commonest single gene diseases. Homozygous or compound heterozygous states of these conditions result in severe anaemia with splenomegaly and skeletal modifications (β-thalassaemia major), in severe haemolytic anaemia (sickle cell disease) and in hydropic foetuses dying during pregnancy or soon after birth (Bart's hydrops foetalis). Although present management of such conditions, with the exception of Hb Bart's hydrops foetalis, gives a probable life expectancy beyond the third of fourth decade, clinical and health complications in affected individuals pose a heavy load on blood transfusion and paediatric services. An alternative approach in addressing this problem is to offer efficient and economical molecular analysis and

prenatal diagnostic services for these disorders. Both deletional and non-deletional mutations produce a-thalassaernias. The a^0-thalassaemias are due to large deletions of the a-gene complex which can be identified directly by gene mapping. DNA analysis for molecular characterization of the a-thalassaernias began with Southern blotting and restriction enzyme mapping and identified the different single a-gene deletions (-a) and heterozygous α^0-thalassaemia ($\alpha\alpha$/--). DNA amplification by the polymerase chain reaction allowed both -aa haplotypes and $\alpha\alpha$/-- genotypes to be diagnosed in either a single or multiplex PCR. DNA analysis for molecular characterization of the P-thalassaemias began with linkage analysis of RFLPs to normal and P-thalassaemia chromosomes in family studies. DNA amplification followed by restriction enzyme digestion was used to identify β-thalassaemia mutations that either abolished or created a restriction site within the P-globin gene. The dot blot-allele-specificoligonucleotidehybridisationtechnique and AmplificationRefractory Mutation System allowed direct detection of point mutations, nucleotide insertions and deletions involved in β-thalassaemias. Molecular techniques have offered rapid, reliable and economical diagnostic tests for the molecular screening and prenatal diagnosis of the thalassaemias. Prevention of the severe thalassaemic syndromes will continue to be one of the more realistic means of reducing the incidence of these disorders.

Haemoglobin F switching and its therapeutic application

Swee Lay THEIN

GKT School of Medicine, Department of Molecular Haematology, King's Denmark Hill Campus, London, United Kingdom

The switch from fetal to adult haemoglobin synthesis occurs just before birth, but the switching process is not complete in that small amounts of HbF production (< 1% of total haemoglobin) persist into adult life. They are restricted to a sub-set of red cells termed F cells (FC) The values of HbF and FC in adults vary considerably with a continuous distribution that is substantially positively skewed, and studies have shown that these values are overwhelmingly genetically controlled (heritability=0.89). The factors known to influence HbF levels include age, sex and genetic determinants both linked and unlinked to the P-globin gene cluster. Against this background of its distribution in normal population, higher levels of HbF in adults have been observed in association with acquired conditions, e.g leukaemias, or as a direct result of an inherited disorder, e.g hereditary persistence of fetal haemoglobin (HPFH). Although increased levels of HbF are present in P-thalassaemia, the increases are limited and appear to be secondary responses to dyserythropoeisis and haemolysis However, there are individuals with sickle cell disease (SCD) and β-thalassaemia who have a genuine increase in HbF levels with a major beneficial effect. The ameliorating effect of HbF in SCD and β-thalassaemia has prompted several pharmacological approaches for the reactivation of HbF synthesis and although these have met with limited success, the fact that HbF synthesis can be reactivated at all in adults, is extremely encouraging. It is hoped that a better understanding of the control of haemoglobin switching might allow its manipulation and provide novel therapeutic approaches to the β haemoglobinopathies

PATHOLOGY SYMPOSIUM 3: CARCINOGENESIS

p53 in carcinogenesis ,

PL CHEAH

Department of Pathology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

p53 mutations have been documented in around 40% of cancers making it the most common genetic event in human malignancies. Located on chromosome 17p13, p53 encodes a 53 kilodalton modular nuclear phosphoprotein, which functions predominantly as a transcriptional regulator. p53 protein within a cell integrates signals arising from a wide range of cellular stresses and directs cellular responses through several downstream genes via its conserved domains viz N-terminal, SH^3-binding,

sequence-specific DNA binding, tetramerization and C-terminal. Under normal circumstances of cell growth, p53 protein has a relatively short half-life, being mainly controlled through an autoregulatory loop in which Mdm-2 binds p53 and targets it for nuclear export and ubiquitin-dependent proteolysis. In times of cellular stress, p53 is phosphorylated by protein kinases at several sites, becomes stabilised, and acts via different pathways that ultimately lead to protection and adaptation of the damaged cell through growth arrest or apoptosis. In the event of mutational change or inactivation of the gene by virally-encoded proteins e.g. HPV E6, p53 protein can lose its protective and adaptive functions, allowing damaged cells to continue in the cell cycle. Missense point mutations within the DNA-binding domain (exons 5-8), form the most frequent alteration of the p53 gene in human cancers. Although much has been learnt regarding its role in carcinogenesis, including recent demonstration of "gain of function" mutants, existence of p53 polymorphisms, gene dosage effects and p53 homologues, many questions still remain unanswered for example it is still even unclear whether cell cycle arrest or apoptosis is the prime factor in oncogenesis.

Telomeres and telomerase in cancers

LM LOOI

Department of Pathology, Faculty of Medicine, University of Malaya, Malaysia

Telomeres are the ends of linear eukaryotic chromosomes that play essential roles in cellular replicative activities and maintenance of chromosomal integrity. Human telomeres consist of a hexameric sequence ^{3}TTAGGG^{5} in tandem repeats of 100-1000s. It has been reported that human telomeres shorten by about 50-200bp after each round of normal somatic division, so that after 50 to 70 divisions, the loss of genetic material reaches a critical stage and the cells undergo senescence and eventual cell death. This hypothesis of progressive telomere shortening as a function of aging in ***vivo*** has been referred to as the "mitotic clock." Telomerase is a ribonucleoprotein, which is capable of synthesizing telomeric DNA onto chromosomal ends using a segment of its RNA component as a template. First discovered in Tetrahymena and other eukaryotes in 1989, it has been convincingly demonstrated in humans in 1995. Studies indicate strong telomerase activity in germ cells (ovary and testis) and various tumours but weak or no activity in normal somatic tissues. This has led to the notion that telomerase plays a key role in the neoplastic cell immortalization process by restoring telomere length. Furthermore, telomerase activity has been shown to be repressed in immortal cell lines at the quiescent phase or during cellular differentiation, providing the basis for a repression-derepression model for telomerase regulation. A review of current literature shows that about 86% of tumours exhibit telomerase activity. Studies at the Department of Pathology, University of Malaya has also demonstrated telomerase activity in 20-60% of neoplastic tissue samples whereas nonneoplastic controls show almost no telomerase activity. That the differential presence of telomerase may provide a potential basis for anti-neoplastic chemotherapy has generated considerable excitement and optimism. The feasibility of using telomerase assay as an adjuvant marker of malignancy has also been mooted. Nevertheless, the telomerase mechanism does not appear to be ubiquitous and it is likely that there are alternative or co-existent mechanisms for cell immortalization.

Recent developments of detecting chromosomal translocations

PUTERI Jamilatul Noor

Haematology Division, Institute for Medical Research, Kuala Lumpur, Malaysia

The general outcome of chromosomal translocations in human cancer (leukemias and solid tumours) is gene fusion, which is easily detectable by cytogenetic and molecular methods. This paper will describe the two proven powerful methodologies that have been successful in land-marking chromosomal regions and genetic changes relevant to tumourigenesis. The molecular cytogenetic technique, in particular fluorescence ***in situ*** hybridisation (FISH) allows us to identify complex chromosome aberrations or subtle rearrangements limited by conventional karyotyping. This

technique can be applied throughout the cell cycle, in non-dividing cells, dead cells, fixed cells and archival specimens. Improved digital imaging and combinatorial fluorescence approaches have also been developed to increase the number of discernable probes resulting in multi-colour karyotyping, which include CGH, multiplex FISH, RxFISH and spectral karyotyping (SKY). On the other hand, PCR-based technology such as RT-PCR, competitive and real time RT-PCR, is useful for detection and quantification of specific fusion transcripts in neoplastic disorders. Diagnostic molecular marker such as AML1/ETO t(8;21) and NHL t(14;18) fusion transcript, has direct application by real time PCR for quantifying MRD levels in various malignancies with specific chromosomal translocations. In known translocation abnormalities, (e.g. AML) the use of poly/monoclonal antibodies as an investigating tool for identification of fusion proteins is widely used. Other new technologies are emerging such as laser-capturemicrodissectionand microarray gene chips which can offer quantitation of a wide panel of genes from clinical samples. The identification and molecular characterisation of specific chromosomal translocations or breakpoint regions as potential hot spots for genes will provide insights into tumourigenesis processes and offer new tools for diagnosis, prognosis and monitoring of cancer patients; in particular of remission and early relapse detection.

ANAESTHESIOLOGY SYMPOSIUM I: ANAESTHESIA IN THE TROPICS

Pre-anaesthetic assessment/routine investigations

Siew Hian NG

Department of Anaesthesia & Intensive Care, Penang Hospital, Malaysia

The ultimate goal of pre-anaesthetic assessment of patients is to reduce the morbidity associated with anaesthesia and surgery. The goals of the assessment are: to educate the patient about anaesthesia, perioperative care, and pain treatment in the hope of reducing anxiety and facilitate recovery; to obtain pertinent information about the patient's medical history and physical and mental conditions; to determine which tests and consultations are needed and, guided by patient choices and the risk factors uncovered by medical history, to choose the care plans to be followed, and to obtain informed consent. Non-expensive multi-phasic batteries of laboratory tests have been used routinely to screen for diseases in asymptomatic patients undergoing surgery. Increasing evidence have shown that routine laboratory tests are not only ineffective in detecting diseases, they increase risk to the patients, increase medico-legal risks to the physicians and add cost. It is recommended that pre-anaesthetic assessment should be based on clinical judgement and any investigations guided by medical history and physical examination. A selective utilisation of routine examination can then accurately supplement the clinician's evaluation. In spite of agreed criteria, there have been errors in ordering diagnostic tests. Ironically, while the number of unnecessary tests has reduced significantly, there has been a corresponding increase in the percentage of tests which were not performed although clinically indicated. Since the risk of not performing indicated tests is greater than that of doing unnecessary tests and for maximal benefits, there is a need to educate the clinicians in the proper conduct of preoperative assessment.

Ethnic and cultural considerations in anaesthesia

MOHAMED NAMAZIE Ibrahim

Department of Anaesthesioldgy, North West Armed Forces Hospital, Tabouk, Saudi Arabia

The homogenous nature of many nations has been gradually breaking down over the last half of the last century and has gained momentum in the last couple of decades. This will continue to be so in the foreseeable future with many restrictive barriers being lifted to allow free movement of people from country to country. Many nations are now being identified as multiethnic, multicultural and multireligious. This phenomenon has made it necessary for health care providers to understand and appreciate the interethnic differences ta be able to provide appropriate health care for their patients of different ethnicity. Genetic variations, cultural practices, dietary practices, environmental and

living habitats, can contribute to the disease patterns and variations that occur among the different ethnic groups. Interethnic differences due to genetic variations have also been found to be important factors accounting for interindividual variations in drug responsiveness and disposition. Interethnic differences have not received much attention in the practise of anaesthesia in Malaysia though we have been multiethnic for a long time. Some of the variations, for example, pain tolerance and experience in a certain group, have often been dismissed as a cultural phenomenon without any scientific basis. Recent investigations elsewhere have shown genetic and/or other molecular basis for drug disposition in different ethnic groups that could explain some of the clinical observations. This presentation will endeavour to highlight some of the ethic and cultural differences that have been documented. The importance of these differences should make us re-evaluate our current practice and individualise not only drug dosages but also our approach to patient care taking into consideration the many cultural practices and religious beliefs of the patient population we are dealing with.

Health economics

Nirumal KUMAR

Malaysia

Abstract not available

ANAESTHESIOLOGY SYMPOSIUM 2: TROPICAL DISEASES – INTENSIVE CARE MANAGEMENT

Intensive care management of viral encephalitis

Augustine YEW

Department of Anaesthesia and Intensive Care, Kuala Lumpur Hospital, Malaysia

Between September 1998 and June 1999, there was an outbreak of severe viral encephalitis in Malaysia associated with a mortality of 106 patients. This mysterious vicious killer is now known as Nipah virus, a newly discovered paramyxovirus. In general, the management of viral encephalitis requires a systemic approach, as its causes are so diverse. Along with a careful history of the symptoms, the physician must consider epidemiological features such as the season, geography and any insect or animal exposures. Some manifestations may influence likelihood of certain diagnoses for example; segmental myoclonus appears to be a common and prominent sign along with fever and headache in Nipah encephalitis. Computed tomography or magnetic resonance imaging should be performed prior to lumbar puncture. Diagnostic imaging is helpful in ruling out treatable causes of altered mental status and also may identify patients with increased intracranial pressure in whom lumbar puncture may be dangerous. Unless contraindicated, an early lumbar puncture should be performed especially if bacterial meningitis need to be ruled out. From a microbiologia standpoint, both serologic and virology studies are invaluable. Among them include detection of the virus via polymerase chain reaction, isolation from brain biopsy and antibody detection, An additional useful tool is electroencephalogram. Treatment strategies are tailored to the severity of the illness and specific antiviral therapy. Intensive supportive care is usually indicated in patients with encephalitis. Relatively few viruses can be treated with specific antiviral chemotherapy. Among them are acyclovir for Herpes simplex and Varicella zoster viruses, ganciclovir for Cytomegalovirus and amantidine for Influenza virus. Counseling of family members and next-of-kin with regards to brain death and care of the patient in those who survive but with neurological sequelae are important considerations.

ICU management of leptospirosis

Lela MANSOR

Department of Anaesthesiology & Intensive Care, Hospital Kuala Lumpur, Malaysia

Leptospirosis should be considered in the differential diagnosis of a patient who presents to ICU with an acute vasculitic febrile illness associated with multisystem organ dysfunction, especially if there is preceding history of contact with animals. This is a zoonostic infection caused by the spirochete ***Leptospira Interrogans.*** Human, the dead end host, become infected when they come in contact directly or indirectly with the urine of infected animals. Increased prevalence is seen during the wet season especially following a flood. Two clinical forms of the disease occur: anicteric (90% of cases) and icteric (10%)but the initial presentation is the same in all patients. The disease follows a biphasic course, with an initial septic phase in the first 3 to 7 days, followed 10 to 30 days later with the immune phase. This phase is associated with some deterioration of body systems. The anicteric patient may then present with aseptic meningitis or with pulmonary infiltrates which may requite ICU care. Patients with icteric leptospirosis (Weil's Disease) have more severe manifestation with early onset of hepatic and renal failure associated with bleeding diasthesis and pulmonary haemorrhage and can present to ICU in prostration and circulatory failure. Management in ICU include ventilation, maintenance of the circulation, correction of bleeding diasthesis, renal support, liver support and cerebral protection if CNS is involved; while confirming the diagnosis and treating the underlying infection as well as preventing further complications and other nosocomial infections. Differential diagnoses such as dengue fever, malaria, typhus, viral hepatitis and bacterial septicaemia need to be ruled out. Diagnostic confirmation is usually by serological studies although cultures may be positive in the blood, CSF and urine. Penicillin is the antibiotic treatment of choice although erythromycin and Doxycycline have been used. Outcome depends on the severity and number of organs involved with high mortality expected when more than two organs fail.

Tetanus and intensive care management

Cheng Cheng TAN

Hospital Sultanah Aminah, Johor Bahru, Malaysia

Severe tetanus should be managed in ICU. Criteria for admission to ICU are.- (1) Generalised spasms, (2) Laryngospasm (3) Uncontrolled rigidity interfering with respiration (4) Autonomic instability. Management in ICU includes:- (1) Passive immunisation (2) Eradication of the organism by wound care and antibiotics (3) Suppression of effects of tetanospasmin by controlling muscle spasms and autonomic instability with diazepam and morphine or magnesium sulphate (4) Early tracheostomy (5) Supportive treatment with particular attention to nutrition. Steps should be taken to prevent nosocomial pneumonias, pressure sores, deep vein thrombosis, pulmonary embolism, gastric haemorrhage and contractures.

ANAESTHESIOLOGY 3: DEBATE – IS THERE A NEED TO REPEAT CLINICAL TRIALS IN TROPICAL COUNTRIES?

Abstracts not available

OBSTETRICS & GYNAECOLOGY SYMPOSIUM 1 : INFECTIONS IN PREGNANCY

Intrauterine infection and preterm labour

Raman SUBRAMANIAM

Malaysia

Abstract not available

HIV in pregnancy: antenatal therapy

Verapol CHANDEYING

Department of Obstetrics and Gynaecology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand

In 1994, Protocol ACTG *076* demonstrated that a three-part regimen of zidovudine (ZDV) could reduce the risk for mother-to-child HIV-1 transmission by nearly *70%.* The regimen includes oral administration of 100 mg ZDV five times daily, initiated at 14-34 weeks'' gestation and continued throughout the pregnancy, during labour, intravenous administration of ZDV in a l-hour initial dose of 2 mg/kg body weight, followed by a continuous infusion of 1 mg/kg body weight/hour until delivery. Postpartum oral administration of ZDV to the newborn (ZDV syrup at 2 mg/kg body weight/dose every *6* hours) for the first *6* weeks at life, beginning at 8-12 hours after birth. Most perinatal transmission likely occurs close to the time of or during childbirth. The short-term safety of ZDV regimen and other regimens are now available, as a result of follow-up of infants and women enrolled in the various studies. However, the recent data concerning the animal studies of potential transplacental carcinogenicity assert the need for long-term follow-up of children with retroviral exposure in utero. These advances have important implications for maternal and child health. The clinicians considering the use of antiretrovirals in HIV- 1 infected women during pregnancy must take into account two separate but related issues: a) anti retroviral treatment of the woman's HIV infection, and b) antiretroviral chemoprophylaxis to reduce the risk for perinatal HIV-l transmission. Alternative strategies, reduction of vertical transmissions, may be appropriate according to each country's policies and standard practices. The use of antiretroviral drugs for reduction of perinatal HIV-1 transmission may differ and will depend on local considerations such as availability and cost of antiretroviral drugs, assess to facilities for safe intravenous infusions among pregnant women during labour, and alternative interventions that may be evaluated. Therefore, providing antiretroviral therapy to HIV-1 infected women during pregnancy, whether primarily to treat HIV-l infection, ro reduce perinatal transmission, or both, should be accompanied by a discussion of the known and unknown short- and long-term benefits and risks of such therapy for infected women and their infants. In the absence of data, drug choice should be individualized and must be based on discussion with the woman and available data from preclinical and clinical testing of the individual drugs. The benefits of antiretroviral therapy in a pregnant woman must be weighed against the risk for adverse events to the woman, fetus, and newborn. Although ZDV chemoprophylaxis alone has substantially reduced the risk for perinatal transmission, when considering treatment of pregnant women with HIV infection, antiretroviral monotherapy is now considered suboptimal for treatment; combination drug therapy is the current standard of care. More aggressive combination drug regimens that maximally suppress viral replication are now recommended. Although considerations associated with pregnancy may affect decisions regarding timing and choice of therapy, pregnancy is not a reason to defer standard therapy. This presentation focuses on antiretroviral chemoprophylaxis for the reduction of perinatal HIV transmission and a) reviews the special considerations regarding the use of antiretroviral drugs in pregnant women, and b) provides updated recommendations on antiretroviral chemoprophylaxis and other interventions for reducing perinatal transmission.

Hepatitis B and pregnancy

R GUAN

Singapore

Hepatitis B infection is a common public health problem in this region. The chronic infection rate is about 6 to 8% in Singapore and Malaysia. It is estimated that around 10% of pregnant women are chronically infected with this virus. About a third to half of them will be positive for HbeAg, indicating a highly infectious stage. Acute hepatitis B infection does not affect maternal morbidity or mortality, although hepatitis occurring in the last two months of pregnancy may cause premature delivery and vertical transmission of the virus to the baby. There is no increased incidence of congenital malformations, foetal wastage and intrauterine growth retardation in pregnancy complicated by acute hepatitis B. Chronic hepatitis B infection is associated with an increased incidence of infertility. Common obstetric complications include toxemia, hepatic failure, and post-parturn haemorrhage. Increased intra-abdominal pressure and therefore portal pressure increases the tendency of oesophageal variceal bleeding. 10-20% of pregnant women with hepatitis B cirrhosis might develop liver decompensation during pregnancy. Management of liver complications during pregnancy is symptomatic. Anti-viral agents like interferon and lamivudine are contraindicated. Vertical transmission of infection is high if the pregnant mother is HBeAg positive and this can be prevented by intramuscular injection of 0.5ml HBIG and an initiating dose of hepatitis B vaccination.

OBSTETRICS & GYNAECOLOGY SYMPOSIUM 2: SCREENING FOR CANCER IN WOMEN

Ovarian cancer screening

BK LIM

Malaysia

Ovarian cancer is one of the most expensive gynecological malignancies to treat with the least rewarding results. Despite the improvement in chemotherapy over the last 20 years, there's only a single digit improvement in terms of survival. The overall 5-year survival remains quite dismal at about 30%. Survival is a lot better in Stage 1 disease (80% 5-year survival). At least 75% of ovarian cancers are diagnosed at advanced stage in view of its ''silent'' nature. The ''Holy Grail'' in the treatment for ovarian cancer lies in the screening. Potential screening methods include ultrasound scanning (transvaginal or transabdominal) and serum CA125 measurement. Colour Doppler imaging has also been incorporated to identify abnormal blood flow to malignant tumours. Serum CA125 has been used in combination with ultrasound scanning or as an initial test followed by ultrasound if the levels are elevated (multi-modal screening). The aim of the entire exercise is to achieve a test of high sensitivity and specificity. The higher the sensitivity the greater the test, the less potential damage it'll cause as a result of unnecessary intervention. The largest multi-modal screening to date (22000 women), by Jacobs et al, reported 79% sensitivity (CI: 49%-95%) at one year. The proportion of ovarian cancers diagnosed at Stage 1 was 36%. The false positive rate was 0.1%. Smaller studies using transvaginal ultrasound (van Nagell 1995) and transabdominal ultrasound (Campbell 1989) have reported sensitivity of 89% and 100%, respectively at one year interval. The false positive rate was 1.3% and 3.5%, respectively. Overall, using ultrasound alone has higher false positive rates (1.2%-5.0%) compared to multi modal screening (0.1%-0.6%). Ultrasound and colour Doppler combination has false positive rates ranged from 0.3%-0.7%. The definitive diagnosis for ovarian cancer can only be made at laparotomy or laparoscopy. Based on an average incidence of ovarian cancer of 40 per 100000 the false positive rates will result in 30 to 120 surgical procedures carried out per cancer detected at annual ultrasound screening. For multi modal screening, between 2.5 to 15 procedures would be carried out for every cancer detected. Screening can generate a lot of anxiety and distress for patients who are tested positive. There will also be a significant number of surgical procedures carried out unnecessarily in the false positive group. For a population screening purpose, one must weigh the cost effectiveness of the screening programme against the effect on ovarian cancer mortality and also the adverse effects experienced by otherwise healthy women. There is

currently no strong evidence to support a routine screening programme for detecting ovarian cancer. Therefore, no screening should be carried out outside the context of clinical trials.

Screening for breast cancer

CH YIP

Department of Surgery, University Hospital, Kuala Lumpur, Malaysia

Breast cancer is the leading cause of cancer deaths in women in Malaysia. The best hope for improving survival is early detection, hence the importance of screening for this disease. Mammography, the most successful method of breast screening has a sensitivity of 80-90% and a specificity of 95%. Other methods such as breast self-examination and ultrasonography of the breast has been shown to be unreliable in detecting early lesions. The first randomised control study of screening mammography was undertaken by the Health Insurance Plan (HIP) of Greater New York from 1963 through 1967. This showed a 30% reduction in breast cancer mortality in the screened group at the end of 7 years. This was followed by similar studies in Sweden, Edinburgh and Stockholm, which showed a benefit in the screened group mainly in women aged 50-74 years. Based on these studies, in the 1980's, screening for breast cancer by mammography was advised for all women above 50 years old. However the appropriate interval between mammographic screening has yet to be determined, and it was felt that the best frequency was probably between 18-24 months, although the American Cancer Society recommendation was for yearly screening. In the 1990's controversy over whether there was benefit in screening younger women arose amid new reports that significant reduction in breast cancer mortality was also seen in women aged 40-49 years who were screened. Based on this, in 1997, the American Cancer Society extended their screening guidelines to include women from the age of 40 years. In January 2000, controversy again arose with a Danish publication in the Lancet, reviewing the methodological quality of 8 major screening trials and concluded that there was no reliable evidence that screening decreases breast cancer mortality However this paper was widely criticised by supporters of mammographic screening. What about population-based screening for breast cancer in Malaysia? Mammographic screening, the only proven method, is costly and involves manpower which is not readily available. The average size of breast cancer in the University Hospital Kuala Lumpur is between 4 and 5 cm and has not changed much in the last 6 years. Breast self-examination and clinical breast examination as a screening method, and ongoing health education programmes, so that women present with smaller tumours is more feasible than mammographic screening.

Endometrial cancer screening - current status

Pritam SINGH

Gynecology Associates Womens Medical Centre, Mount Elizabeth Medical Centre, Singapore

Endometrial cancer (EC) is a common female genital malignancy and in the majority is associated with a good prognosis though subgroups of women are at risk of more aggressive disease with poor prognosis. Screening of the general population is neither justified nor proven to be cost effective; both exfoliative cervical and endometrial cytology are unsuitable techniques for EC screening. Transvaginal (TV) ultrasonography has recently been evaluated to screen women with known risk factors for EC (age, obesity, post-menopausal status, nulliparity, anovulation, HRT usage) and is proving to be a feasible and sensitive screening technique. TV ultrasonography which measures endometrial thickness (double layer) both in asymptomatic post-menopausal women and those with post-menopausal bleeding identifies a high risk group ($\geq$8mm endometrial thickness) in whom there is a very high likelihood of EC (20%). Endometrial thickness in post-menopausal women better discriminates patients at high risk of EC & complex hyperplasias then either presence or pattern of post-menopausal bleeding. TV color Doppler ultrasonography is able to detect important differences between benign and malignant endometrium and identifies both neovascularisation with abnormal blood flow patterns and differential flow indices (Resistance Index significantly lower in ECs) and

is also able to detect myometrial invasion. TV ultrasonography is a potential screening technique which identifies women P high risk of EC and TV color Doppler ultrasonography is able to identify those with EC and with myometrial invasion. TV color Doppler ultrasonography is thus an aid in tumor staging and identifies a subgroup with aggressive disease and poor prognosis. This in turn facilitates appropriate referral and tailoring of treatment with most efficient utilization of available resources and expertise to obtain optimal outcome in patients with EC. EC screening is appropriate for women with risk factors using conventional TV ultrasonography and to identify the subgroup with aggressive disease and poor prognosis TV color Doppler ultrasonography is an effective tool. These 2 ultrasonographic techniques hold promise for wider application as methods for EC screening in the future.

OBSTETRICS & GYNAECOLOGY SYMPOSIUM 3: ANAEMIASI HAEMOGLOBINOPATHIES IN PREGNANCY

Prenatal diagnosis for thalassaemia

E GEORGE

Unit Hematology, Depdrtment of Pathology, Hospital Universiti Kebangsaan Malaysia.

Prenatal diagnosis is done when a couple has thalassaemia trait, have a history of producing a child with beta-thalassaemia major or Hb Bart's hydrops fetalis and when hydrops fetalis is identified in a pregnant woman during antenatal check-up. Hb Bart's hydrops fetalis is nearly always the result of the co-inheritance of two α-thal 1 (a^0) gene determinants where both a globin genes are deleted. The most common α^0 gene determinant in Southeast Asia is the $--^{SEA}$, which deletes 17.5-20 kb of the α globin gene complex leaving ζ1 globin gene intact. The molecular basis for Hb Bart's hydrops fetalis is $--^{SEA}/--^{SEA}$, $--^{SEA}/--^{THAI}$, $--^{SEA}/^{FIL}$. The most severe form of beta-thalassaemia is transfusion dependent and results from the homozygous state of β^0 ($\beta^0/+\beta^0$). In Asia, the common β^0 mutations are -28 (A to G). -29 (A to G), IVS 1-1 (G to T), CD 17 (A to T), CD 35 (-C), FSC 41-42 (-TCTT), FSC 71-72 (+A), -619 bp, $-\beta^{FIL}$, and FSC 8-9(+G). It is mandatory to get informed consent prior to any procedure; the safety of the invasive procedure, accuracy of laboratory diagnosis, and abortion of the affected fetuses are areas where information need to be provided. Fetal sampling procedures depend upon gestational age of the fetus. Fetal DNA is obtained from chorionic villi (CV), amniocytes, and fetal blood (FB), at 10-12, 14-16, 18-24 weeks gestation respectively. Prenatal diagnosis is not recommended after 24 weeks gestation except for Hb Bart's hydrops fetalis. FB samples obtained with cordocentesis by experienced obstetricians are pure. In contrast CV samples always have a risk of maternal contamination. With FB samples both the phenotype and genotype of the fetus can be identified. Studies on CV samples provide only genetic information. Errors arise as a result of incorrect diagnosis in parent., non-paternity and contamination of fetal samples with maternal tissue/blood. In Asia, there is ethnic diversity, with a possibility of number of mutation combinations and where patients may come in quite late in pregnancy makes routine methods not feasible. Techniques that are used in DNA analysis are selected such that they are able to define a number of mutations simultaneously. Screening for DNA sequence variations may be identified by single strand conformation polymorphism (SSCP), denaturating gradient gel electrophoresis (DOGE), and chemical cleavage mismatch (CCM) and then the actual analysis of DNA done by two separate PCR analysis. If the DNA analysis is not informative by these latter techniques, DNA sequencing is done.

Management of haemoglobinopathies in pregnancy

Qunasegaran PT RAJAN

Malaysia

Abstract not available

Anaemia in pregnancy

Kwee Boon **NG**

Tung Shin Hospital, Kuala Lumpur

The incidence of anaemia in pregnancy depends on the definition. Taking an arbitrary nidus of Hb concentration of 100 g/L, it is safely estimated that 10-15% of the local population are anaemic during pregnancy. The causes of anaemia in pregnancy are primarily physiological haemodilution and nutritional, although haemoglobinopathies, haemolytic anaemias and myeloproliferative disorders may also be found. Screening for anaemia should begin in early pregnancy with a thorough history and examination. A finger-prick Hb estimation can be done in suspicious situations at 28 weeks. Investigations for the anaemic patient generally include a FBC, PBF and perhaps serum assay for TIBC, folate and B12 together with a stool examination for occult blood and parasitic infestation. Other tests should ideally be done in consultation with a haematologist. Antenatal care and assessment of the fetus are routine with no additional monitoring necessary unless indicated. Management of anaemia should be jointly undertaken with the haematologist. Haematinics and dietary supplementation have been shown to improve the Hb in compliant antenatal patients. The cost and side effects of oral iron therapy are well tolerated and mild. Folic acid deficiency has been reported to increase the risk of fetal loss, fetal anomalies especially neural tube defects, preterm delivery and PET aside from megaloblastic anaemia. Iron deficiency has no associated adverse fetal outcome. The recommended minimal daily Fe and folate requirements in pregnancy are 100 mg and 0.6 mg respectively. The perinatal and maternal events in patients with physiological anaemia in pregnancy are highlighted in a prospective study performed in UHKL.

PUBLIC HEALTH SYMPOSIUM 1: HEALTH INTERVENTION IN THE NEW MILLENNIUM

Modifying cancer risk through behavioural changes

ZARIHAH Mohd **Zain**

Malaysia

Cancer is a world health problem, causing more than 6 million cases and 4 million deaths annually in 1980s and has now risen to 9 million and 5 million respectively. It is predicted that the toll will escalate further to 300 million new cases and 200 million deaths in the next 25 years, with almost two-thirds of these arising in developing countries. The disease pattern has been attributed to population aging and changes in living environment and lifestyle. Although major intrinsic cancer contributing factors like age and genetic predisposition are fixed, most other risks are quite largely changeable. This dreadful disease, cancer, develops principally as a consequence of conditions of life, i.e. exposure of individuals to carcinogenic agents in the atmosphere and in what people consume. Personal habits such as tobacco use and occupational exposure to carcinogens as well as certain biological factors such as hepatitis B infection, play particularly significant roles in the aetiology of cancer. Many of these factors can be exploited and hence prevent or delay the occurrence of cancer. Tobacco is the most widely disseminated carcinogen in the world. Its use in all forms is responsible for about 30% of all cancer deaths in developed counties and a rapidly rising proportion in developing countries. For public health reasons, the present and potential burden of tobacco-induced cancer in Malaysia must be given immediate priority. There is a dire need to keep the prevalence of tobacco use especially cigarette smoking checked. Dietary modification is another approach to cancer control. In recent years, substantial evidence has pointed to a causative role of excessive dietary fat in certain cancers, and protective effect of increased intake of whole grains, fruits and vegetables. Eating habits that may inhibit the development of diet-associated cancers will also lower the risk of cardiovascular diseases. Alcohol may increase the risk of cancer of the oral cavity, pharynx, oesophagus and liver, hence control of alcohol consumption in the population is also necessary. Other known cancer risk factors that can be modified include occupational and environmental exposure to carcinogenic chemicals, hepatitis B infection, human papilloma virus infection, ionising and ultraviolet radiation. Knowledge regarding all these provides obvious and ample scope for action to reduce cancer burden.

Case control study: evaluation of impact

OMAR HASAN Kasule

Faculty of Medicine, UIA, Kuantan, Malaysia

The case-control methodology has been popular for 7 decades for preliminary evaluation of causal relations using small numbers of study subjects. It has also been used, inappropriately and extravagantly, for confirmatory large studies. It is destined to become even more popular for cheap and rapid identification of causal relations that can be confirmed later by molecular and other laboratory studies. It is an intuitive comparison of exposure in diseased and non-diseased subjects. The cases, all incident or newly diagnosed, are from the same population base as the controls to ensure comparability. Results of a case control study are set out in the familiar 2 x 2 table. The exposure odds ratio, Pr(E+/D+) I Pr(E+/D-) is computed as ad/bc with 95% confidence bounds. The case-control study design has 4 advantages that explain its popularity. 1. Easy estimation of the risk ratio using the odds ratio. 2. Economy: few subjects are adequate to answer epidemiological questions in a short time. 3. Compression of time: exposure information is obtained from history or records. 4. Convenience: study subjects are seen only once with no follow-up. The case-control design suffers from 7 disadvantages. (a) It gives an approximate parameter, OR, rather the real one, RR (b) It gives probability of exposure among the diseased, Pr(E+/D+), but real interest is the probability of disease among the exposed, Pr(D+/E+). (c) It is not possible to obtain a direct estimate of incidence or the prevalence because of sampling design constraints. (d) The time sequence between exposure and disease is not certain. (e) It is very vulnerable to information, selection, and confounding bias (f) It can not be employed to study multiple outcomes from the same exposure (g) historical information about exposures used in case-control studies can not be validated.

Management of occupational hazards in petroleum industry

ABU HASAN Samad

Esso Production Malaysia Inc., Menara Esso, Kuala Lumpur, Malaysia

Petroleum industry involves various activities in both the upstream and downstream sectors. Each facet of these activities carries its own risks and hazards to the workers, public and environment. These include physical, chemical, biological, ergonomics and psychosocial hazards. In Malaysia, the logistics of working in the middle of the South China Sea make the industry even more challenging. In line with OSHA Act 1994, management commitment with workers involvement is necessary to ensure safe and healthy operations at all work sites. Occupational Health Management System and all hierarchy of hazards controls are in place and stewarded together with emergency preparedness for possible disaster. With these measures, the petroleum industry can continue to contribute to the country's economy without impacting the health and safety of the workers, public and environment.

PUBLIC HEALTH SYMPOSIUM 2: POPULATION AND ETHICAL ISSUES IN NEW PUBLIC HEALTH

Reassessing population expansion policy: global perspective

Raj KARIM

Malaysia

Abstract not available

How to develop an informed patient

MOHD HISHAMUDDIN Harun

Medical Online Sdn Bhd, Malaysia

Consistent with Malaysia's Vision **2020** the healthcare vision of **creating 1 nation** of healthy individuals, families and communities will be realised by **promoting** a lifelong focus on wellness where individuals and families are empowered **to** play the major **role** in managing their health. Individuals must have greater knowledge of health issues, the capacity to make informed health decisions and the ability to play a central role in both health and illness management in order to fulfil this vision. The MSC Integrated Telehealth (telemedicine) project has been envisaged to **support and** strengthen the future health care system based on the healthcare vision. **Telehealth will promote** wellness through personal empowerment and responsibility **for healthcare** management via a protective lifelong plan. The two applications of the Telehealth project which will help to empower patients as to the management of their health is the Lifetime Health Plan **(LHP)** and Mass **Customised/Personalised** Health Information and Education (MCPHIE). The **Lifetime** Health Plan (LHP) is a health plan which is a network-based personalised health management of an **individual** based on electronic medical records. Mass **Customised/Personalised** Health **Information** and Education (MCPHIE) comprises the dissemination of tailor-made information **and education** to the individual and community via appropriate tools and media **e.g. Personal computers, E-mail,** web-tv, pamphlets etc. In order to develop such informed individuals, a multiple prang strategy needs to be developed which include: User-friendly **interfaces/access** points; Multiple delivery channels; Personalised information and education rather than generic; Interactive elements within the delivery services to attract individuals to participate in health-related events; Functional and easy to use LHP so that the individual sees it as a valuable tool for personal health management; Easy to access, high quality virtual health services (as compared to current physical service provision); Incentives to promote the use LHP - may be financial or non-financial; Promotion of programmes sponsored by Government, private sector, media, sports and **NGO's** to help entrench health-related issues and behaviour. The advent of Integrated Telehealth in Malaysia will greatly assist in developing informed patients who can make decisions regarding their health and be responsible for their health management. Services, resources and technologies will be structured to empower and enable patients to take the utmost advantage of **online** services. The challenge will be to motivate the individual to take appropriate action to lead a healthy lifestyle.

Radioactive contamination of food: magnitude and prevention

HARRISON AZIZ Shahabudin

Food Quality Control Division, Department of Public Health, Ministry of Health, Malaysia

Everything in our environment, including food, contains trace amounts of natural radioactivity and this cannot be avoided. Drinking water, edible plants and animals and even dust in the air contain isotopes. Radioactive materials are particularly concentrated in some foods, thus consuming these foods would expose consumers to higher doses than average. Our food supply is k i n g contaminated with contaminants and one of the major contaminants is radioactive isotopes. When food is contaminated with radioactive isotopes, the term radioactiye food is used and this refers to accidental contamination from **nuclear** accidents and the like. Early inclusion of isotopes into the food chain had been demonstrated where increased radiation levels were found in leafy greens growing in the contaminated fields and in cow's milk. Rain becomes radioactive and soils are also contaminated, Animals grazing on contaminated fields will concentrate isotopes in their tissues and this will be passed on to the carnivores that feed on them. This paper will discuss the magnitude of radioactive contamination of food, giving emphasis to accidents that had occurred and would also suggest ways of prevention of such contamination.

Ethics in occupational health

Krishna Gopal RAMPAL

Department of Community health, Medical Faculty, Universiti Kebangsaan Malaysia, Malaysia.

Professional ethics should always determine the manner in which occupational health doctors practice. Like all doctors the occupational health doctor has a duty to do good, to do no harm or minimise harm and promote autonomy of the patient. They are bound to act according to their duties and rights (being duty driven) and on occasions is to act in a manner, which may not be what the patient wants but, which has the best overall consequences (public good vs individual good). The occupational health doctor, because of the unique role they play are constantly faced with a number of ethical problems. The nature of their practice places them in a "double agent" role being paid by employers to take care of employees. Questions are continuously raised about where their loyalty lie - the worker (their patients) or the employer (their client). They work in a social context which is riddled with competing interests coupled with unequal distribution of power between their patients and their clients. With emergence of "managed care" this issue is further compounded in their effort to provide the best possible care for their patients. In Malaysia it is all the more complex as there is no clear demarcation between the primary care they provide and the occupational health role they play. Some of the common issues faced by the occupational health doctor include: confidentiality of medical information, ownership of medical records, pressure to reduce sickness absenteeism and loss time injuries, company's trade and business secrets. Their professional autonomy is always being challenged. Ethical guidelines like those developed by professional societies overseas need to be drawn, adopted and communicated to occupational health practitioners in the country.

PUBLIC HEALTH SYMPOSIUM 3: HEALTH MANAGEMENT ISSUES OF THE NEXT CENTURY

Rewarding the health care staff

Ahmad TAJUDDIN

Malaysia

Background: All public employees are subjected to similar forms of rewards by the Government. Rewarding specifically to the health care staff of the Ministry of Health is generally not addressed by any circulars, programmes of systems holistically, having both objective as much as subjective elements in its process and implementation. It is both important we reward public healthcare employees in accordance with their contributions, and in turn provide incentives for continued and improved performance for the Ministry of Health. ***Objective:*** To understand the development and implementation of reward systems applicable for health care staff of the Ministry of Health. ***Method:*** This is a narrative paper that describes how systems relate to personnel satisfaction and organisational goals; followed by analysing the principles and processes involved in the development of the reward systems, and explained by the responsibilities of managers/supervisors in the development and administration of the reward systems. ***Results:*** Discussion of how rewards and reward systems relate to salary administration, human resource motivation, career progression (career development progression, performance planning and appraisal, promotion and transfers) role of organisational and supervision, teamwork (teams and self-managed groups), learning organisation, innovation, organisational climate, benefits and services are described. ***Conclusion:*** Key factors for a successful reward system and guidelines for rewarding are recommended. To achieve health care staff personal achievement and organisational effectiveness, performance management processes practices are of imperative importance. A critical success factor is to design a flexible and focused reward system to support this performance thus emphasising the linkages and ensuring the desired results.

Communicating during health crisis

SULAIMAN Che Rus

Malaysia

Effective planning and communicating of risk to the public is an important component of managing any health crisis. The Ministry of Health has had numerous positive and negative experiences in the past of health crises such as the Nipah virus outbreak, the haze, and Dioxin contamination of imported food. Planning of risk communication involves identification of potential health issues, which are among others influenced by 'fright factors' and 'media triggers'. An analysis of communication situation involving internal and external stakeholders need to be undertaken. Communication objectives must be clarified and set. The "Dos's and Don'ts" in public presentation is discussed.

Benchmarking of public hospitals

Syed Mohamed ALJUNID

Malaysia

In Malaysia, public hospitals are the main providers for in-patient services. As in most countries, in-patient care usually absorbed the highest proportion of funds allocated for health care. Hence, cost-management efforts targeting at expenses spent for hospital care would bring significant improvement in overall efficiency of health care system. Benchmarking is a strategic tool, which could be utilised by public hospitals for the purpose of improving quality and efficiency. It is defined as a process of identifying, learning and adapting outstanding practices from other organisations to help the hospital its performance. Hospital managers can choose any of the four types of benchmarking to implement: best practice studies, cooperative benchmarking, collaborative benchmarking and competitive benchmarking. Forming a benchmarking team sponsored by influential practitioners in the hospital is the first step that needs to be taken in the benchmarking exercise. Finding suitable benchmarking partners can be problematic because public hospitals are organised at various levels with different facilities and staffing mix. Indicators for comparison include general performance indicators such as average length of stay, bed occupancy rate, turnover interval, cost per in-patient day, cost per admission and specific indicators such as cost per DRGs, peri-operative mortality rate, hospital acquired infection rate and mortality rate for specific operative procedures. For benchmarking to be successful, it is important that the benchmarking team must receive adequate support from all levels of staff in the hospitals. It is important that benchmarking code of conduct be observed at all time by all parties involved. Benchmarking exercise should be a continuing exercise and adequate time and resources should be allocated to implementation of changes.

Effective partnership in community based rehabilitation (CBR)

SAMIAH YASMIN Abdul Kadir

Malaysia

Community Based Rehabilitation (CBR) was initiated by the World Health Organization (WHO) and has its beginnings in the 1970's. Over these past decades CBR has undergone tremendous evolutions and refinements and towards the new millennium CBR is being regarded as an appropriate model of disability service delivery in many developing countries. In the 1994 United Nations Joint Position paper, CBR is defined as a strategy within the realm of community development to facilitate rehabilitation, equalization of opportunities and social integration of all people with disabilities. In short, CBR requires combined effort of people with disability, their families and communities and the appropriate health, education and social authorities of the local government. With heavy emphasis on community involvement, implementation requires Participatory Rural Appraisal (PRA), which evolved on four tasks namely, (a) identification and gaining entry to the local community, (b)