

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

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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 Lumpur, Malaysia*

Informed consent (IC) is a prerequisite for participating in a trial, especially in protocols planned for regulatory submission. The 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 defined by ICH 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

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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

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Throughout the world, thousands of drug trials are performed each year for efficacy and safety 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 pre-congress activity of a regional Hepatobiliary Meeting "The Liver Update". A **spinoff** from this pre-congress workshop were a series of other GCP workshops conducted in the country. In 1999, during the 3rd Liver Update, another pre-congress 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

Erike DE VERGA

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.

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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, commercialisable 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, debureaucratization of procedures and mechanisms, internalization and internationalization of research as well as the emplacement of a seamless research continuum.

Prion disease

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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 transmissible 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 transmissible 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 corneal 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

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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

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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?

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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 burns 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 burn 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 antibiotics 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

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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 propionic 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 (⁵¹Cr 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 assess the overall safety of COX-2 specific inhibitors, especially in organs outside the GI tract.

MIXED SYMPOSIUM 1: MALARIA UPDATE

Malaria vaccines**FEG COX**

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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 incorporating 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 (5) 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

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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®. Artemisinin derivatives such as artesunate, artemether, 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%. Artemether, 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 use 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 recrudescence rate is rather high (10-30%). The recrudescence rate depends upon the dose, duration of artemisinin derivatives used and severity of disease: the more severe the higher the recrudescence 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 treatment 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

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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 β -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

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Sepsis and its sequelae represent a continuum of clinical and pathophysiological severity. The following clinically recognizable stages can be seen: (1) sepsis - the systemic response to infection manifested by two or more of (a) temperature of $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, (b) tachycardia (>90 beats/minute), (c) tachypnoea (>20 breaths/minute) or $\text{PaCO}_2 < 32$ mm Hg, (d) white blood cell count $>12 \times 10^9/\text{L}$, or $<4 \times 10^9/\text{L}$, 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 fluid 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 χ , 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

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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**

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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 α -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

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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 thrombocytopenia. A condition in pregnancy invariably associated with a platelet count of greater than $100 \times 10^9/L$ and is associated with a very low incidence of fetal thrombocytopenia. 2. Thrombocytopenia 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 than $50 \times 10^9/L$ are generally delivered by cesarean section whereas those with counts greater than $50 \times 10^9/L$ 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 thrombocytopenia

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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 $100 \times 10^9/L$) 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 II 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

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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'

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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

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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 modern 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

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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 to 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 burns 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

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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 but 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?

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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 relieve 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 PICU 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

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Abstract not available

Re-emerging diseases: tuberculosis

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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.

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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

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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 marneffeii*, *Paecilomyces* species. *Chrysosporium* species and *Fusarium* species. *Nocardia asteroides*, an Actinomycetes, 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* species are eminent.

Epidemiology, diagnosis and treatment of systemic candidiasis

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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**

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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 kernicterus 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

