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The 5th Scientific Meeting of the College of Pathologists, Academy of Medicine Malaysia was held at the Swiss-Garden Resort and Spa, Damai Laut, Perak from 2-4 July 2004. Abstracts of poster presentations follow:

P1. Acid fast bacilli screening in tissue biopsies

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The varied histopathological findings of tuberculosis in tissue biopsies confer screening of acid-fast bacilli (AFB) a necessity to confirm diagnosis. However, the latter is not always possible with results of tissue biopsies most often reported as consistent with tuberculosis. To study the pattern of AFB positivity in biopsied tissues of suspected cases of tuberculosis in relation to the patients' age, sites of infection and histopathological presentations, 42 cases with histopathological reports of chronic granulomatours inflammation and AFB positivity were reviewed. The cases were of patients with clinically suspected tuberculosis seen at Hospital USM (HUSM) from 1992-2003 with tissue biopsies sent to the Pathology Department. The histological features were categorized under two groups, viz. epithelioid granuloma without necrosis and epithelioid granuloma with necrosis. AFB counts were grouped into less than 5, between 5-10 and greater than 10 bacilli per 500 oil immersion fields. Descriptive analysis on the pattern of AFB positivity on histopathogical examination as well patients' age and biopsy sites were conducted. 12/42 (28.6%) cases with AFB positive were lymph nodes, followed by pulmonary (19.0%) and intestinal (16.7%) tissues. In 7 cases where the site of lymph node biopsy were stated, majority (3/7) were cervical lymphadenitis as compared to other lymphadenopathies. Only 16.2% (6/37) of those with necrosis were AFB positive. The majority of AFB was found to be in the giant cells (25/37) and some were found to be in macrophages (5/37). The bacillary count were less than 5 in majority of cases (56.8%) followed by count greater than 10 (11/37). Only 5 cases had countin between the former and the latter groups. Absence of caseous necrosis or AFB positivity did not seem to correlate with extremes of age. AFB was seldom found in the necrotic center of the granulomas but was present more frequently in the giant cells.

P2. Pancreatoblastoma – a case report

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Pancreatoblastoma. a term coined in 1977 and subsequently employed to describe tumours previously known as infantile carcinoma of pancreas is an extremely rare tumour. It is usually seen in infants and children. Pancreatoblastoma is also known to occur in adults and is more aggressive. Clinical presentations of this tumour are usually non-specific and many times it is not noticed until the tumour is large enough to cause grave harm to the individual. Genetic alterations have also been recently identified. This tumour has a good prognosis if diagnosed early and resected completely hence it is important to know more about its clinical presentation and behaviour so that it can be identified early and treated promptly. A 13-year-old girl presented to casualty with history of fall from a motorcycle. She complained of pain and swelling over the left upper abdomen and had vomited 3 to 4 times. Physical examination revealed a tender lump in the left hypochondriac region. The rest of the abdomen was soft and non-tender. Provisional diagnosis of solid organ injury due to motor vehicle accident was entertained and the patient was subjected to radiological investigations. This revealed

a malignant pancreatic cyst with secondaries in the liver. Splenectomy and resection of the tumour mass was performed. The tumour was encapsulated and nodular, situated in the body of pancreas and adherent to the mesentery. Histopathological examination of this mass showed features of pancreatoblastoma. The patient was advised chemotherapy, which she has refused, but she is under close surveillance by oncologists. She is currently doing well. Pancreatoblastoma is a rare tumor. It is amenable to treatment if identified in its early stages before it metastasises. There are no characteristic clinical symptoms, signs or investigations recognized which can help in making an early diagnosis. The varied epidemiology, clinical presentation, histogenesis, genetic alterations, investigations and treatment modalities proposed are discussed.

P3. Congenital arteriovenous malformation of kidney in a post-menopausal woman

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Congenital arteriovenous malformation (AVM) of kidney is an exceedingly rare condition, almost always unilateral, predominantly affects the right kidney, and is usually asymptomatic until adulthood. We report a case of congenital AVM in a 56-year-old post-menopausal Malay woman who presented with one day history of sudden onset of colicky pain in right loin and haematuria. She had a similar episode 20 years age which resolved spontaneously after two days of conservative management. She is a known case of thyrotoxicosis for the past 30 years and mitral regurgitation on regular treatment. Clinical examination revealed a palpable thrill over the right side of abdomen. CT scan showed enlarged right kidney with features suggestive of malignant tumour. However, renal angiogram showed features suggestive of AVM and embolisation was done using n-butyl 2-cyanoacrylate and gel foam which caused occlusion of AVM but unfortunately spilled over into inferior vena cava and extended up to right atrium. Following embolisation, right nephrectomy was done and the embolus was also removed. Gross examination of the kidney showed dilated pelvi-calyceal system coated with blood and blunting of the renal papillae. The renal parenchyma of both poles showed few dilated blood vessels and a large area of haemorrhage. Histopathological examination showed typical features of AVM involving both poles of kidney and features of infarction secondary to embolisation. This case is reported here because of its rarity and successful outcome after a grave complication developed during management. This is the first reported case of congenital AVM with gel foam embolism to the best of our knowledge.

P4. NeuralPap, the answer to limited real brain! A Malaysian invention

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Cancer of the cervix is the second most common cancer in women after breast cancer. Annually there are 450,000 new cases every year and the bulk of these cases are in Asia. Mass screening has been a problem in many developing countries including Malaysia because there is a shortage of pathologists. Pathologists do feel fatigue after reading about 30 slides at a stretch. Fatigue may lead to errors. When real brain is limited, one resorts to artificial brain. That was how NeuralPap was born. Essentially it is an artificial pathologist.. NeuralPap is a conjoint effort between an engineer and a pathologist in Universiti Sains Malaysia. Their idea was materialized in the form of a software by their post-graduate student. This is an artificial brain using combined Hybrid Neural Network (NN) and hierachical NN thus giving accuracy, specificity, sensitivity approaching 100%. The conventional NN gives specificity up to only 80%. Incorporated in the system is a specialized image

processing procedure which gives focused images of cells of interest. Good crispy images give rise to high accuracy in diagnosis. NeuralPap detects abnormal cervical cells and classify the abnormality according to the grades based on The Bethesda System. It has a high accuracy up to 98%, sensitivity 96% compared to the sensitivity of conventional pap smear which is between 36-80% and it has a high specificity up to 100% meaning there is no false positivity (the specificity of conventional pap smear is only up to 86%). NeuralPap also gives the percentage of confidence level of each diagnosis made. Diagnosis can be obtained within a few seconds after the user gives command to the system therefore a larger volume of samples can be processed over a short duration of time. The good thing about an artificial brain is it does not get fatigue with time, therefore mass screening is possible. NeuralPap has won several awards at local and international innovation competitions:

1. Itex 2003 [May 2003] . Gold medal
2. The Michael Chai IT award May 2003
3. Moste S&T Innovation Competition [August 2003] . Gold medal
4. IENA 2003, Nuremburg Germany [October 2003] . Bronze medal
5. Excellence in Engineering Research . Awarded by Perak State [November 2003] with a cash prize of RM 7500.00

We are in the process of refining this system for commercialisation.

P5. Nipah Virus the newly discovered paramyxovirus infection in Malaysia: Pathological findings of 9 fatal cases from Ipoh

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Ipoh city is the first focus of the newly discovered Nipah virus, which affect pigs and humans closely in contact with pigs. During the epidemic from December 1998 until April 1999, Ipoh reported 15 deaths and 27 cases out of total 105 deaths and 265 cases throughout Malaysia. This study is to report the pathological findings of the 9 post-mortem cases from Ipoh. Full post-mortem was done on the 9 cases. Representative specimens taken from all organs and examined using the routine H&E slides and immunohistochemistry studies using Nipah antibody were done by laboratory in CDC, Atlanta. The virus causes systemic manifestation affecting the lung, kidney, spleen, heart with predilection to the brain. This could be explained by vasculitis along with microinfarction seen microscopically. Other unique microscopical characteristic findings are syncytial cell formation and eosinophilic inclusion. The immunohistochemical studies show the presence of antigens in neurons, epithelial, stromal and inflammatory cells. All the 9 post-mortem cases died of encephalitis and lung infection. The fact that the virus consistently affects the endothelial cells, neurons and only some of the organs, indicates the presence of tissue tropism of Nipah virus. The pathological study may also help deduce the pathogenesis of the disease and the possible mode of transmission.

P6. Intracellular invasion and survival of *B. pseudomallei* in human macrophages: an electron microscopic study

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Burkholderia pseudomallei, which causes melioidosis has the capacity for latency, relapse and recurrence. This has been attributed to its intracellular survival in the human host. Intracellular replication and localization of the bacterium has been documented *in vivo* as well as *in vitro* in both phagocytic and non-phagocytic cell lines. Mononuclear phagocytes were isolated from heparinized whole blood obtained from a healthy donor using Ficoll Paque (Pharmacia) density gradient centrifugation and subsequently infected with opsonized *B.pseudomallei*. Following fixation of cell

pellets at varying time points with glutaraldehyde, routine electron microscopy procedure was carried out. We have shown the internalization of *B. pseudomallei* by macrophages via conventional phagocytosis, enclosed within membrane-bound vacuoles or phagosomes. Fusion of lysosomes with phagosomes occurred within 20 minutes of post-infection. Evidence for fusion of phagosome with lysosome was indicated by the presence of ferritin or dense material resembling lysosomal contents within phagosomes. Ingested bacilli were classified as "intact" or "damaged" on the basis of their ultrastructural features. Our observations indicate that the phagosome-lysosome fusion mechanism in *B. pseudomallei*-infected macrophages failed to ensure complete clearance of the organism. The resistance of some *B. pseudomallei* to lysosomal killing facilitates intramacrophage survival and proliferation, thus giving rise to relapse and recurrence of melioidosis. In conclusion, we have demonstrated in human macrophages that *B. pseudomallei* is able to invade, survive and multiply intracellularly and eventually escape into the extracellular milieu thus initiating a new cycle of infection.

P7. Development of a DNA vaccine against human breast cancer

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Breast cancer is the most common malignancy in women in Malaysia. While the specific aetiology of breast cancer remains unknown, DNA vaccines directed at eliciting an immune response toward tumours appear to offer promise for both the prophylactic and therapeutic treatment of cancer. In this study, DNA encoding human breast tumour antigen, MUC-1 and cytokine, interleukin-18 are being investigated. The cDNAs of human IL-18 and MUC-1 with 22 tandem repeats were cloned into plasmid, pVax1. Subsequently, IL-18 cDNA was subcloned and expressed in *Escherichia coli*. To express the MUC-1 protein, the pVax1/MUC-1 clones were transfected into COS7 cells by liposomal mediated transfection. Translated proteins were detected by SDSPAG followed by Western blotting. Indirect immunofluorescence staining of fixed COS7 cells was also performed using the monoclonal antibody anti-human MUC-1 and the binding visualized using a fluorescein isothiocynate (FITC)-conjugated goat anti-mouse. The results revealed the presence of MUC-1 in about 40% of the transfected cells, demonstrating that MUC-1 was indeed expressed in the membrane. These successfully expressed clones can then be used as DNA vaccine in further studies.

P8. Detection of IMP metallo-ß-lactamases in multiresistant strains of *Acinetobacter sp.* isolated in University of Malaya Medical Centre

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Carbapenem-resistant *Acinetobacter sp.* have gained increasing significance as opportunistic pathogens in hospitalized patients. Reports of multidrug resistant isolates have increased considerably during the last decade and may partly be due to the extensive use of broad-spectrum antibiotics (Amyes *et al*., 1996). Carbapenem resistance is often associated with the loss and /or decrease in outer membrane protein and overexpression of multidrug efflux systems. However, carbapenem-hydrolyzing b-lactamases of Ambler Class B (metallo-enzymes) and Ambler Class D (oxacillinases) have also been detected in *Acinetobacter sp.* In this study, we describe the screening of carbapenem-resistant *Acinetobacter sp*. for the presence of carbapenemases. A total of 40 carbapenem-resistant clinical isolates of *Acinetobacter sp.* were obtained from in-patients of University Malaya Medical Center (UMMC) from August 2003 until March 2004. The identity of the isolates was confirmed using the

API20NE system. Growth at 44°C was performed to differentiate between *A. baumannii* and *A. calcoaceticus*. The antibiotic susceptibility profiles to b-lactams were determined by the minimum inhibitory concentration (MIC) using the agar dilution method as described by the NCCLS. ATCC strains of *Escherichia coli* 25922 and *Pseudomonas aeruginosa* 27853 were used as controls. The antimicrobials used included imipenem, meropenem, ceftazidime, cefotaxime, and aztreonam. Preliminary screening for carbapenemase production was carried out using the Modified Hodge, EDTA and 2MPA double disc synergy tests (Lee *et al*., 2001; Arakawa *et al*., 2000). The isolates were then analysed for the presence of the *blaIMP* gene using PCR (Yum *et al*., 2002). The 448bp PCR products from *blaIMP*-positive isolates were sequenced to confirm the identity of the amplified products. Among the 40 imipenem resistant strains, 36 were identified as *A. baumannii* whereas only 4 were identified as *A. calcoaceticus*. Only 3 strains out of the 40 strains were positive for metallo-beta-lactamase production using the double disc synergy and Modified Hodge tests. All 3 strains were *A. calcoaceticus*. However, 6 other isolates were characterized as equivocal by the Modified Hodge test although they were negative for metallo-beta-lactamase production using the double disc synergy test. PCR amplification of the *blaIMP* gene was positive in the 3 *A. calcoaceticus* isolates that were positive by both the Modified Hodge and double disc synergy tests. Preliminary sequencing data obtained from the 3 PCR products showed a 100% homology with *blaIMP-4*. Amplification and sequencing of the entire *blaIMP* gene is being carried out to confirm the finding. Although carbapenem resistance in *Acinetobacter sp.* in UMMC is a increasing problem, our findings indicate that only 7.5% of the isolates harboured the *blaIMP* gene. Screening for the presence of *blaVIM* has to be carried out to detect other carbapenemases. The findings suggest that the resistance to extended spectrum ß lactams in *Acinetobacter* sp.is predominantly due to non-enzymatic mechanisms such as altered permeability and efflux systems. Further studies have to be carried out in order to confirm this hypothesis. Strains classified as equivocal by Modified Hodge test but negative by double disc synergy test, may be low level producers of metallo-beta-lactamases. This is concurrent with the findings of Lee *et al.* (2001) that showed that the EDTA-disc synergy test is more specific for the detection of metallo-enzymes.

P9. Rapid identification of ESBL-producing enterobacteriaceae in blood cultures by fluorescent *in-situ* hybridization (FISH) technique

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Bacteremia infections are associated with increased morbidity and mortality and the rapid identification of the pathogen and its antimicrobial susceptibility is important for improved clinical outcome. Infections with drug-resistant strains of Enterobacteriaceae especially *Klebsiella pneumoniae* and *Escherichia coli* pose a serious threat to available therapy. A number of rapid detection methods have been described for the identification of Enterobacteriaceae, includes fluorescent in-situ hybridization (FISH), Real-Time PCR and DNA chip microarray (Fluit *et al*., 2001). In this study we describe the application of FISH technique directly on smear-positive blood cultures for the rapid identification of multi-resistant *E. coli* and *Klebsiella pneumoniae*. Blood cultures that were smear and culture positive for gram-negative bacilli were obtained from the Diagnostic Bacteriology Laboratory of University Malaya Medical Centre. The culture findings were confirmed by standard biochemical tests. Oligonucleotide probes specific to *E. coli* and *Klebsiella pneumoniae* were designed and synthesized based on the 16SrRNA gene sequence. The probes were labeled with fluorochrome Cy3 (red signal) and Cy5 (green signal) respectively. Universal eubacteria probe labeled with FITC (green signal) was used as positive control. Oligonucleotide probes specific to the antibiotic resistance gene of both the non-ESBL and ESBL subtype of SHV (SHV-1 and SHV-5 respectively), that confers resistance to the beta-lactam antibiotic were synthesized and the difference between the two were based on the mutation at three crucial codons, that is codon 179, 238 and 240 of the defining part of the ESBL *bla*SHV gene. The two probes responsible for the detection of antibiotic resistance were labeled with fluorochrome FAM-6 which emmits a yellow-green signal. The probe specificity

could differentiate between SHV ESBL gene and SHV non-ESBL gene. Whole-cell hybridization was carried out as described by Jansen *et.al*.(2000) and slides were viewed under an epifluorescent microscope (Zeiss). Positive control (smear-positive culture hybridized with universal eubacteria probe) confirmed that the green and red rod shapes identified by the genus specific probes were bacteria and not artifacts. *E. coli* and *K. pneumoniae* probes successfully hybridized to smears of culture containing *E. coli* (red) and *Klebsiella sp* (green) respectively. In contrast the pure culture smears containing *Proteus sp*., *Pseudomonas sp*., *Enterobacter sp.* and *S. typhi* (negative controls) did not show distinct signals thus suggesting the sequences of the probes to be intragenically specific. The two SHV probes successfully hybridized to the positive controls which were pure cultures of *E. coli* expressing SHV-1, a non-ESBL enzyme and pure cultures of *E. coli* expressing SHV-5 enzyme and thus discriminating between the SHV ESBL gene and SHV non-ESBL gene. FISH technique could be a potential rapid diagnostic tool for identifying Enterobactericea and determining susceptibility to ß-lactams in smear-positive blood cultures, with a turnaround time of approximately 1 hour.

P10. Computerised morphometric analysis of distortion artefacts related to microwave stimulated formaldehyde fixation of experimental renal biopsy tissues

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The use of the microwave oven is well-established in histopathology practice, especially in bringing about better exposure of antigens in tissue sections for immunohistochemical staining. The use of the microwave in enhancing fixation of tissues have also been often mooted for situations when rapid diagnosis is needed, such as in the examination of renal transplant allografts for evidence of rejection. However, as with the adaptation of any new technique into a diagnostic repertoire, it is important to be aware of any artefacts introduced that may impact on the quality of the examination. We have observed that such changes may be very subtle and its interpretation may be subjective. In order to investigate for changes in an objective manner, we turned to the use of computers and bioinformatics in its documentation and analysis. We report here our experience with computerised morphometric analysis to investigate glomerular artifacts caused by microwave-stimulated fixation of renal tissues. 39 rat and 33 human autopsy kidney samples were subjected to (1) fixation in formaldehyde (control), (2) microwave stimulated fixation followed by formaldehyde, and (3) formaldehyde followed by microwave irradiation. In addition, the effect of post-fixation in 70% ethanol was also investigated. Microwave irradiation was delivered through a dedicated laboratory microwave oven at 80% power and at 55^{o}C for 3 minutes. The different fixation methods were compared with regards to shrinkage (distortion) to glomerular structures (glomeruli and Bowman's spaces) on H&E sections, as determined by morphometric image analysis using a temporary assembled-system consisting of a trinocular microscope, a digital video camera and personal computer. A FlashPoint VGA 3.3 film-grabber card was used to capture images for morphometric analysis by using a *Scion Image* program. Morphometric analysis of glomerular structures showed that microwaves caused more shrinkage to the area bounded by the Bowman's capsule than the glomerulus proper, but post-fixation with ethanol reduced this shrinkage. These findings have implications on the logistics of tissue preparation of renal biopsies in clinical practice.

P11. Misdiagnosis of tuberculosis due to atypical clinical presentation and conflicting laboratory results leading to death of a young indonesian worker: a case report illustrating the importance of post-mortem examination

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A typical presentation of tuberculosis with conflicting and negative laboratory results may give rise to undue delay in starting treatment and may lead to increased mortality. A 25-year-old Indonesian rubber plant worker was admitted in a general hospital with complaints of headache, irregular fever with chills and rigor and vomiting for last two weeks. CT scan revealed multiple ring enhancing lesions with cerebral oedema. CSF with Indian ink preparation showed cryptococci. His ESR was 58 in the 1st hour. Chest X ray and other laboratory investigations including sputum for AFB, routine hematological investigations, liver, renal function tests, electrolytes were normal and hepatitis and HIV panel were negative. He was treated with Amphotericin B for two weeks and did not show any improvement. Due to his deteriorating condition antituberculous treatment was initiated after two weeks of anti-fungal treatment. The patient died after one week. To determine the cause of death in this patient, external and internal post-mortem examination was done. Microscopical examination of brain, meninges, lungs, liver, spleen, kidney, hilar lymph node show multiple epithelioid cell granulomas with caseation necrosis, infiltrated by lymphocytes, Langhans and foreign body type of giant cells. Post-mortem examination is an essential and important tool to confirm diagnosis of diseases in patients who die during treatment either due to misdiagnosis or conflicting laboratory and imaging results. This facilitates better understanding of disease processes, helps expand our present knowledge of disease presentation and define better strategies for the management and treatment of diseases in future.

P12. Non-alcoholic fatty liver disease: a histopathological study in a university hospital setting

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Non-alcoholic fatty liver disease (NAFLD) has emerged as one of the major causes of chronic liver disease in developed countries. It is envisaged that with the rapid development in Malaysia, NAFLD will soon become an important disease in our population. A study was conducted to histologically classify our cases of NAFLD. Between the last quarter of 2002 and the first quarter of 2004, 39 patients underwent liver biopsy at the University of Malaya Medical Centre to histologically substantiate the presumptive diagnosis of NAFLD in patients with prolonged rise of serum transaminases (> 6 months). Histological examination was also undertaken with the intent of classification of NAFLD to benign steatosis and nonalcoholic steatohepatitis (NASH) for management and prognostication purposes. Apart from a lack of history of alcohol intake, viral, autoimmune, metabolic and genetic causes of chronic liver disease were also excluded in these patients. Of the 39 cases, the histological sections were available for review in 27. The cases were classified into benign steatosis and NASH based on the presence or absence of liver injury. The patients' ages ranged between 23-66 years (mean= 47 years). There was a slight female preponderance with the male to female ratio of 1:1.7. Ethnically, 14 were Malays, 8 Chinese and 5 Indians. Histologically, 5 were considered benign steatosis while 22 were classified as NASH. Cases of NASH were further classified according to Brunt's grading and staging system. One case was graded as I, 14 as II and 7 as III based on the amount of necroinflammatory changes seen. 11 were staged as I, 3 as II, 6 as III and 2 as IV depending on the location and amount of fibrosis. From this study, it appears that majority of our cases presenting with prolonged, raised serum transaminases without a history of alcohol intake and in whom other causes of chronic liver disease have been excluded were NASH

rather than benign steatosis. For the cases of NASH, most showed moderate inflammation with ballooning degeneration and disarray of the hepatocytes. Fibrosis was usually confined to the perisinusoidal region.