NEWSLETTER OF THE HONG KONG COLLEGE OF PATHOLOGISTS

PATHOLOGUE

The Hong Kong College of Pathologists, Incorporated in Hong Kong with Limited Liability

THE HONG KONG COLLEGE OF PATHOLOGISTS
SCIENTIA ILLUMINAT MEDICINAM
香港病理學專科學院

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FROM THE CHIEF EDITOR

In the Message from the President, Dr. K.C. Lee has helped us to clarify the issue related to the 'professionally qualified directorship' in the Supplementary Medical Professionals Ordinance. The College has worked very hard in the past years to solicit this clarification from the Government.

The Editorial Board is interested in the current medical curriculum, the ways to promote the image of Pathology to medical students and public, and hearing the voices of the new trainees. With the featured article Paving the Way for Our Next Generation, we aim to explore this area in a coherent manner.

In the Topical Update from the Education Committee, Dr. Cheuk Wah discusses the Impact of Molecular Methods in the Diagnosis of Lymphomas. This well-referenced article provides us with the basic as well as the latest up-to-date information regarding this rapidly advancing topic.

In the Out of the Whitecoat section, three of our Fellows share with us their precious experience in the Yunnan province of the Mainland. Dr. H.K. Mong and Mrs. Marie Mong drove to Yunnan with the HK Police Motoring Club (香港警察汽車會), while Dr. Tony W.H. Shek and his better half, Dr. Ivy S.C. Luk, joined the fund-raising walk by the Sowers Action (苗圃行動).

The College AGM will take place on 24 November, 2007 (Saturday). The T.B. Teoh Foundation Lecture, entitled 'H. pylori and its related diseases: 25 years after the discovery', will be delivered by Prof. Joseph Sung from the Chinese University of Hong Kong. The 3rd Trainee Presentation Session will also take place on the same day. Please come and show your support to our trainees.

See you all at the AGM!

Dr. Alexander C.L. Chan
Chief Editor

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Message from the President

"Pathologists cannot legally direct medical laboratories." To us pathologists, leaders of the profession of laboratory medicine, this statement seems totally incomprehensible, if not arousing indignation. Yet apparently it is what the law currently states, at least many would interpret it as such as from the relevant section in the Supplementary Medical Professionals Ordinance (SMPO), which requires that every medical laboratory must have at least one registered medical technologist, but not pathologist, as the "professionally qualified director."

Of course pathologists are medical doctors and therefore the Ordinance, which is meant to govern the supplementary medical professions, may not be applicable, as there is the Medical Registration Ordinance. However, SMPO is the only piece of legislation in which regulation of medical laboratories is being stipulated. Therefore I know many of our Fellows in the private sector have not taken chances, and have partnered with medical technologists so as to comply with the legal directorship requirements.

To clear the confusion, and to rectify the situation if necessary, the College has, over the past years, tried again and again to engage the Government and the legislators in expressing our concerns, and to seek their help, when required, in making amendments or at least granting exemption to pathologists on the directorship requirement. However our voice seemed to have fallen on deaf ears.

Four years ago when I took up the College President position, there appeared to be a good opportunity to renew our effort and to revisit the whole issue afresh, as we had a new Secretary for Health, Welfare and Food (SHWF), Dr York Chow, and a new legislator representing the Medical Functional Constituency, Dr Kwok Ka Ki, more or less at the same time. Indeed they have been very helpful, though understandably the process of dealing with legal issues took time, and consultations were required back-and-forth with other stake-holders such as the Medical Laboratory Technologist Board. After all these deliberations, we have received the following response from the HWF Bureau:

"[The SMPO…] aim to regulate the practice of the profession of Medical Laboratory Technologists and not the laboratory work environment per se. It does not appear that pathologists may not practise its profession in medical laboratories. Currently there are no specific provisions restricting companies providing medical services, including pathological services, but of course the medical practitioners and the medical laboratory technologists employed to assist the medical practitioners in their medical practice should be regulated."

So to me it effectively says, in black-and-white and for the first time, that in the Government's view the SMPO is not applicable to pathologists, who are medical practitioners, and pathologists can direct laboratories as it is part of their professional practice. This indeed is a welcome clarification.

Perseverance and seizing the timely opportunity have been the keys in achieving the outcome. But the bigger lesson I have learnt from dealing with this issue is on the role of the College in representing the interests of the profession. Empowered by its members and driven by a shared vision, a confident College is most essential to take on any issue that may affect all of us.

A divided College, on the other hand, can jeopardize its ability to face challenges.

That is also why the Council has now put together a consultation paper on inter-disciplinary matters, and has taken the opportunity to communicate with members our views on several more controversial issues. This consultation paper has been sent to all fellows earlier, and is also available at the College website (http://www.hkcpath.org). You are of course welcome to disagree with the Council and express your own perspectives on those or other related issues. Whatever views you may hold, we want to hear from all of you by the end of October 2007. After all, diversity yet with a shared vision is the strength not weakness of our College. With this shared vision, we can go past the need to focus inwardly on divisions between members and sub-disciplines, and move forward into an unpredictable and challenging future.

Dr. K.C. Lee, the President

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Featured Article -

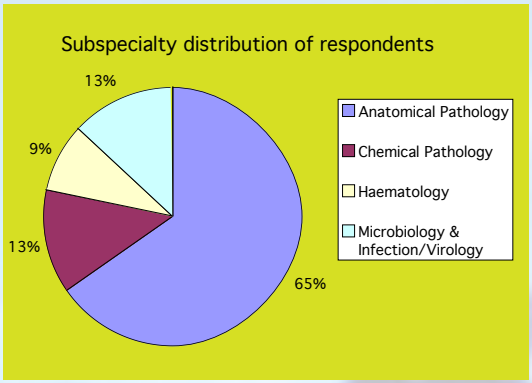
Paving the Way for Our Next Generation

The world is evolving: the way Pathology is taught in medical schools, the perception of the Pathology specialty by the medical graduates, and the expectation and mentality of the new generation of trainees may all be quite different from what they used to be. By understanding the current situation, we can better prepare ourselves to recruit and train a suitable group of successors in the future.

To investigate these related issues, the Editorial Board has obtained valuable input from the heads of the Pathology Department of the two local universities (Prof. L.C. Chan of the University of Hong Kong (HKU), and Prof. H.K. Ng of the Chinese University of Hong Kong (CUHK), the Chiefs of Services of two regional HA hospitals (Dr. S.W. Pang of Pamela Youde Nethersole Eastern Hospital and Dr. K.F. Wong of Queen Elizabeth Hospital), and Dr. K. L. Hau, Consultant Forensic Pathologist i/c of Forensic Pathology Service of Department of Health (DH). In addition, with the help of Dr. Regina Lo, we have conducted an anonymous survey on 37 new trainees registered since 2004, collecting their opinion regarding the current training situation and career-related issues. We received a total of 23 responses from these trainees (response rate: 62%), and the distribution of the respondents according to subspecialty is shown in Chart 1. We take this opportunity to thank all those who have contributed to this article.

IS IT TRUE THAT FEWER MEDICAL GRADUATES ARE INTERESTED IN CHOOSING PATHOLOGY AS THEIR CAREER?

Some fellows have observed that there are currently fewer trainees joining our specialty, and they wonder whether it is because new medical graduates are no longer interested in choosing Pathology as their career. Prof. Ng, Dr. Wong, and Dr. Pang have all expressed that this speculation is not true: many application letters were sent in each year for different subspecialties in Pathology, and many graduates requested visits to laboratories to familiarize themselves with the daily routine. Dr. Pang has noticed that among those who applied for training posts in Pathology, most of them showed enthusiasm during their interview, meaning they chose Pathology as their first choice and not as back-up. Dr. Hau also received enquiries from medical graduates from time to time indicating their interest in forensic pathology. There is no difficulty in recruiting new trainees. However, few trainee positions have been created in recent years, and the observed decline in number of new trainees probably accounts for this misconception in some fellows. We believe that HA and DH should have a careful manpower plan at hand, so as to ensure that our specialty can have an adequate number of successors in the future.



▲ *Chart 1*

Many graduates are interested in choosing Pathology as their career, but there are few trainee positions available.

HOW IS PATHOLOGY TAUGHT IN THE MEDICAL CURRICULUM NOWADAYS?

In the past decade, there has been a significant change in the mode of teaching in both medical schools. Prof. Chan of HKU has pointed out that we now emphasize 'stimulating learning' by adding new learning formats, as opposed to standard teaching in the past. Students are expected to take an active role in acquiring knowledge. At HKU, only a certain degree of basic teaching in the principle of Pathology is delivered in form of lectures and practicals: most of the material has been integrated in form of problem-based learning (PBL) sessions. In these PBL sessions, which are centred around a clinical problem or a case scenerio (e.g. a middle-aged man with chest pain), students are expected to find answers themselves, through group discussion, and guidance and facilitation by tutors (who are clinical or scientific staff trained in leading PBL sessions). Knowledge covering different branches of medicine, including Pathology, will be discussed in each session, all centred around the clinical problem (e.g. anatomy of the heart, pathology of ischaemic heart disease, clinical feature of ischaemic heart disease). Pathology will be viewed as part of the whole picture. During senior clerkship, the role of Pathology in the clinical practice of medicine will also be introduced to the students through 'structured display' sessions and clinicopathologic conferences (CPC). In the former, students are presented with an acute clinical emergency scenerio, where the importance of relevant laboratory testing in patient management is introduced (e.g. frozen section diagnosis, laboratory investigation for bleeding disorder, biochemical testing for hypokalaemic crisis). The importance of pathologists in making a quick diagnosis and advising on clinical management is emphasized. In CPC, students present the clinical case including the pathology findings. During the exercise, students are shown the importance of pathologists in making a final diagnosis and being the 'doctor's doctor'. The message 'Pathologists play an active part in clinical management' is repeatedly reinforced in these sessions. Visits to the public mortuary are also organized to introduce students to the importance and relevance of autopsy in the practice of medicine.

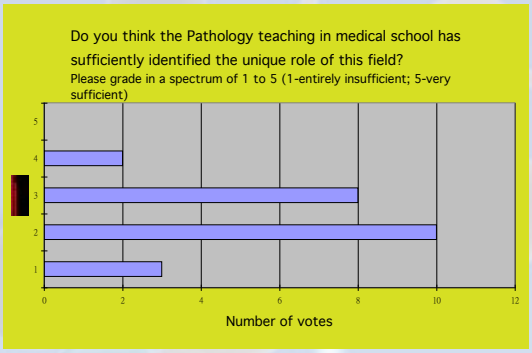
Similarly at CUHK, as mentioned by Prof. Ng, Pathology is no longer taught as an independent curriculum, but within a system-based integrated curriculum. For example, neuropathology is taught in the nervous system panel, the teachers of which range from neuroanatomists, to neuropathologists, neurosurgeons and neurologists.

Pathology is now taught within an integrated curriculum in both Universities.

IS THERE A POTENTIAL PROBLEM IN IDENTIFYING PATHOLOGY AS A SPECIALTY DURING MEDICAL TEACHING?

It has been argued that with the integrated teaching in the current medical curriculum, Pathology may lose its identity and students may have difficulty in identifying Pathology as a specialty. Prof. Ng believes it should not be a problem in CUHK because clinical students meet pathologists during their clinical rotations at the multidisciplinary CPC, and their department is involved in 15 such meetings per week. Students should know precisely the roles of pathologists in patient management. Also, their curriculum has an element of interface between basic science and clinical medicine, and there are sessions in the fifth year in which non-clinicians, pathologists included, participate. For example, the students may present a case of myocardial infarction in one session. They need to prepare several parts involving anatomy, ECG, chemical diagnosis and pathology. The clinicians will line up anatomists, pathologists (including anatomical pathologists and chemical pathologists), and physiologists. The pathologists' role is to comment on the students' presentation in their specialized area. At HKU, Prof. Chan stated that medical students love Pathology in the first two years, as reflected by the students' returned comments. However, he admitted that after going to the wards, students' interest is switched to life-saving skills in clinical medicine. Based on our own survey, our new trainees also feel that the Pathology teaching in medical school may not have sufficently identified the unique role of this field (Chart 2).

Students' interest switches from Pathology to life-saving skills in clinical medicine after going to wards.



▲ *Chart 2*

HOW CAN WE PROMOTE PATHOLOGY TO MEDICAL STUDENTS?

Since many of our new trainees feel that the Pathology teaching in medical school may not have sufficently identified the unique role of this field, how can we promote our specialty to the new medical students? Prof. Chan raised the possibility of introducing a short Pathology clerkship, as a bridge, to show students how pathologists work in their daily practice, and how they collaborate as a team with clinicians, scientists and technicians. The students should learn how specimens are handled, how important is the quality of report, how to extract relevant information from pathology reports, and how important is the pathologist as an expert. Meanwhile, attachment to Pathology Department during special study modules in the current curriculum should be encouraged. The Universities should facilitate and provide the link for the students, by inviting HA, DH and private hospitals to participate in this sort of attachment programme. Interestingly, our trainees have made similar suggestions: such as adding a brief introduction on the daily routine work of Pathology, increasing the chance of bench attachment and hands-on experience, and arranging more structured attachment programmes. They also proposed organizing career talks including talks about the different subspecialties and the work involved in the various fields. Dr. Hau suggested that the College can consider posting up more information regarding career pathways in different subspecialties of Pathology on its website, so as to give medical students and new graduates better ideas about pursuing careers in Pathology. We think a career brochure by the College can serve similar purpose.

Student attachment to Pathology Department should be facilitated and encouraged.

HOW CAN WE PROMOTE PATHOLOGY TO THE PUBLIC?

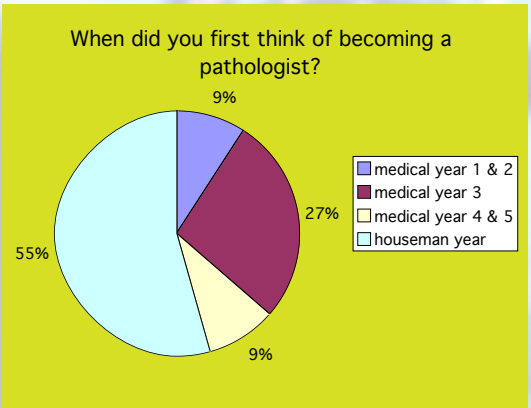
In addition to exploring ways of promoting Pathology to medical students, we have also taken this opportunity to consider the need and ways to promote Pathology to the public. Compared to other medical specialists, pathologists have always been low-key, and stay in the background. Prof. Chan believes there is a need to promote Pathology to the public, and Dr. Hau commented that the successful CSI TV series is a good example in attracting medical graduates (and the public) to Forensic Pathology. Prof. Chan has rightly pointed out that the public still does not know what pathologists do: some have the misconception that the work of these specialists only involves dissecting bodies, and is not related to living people. He thinks that the College and both Universities can consider holding regular exhibitions or talks on Pathology-related topics, in a co-ordinated and repeating manner. Meeting the media and providing press releases and weekly columns in the newspaper are other means. Prof. Ng and Dr. Wong similarly suggested submitting prepared news items and educational columns to friendly media and newspaper. Along a different line, Dr. Wong commented that the College should assist in promoting laboratory accreditation, which will help in improving the quality and thus the image of Pathology.

The College, Universities and media may play useful roles in promoting Pathology to the public.

WHAT ATTRACTED OUR NEW TRAINEES TO JOIN PATHOLOGY?

From our survey, 55% of our new trainees first thought of choosing Pathology as their career during their houseman year, but 36% made their decision even when they were in medical year 1 to year 3 (27% in year 3) (Chart 3). Since 30% of them have taken elective attachment or intercalated degree before, it is possible that their previous exposure has helped them to understand the real life in Pathology, and has primed them to choose our specialty as their career. To the new trainees, our field is a state-of-the-art integration of science into medicine with ever growing technology, and our problem-solving work is interesting and of 'detective' nature. However, it is intriguing to learn that some trainees were at first attracted by our 'regular working hours', and 'minimal patient/relative-doctor conflicts'. They should know by now that these are general misconceptions: many of us do work overtime and need to be on-call, and we are not completely immune to relative-doctor conflicts (e.g. at interviews for Coroner autopsy for Anatomical Pathology). In fact, a trainee has indicated that we should not promote the advantage of 'regular working hours': pathologists need to do a lot of reading and it is best to inform the students/interns before they apply for the position.

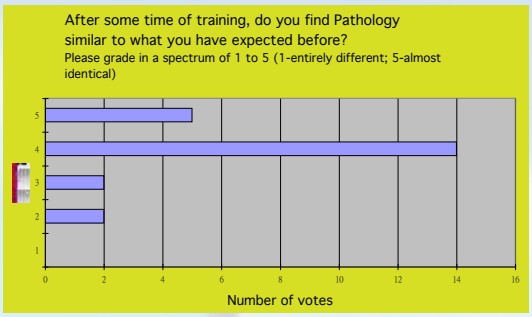
Some apparent attractions to Pathology prove to be misconceptions.



▲ *Chart 3*

HOW DO OUR NEW TRAINEES VIEW THEIR CURRENT TRAINING AND THEIR FUTURE CAREER PROSPECT?

It is comforting to know that after working some time in the field, most new trainees find Pathology similar to what they have expected before (Chart 4). This indicates that most of them have made appropriate and adequate enquiry regarding the job nature before they apply for the positions. Despite this, it has been observed that a small number of trainees still gave up training in Pathology. Dr. Pang is interested to find out why: although trainees left for multiple reasons, we can prevent wastage of time and effort of all concerned parties by identifying areas that need improvement (our blind spots). He suggested that the Training and Education Committee of the College can consider a standard questionnaire to all departing trainees and their supervisors, or the Editorial Board can consider exploring this issue in future featured article.



▲ *Chart 4*

Our new trainees have expressed some of their difficulties when they first joined our field. They need to absorb a large amount of information in a short period of time, and are expected to pick up many new terms and professional language. Some admitted that they had to catch up on lots of things at the start, because of their lack of basic Pathology knowledge. They need time to be familiar with the use of microscope and different equipment, the laboratory routines, and the management issues. They are required to learn how to write comprehensive and informative reports, and work unexpectedly long hours. Some commented that there is relatively insufficient guidance in some centres, and teaching is mostly limited to a case-to-case basis. Other problems include a great interobserver discrepancy in the criteria of diagnosis without

clear-cut consensus, limited autopsy availability to reach the training requirement, lack of philosophy of approach, and need to adjust to an 'ultra cautious work manner'. These pieces of feedback information will be very useful to our fellow supervisors in designing or modifying their future training programme.

Understanding the difficulties encountered by the trainees can help supervisors to improve the training programme.

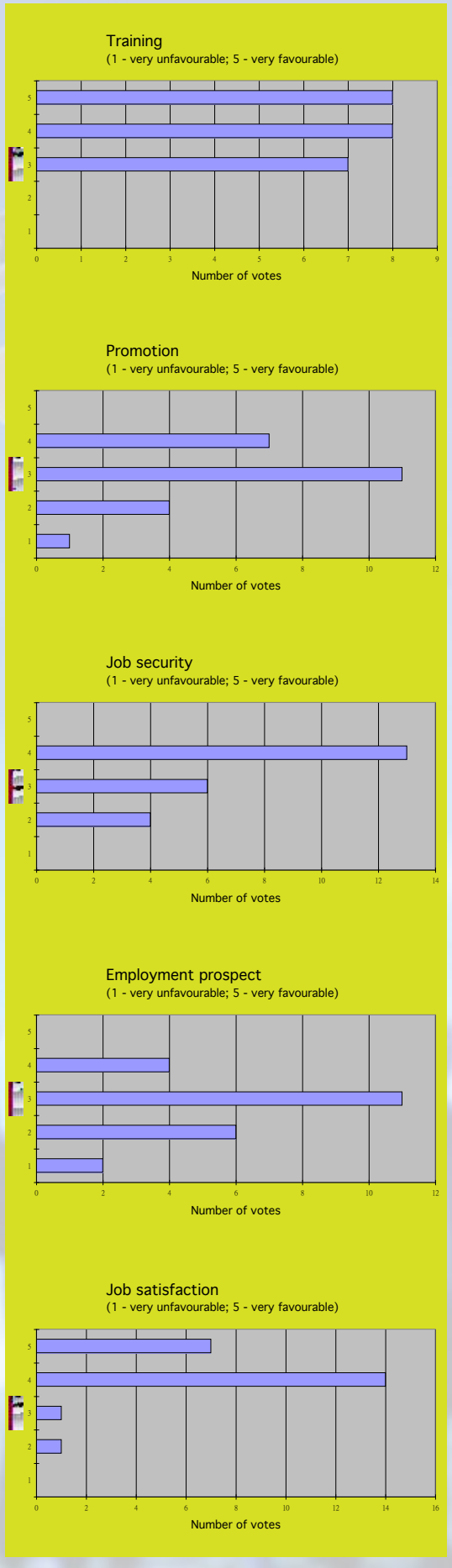
When trainees were asked about the career prospect as a pathologist, they are all very positive about the current training programme, job security (low risk of being fired or contract not renewed) and job satisfaction. On the other hand, they are more neutral with respect to promotion and employment prospect (whether it is difficult to find a new job). (Chart 5) Regarding career aspiration, most trainees are very realistic, and concentrate on passing the examination, and becoming a competent diagnostician who can provide good quality service to our clinical colleagues. Some want to subspecialize and excel in special fields, and develop research interest and educate students.

What will the future be for the newer generations of Pathology trainees? Dr. Pang pointed out that the application of Molecular Pathology will be increasingly important not only in understanding disease process and supporting diagnostic work but also in treatment and monitoring response. Though he does not think it is the sole responsibility of our College to promote this area, he believes that our College should support both Universities in recruiting suitable candidates and liaise with HA/DH/Universities/government in establishing some career structure to enable interested students in considering taking up this field as life-long vocation.

CONCLUSION:

In summary, there are ways to further promote the unique role of pathologists in the practice of clinical medicine to our medical students. The better-informed graduates will be more prepared for our training programme, and can adjust to our professional lifestyle more easily.

▼ *Chart 5 : What do you think about your career prospect as a pathologist, in terms of the following?*



THE HONG KONG COLLEGE OF PATHOLOGISTS:

TOPICAL UPDATE

Volume 2, Issue 2 2007

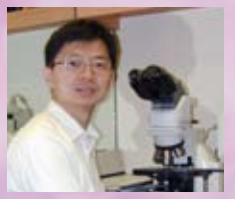
(This article is reproduced from the publication of the Education Committee, Topical Update, Volume 2, Issue 2.)

Editorial note from the Education Committee:

In this issue of Topical Update, Dr. Cheuk takes us through the evolution of applications of molecular methods in pathology using examples in haematolymphoid pathology. He also explains the new technique of microarray with its various abilities in understanding diseases and application on individual patients. This article illustrates how advances in basic sciences and informatics technology can be harnessed and applied in the diagnostic laboratories.

We welcome any feedback or suggestions. Please direct them to Dr. Polly Lam (e-mail: lamwy@ha.org.hk) of Education Committee, the Hong Kong College of Pathologists. Opinions expressed are those of the authors or named individuals, and are not necessarily those of the Hong Kong College of Pathologists.

Impact of Molecular Methods in the Diagnosis of Lymphomas



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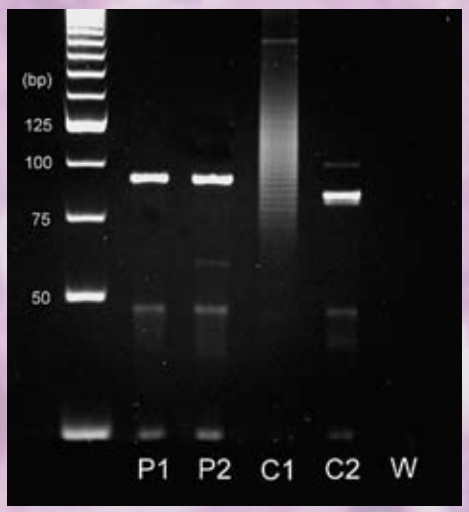
Overview of conventional molecular techniques in lymphomas

The use of molecular techniques in hemato-lymphoid pathology started with cloning of the immunoglobulin and T cell receptor genes. [1] This is followed by the cloning of a number of translocation breakpoints in some common lymphoma types.[2-4] Assay of chromosomal breakpoints not only helps in confirming a clonal proliferation but also provides an indication of the type of lymphoma. The main application is to establish clonality or lineage of a lymphoid proliferation.



▲ *Figure 1. PCR for immunoglobulin gene rearrangement. Left lane, molecular size ladder (bp, base pair); lanes P1 and P2, tumor sample in duplicate showing a single band of identical size; lance C1, polyclonal positive control; lane C2, B-cell lymphoma positive control; lane W, water negative control.*

Southern blot analysis was the standard technique in molecular studies. The advent of the polymerase chain reaction (PCR) provides an alternative technical approach to Southern blot analysis, allowing molecular studies to be performed in many diagnostic laboratories. PCR technique is technically simpler, has a much faster turnaround time, requires a much smaller quantity of clinical materials, and can be performed on archival, formalin-fixed, paraffin-embedded samples (Figure 1).[5] Advances in PCR techniques allow accurate quantitation of the template (real time PCR) and make it possible to use RNA as the starting material (reverse transcriptase PCR).[6] Fluorescence in situ hybridization (FISH) utilizes oligonucleotide probes to localize specific chromosomal segment so that translocation can be visualized under the fluorescence microscope.[7] This "interphase cytogenetics" technique obviates the need of fresh specimen and cell culture and revolutionizes the traditional cytogenetics.[8] Although FISH may not be as sensitive as PCR-based methods, it is superior in detecting complex karyotypic abnormalities involving multiple fusion partners and has lower false negative rates in detection of chromosomal translocations in some lymphoma types.

At this juncture, molecular technologies not only provide diagnostic aid, but also data useful in prognosis and clinical management. For example, for gastric mucosa-associated lymphoid tissue (MALT) lymphoma, the presence

of API2/MALT1 gene translocation indicates that the tumor is unlikely to respond to Helicobacter-eradication therapy,[9, 10] yet progression to a large cell lymphoma is very rare.[11] Quantitation of t(14;18) translocation products and Epstein-Barr virus DNA in patient's plasma can be used to detect minimal residual disease and monitor the clinical course of patients with follicular lymphoma and NK/T cell lymphoma respectively.[12, 13]

Southern blot analysis, PCR and FISH are conventional molecular techniques used in lymphomas.

Microarray technique

Yet the world is about to witness another major breakthrough in molecular biology. Like many important technological advances in the past, this major breakthrough is made possible with three contemporary developments, namely, the completion of the Human Genome Project,[14, 15] the availability of high-throughput array-based technique,[16] and the advancement of sophisticated bioinformatics strategies (Table 1).[17] The microarray technique uses gene-specific probes that represent thousands of individual genes. The probes are arrayed on an inert substrate and quantities of individual genes in a target sample are assayed. RNA is extracted from the tumor, labeled with fluorescent dye and allowed to hybridize to the arrays. Images are registered by confocal laser scanning. The relative fluorescence intensity of each gene-specific probe is a measure of the level of expression of the particular gene. A greater degree of hybridization manifests as more intense signal, implying a higher level of expression. The data are typically presented in a matrix in which each row represents a particular gene and each column represents a tumor sample. In the most common convention, the color codes used are based on the log ratio for each sample measured compared with a control sample; log-value close to zero are rendered in black, greater than zero in red (indicating upregulation) and negative values in green (downregulation) (Figure 2). DNA samples can also be analyzed to look for amplifications or deletions of genes, or to detect known DNA sequence mutations.

New lexicology

The first, and usually the more widespread, impact a technology brings are the new terms that come with it. Because of the Human Genome Project, the meaning of the word "genome", which refers to the complete collection of genes in an organism, is well known to most people nowadays.[14, 15] Genomics, therefore, is the study of genomes. Not long afterwards, as molecular biology spreads its influence, the vogue of the suffix "-omics", that is, the study of "-omes", becomes almost unstoppable. Oncogenomics is the study of cancer-related genome; proteomics, the totality of proteins; transcriptomics, the mRNA complement of an entire organism, tissue type, or cell; spliceomics, the alternative splicing protein isoforms; ORFeomics, the DNA sequences that begin with the initiation codon ATG, end with a nonsense codon, and contain no stop codon; kinomics, the protein kinase in a cell; metabolomics or metabonomics, the metabolites; lipidomics, the lipids; glycomics, the glycans, carbohydrate structures…
The use of "-ome" and "-omics" is limited only by the imagination, and omeome refers to a complete set of "omes" and omician and omists are people who study omes and omics.[43]

▲ *Table 1. New lexicology*

The microarray allows, in one assay, the entire genome to be analyzed globally, so-called "gene profiling", instead of aiming at one or a few specific targets as in the traditional molecular techniques. This approach provides an overall view of the genomic make-up, and provides functional aspects of the genome in action. It not only identifies the aberrantly expressed genes, but also highlights functional groups of genes that are regulated in a similar fashion or involved in a common pathway that underlies many fundamental biologic processes such as lineage differentiation, proliferation, and survival, which may provide insight into the mechanistic aspects of the diseases being studied. The focus in genetic pathways rather than on single genes significantly enhances the power to understand molecular mechanisms of tumorigenesis, as the magnitude of changes in individual genes is very often too small to appear significant.[18]

The microarray technique allows, in one assay, the entire genome to be analyzed globally, so-called "gene profiling".

Gene expression profiling in lymphomas

Diffuse large B-cell lymphoma (DLBCL) is the commonest, high-grade lymphoma with considerable clinical and biological heterogeneity within this diagnostic entity.[19, 20] Gene expressing profiling has identified at least three distinct molecular subgroups that are morphologically indistinguishable: germinal center B-cell-like (GCB) DLBCL, activated B-cell-like (ABC) DLBCL and primary mediastinal B-cell lymphoma (PMBL), by their differences in expression of differentiation-related genes and oncogenetic

▲ *Figure 2. Three distinct subgroups of DLBCL represented in separate columns. Each row represents a group of differentially expressed genes among these subgroups. Red indicates overexpression and green indicates underexpression.*

pathways.[21-24] The five-year survival rates of patients with GCB DLBCL, ABC DLBCL and PMBL are 59%, 31% and 64% respectively. [21-24] PMBL, currently diagnosed predominantly based on clinical findings, demonstrates distinctive clinical features such as young age at presentation and involvement of the mediastinum or intra-thoracic structures.[25] By gene expression profiling, PMBL possess a distinct molecular signature in comparison to either GCB and ABC DLBCL.[22, 26] In addition, an unanticipated finding is that PMBL shares a strikingly similar expression profile with nodular sclerosis Hodgkin lymphoma, a tumor that is well known to demonstrate many clinicopathologic similarities to PMBL yet belonging to a different class of lymphoma.[22, 26] Gene expression profiling seems to offer a molecular explanation to this paradox. It has been proposed that PMBL and nodular sclerosis Hodgkin lymphoma may arise from a common precursor B cell in the thymus, or that these two entities may represent opposite ends of a biologic continuum, with the intermediate form manifested as mediastinal gray zone lymphoma.[27] Despite these molecular similarities, the gene expression profiles of the PMBL and nodular sclerosis Hodgkin lymphoma are still clearly distinguishable. [22, 26]

Apart from subclassifying DLBCL, gene expression profile also identifies genes whose expression levels correlate with survival regardless of DLBCL subgroups. [23, 28] Overexpression of genes like PRKCB1, PDE4B, bcl2 is associated with a poor outcome, whereas overexpression of bcl6 and LMO2 is associated with a good outcome, [23, 28, 29]although it is not surprising that some of these genes represent the same genes that distinguish DLBCL subgroups. Those genes that most correlate with survival have been selected out to create a panel of "survival predictor genes". [23] A survival predictor score can be calculated based on the gene expression with significantly different 5-year survival. Meanwhile, monoclonal antibodies against protein products of genes that are useful in distinguishing GCB and ABC DLBCL have been developed, and subclassification of DLBCL based on immunohistochemical staining with a panel of these markers has been found to correlate with prognosis.[30] It shows that findings obtained from microarray studies can be applied using more accessible procedures carried out in the diagnostic laboratory.

Follicular lymphoma is the second most common and indolent lymphoma with a highly variable clinical course. Some patients may survive more than 15 years following diagnosis or even undergo spontaneous regression, whereas others may succumb in less than 5 years.[31-33] It has been shown that the length of survival of patients with follicular lymphoma can be predicted by gene expression profiling at the time of diagnosis. Two signatures, "immune response-1", which is associated with a longer survival and "immune response-2", which is associated with a shorter survival, have been identified.[34] These two signatures, interestingly, are not attributable to gene expression patterns of the neoplastic lymphoid cells, but reflect the character of the tumor-infiltrating immune cells. Immune response-1 indicates the presence of mainly T cells in the immune infiltrate, whereas immune-response-2 indicates an immune infiltrate that is relatively low in T-cell content and relatively enriched in macrophages and dendritic cells.[34]

Gene expression profiling can potentially subclassify the existing heterogeneous diagnostic categories into more homogeneous subgroups, and provide prognostically

relevant parameters. At times, it may even outperform the diagnosis rendered by expert hematopathologists. A gene expression signature of Burkitt lymphoma has recently been established, which is characterized by high expression of c-myc target genes, expression of a subgroup of GCB genes, and low expression of MHC class I genes and NF□B target genes.[35, 36] Patients with Burkitt lymphoma diagnosed by gene profiling have a significantly better survival than those having high-grade B-cell lymphoma that lacks the Burkitt lymphoma signature (5-year survival 75% vs 39%), which is an expected clinical outcome for a correct distinction between Burkitt lymphoma and DLBCL. However, in the same study, some cases of Burkitt lymphoma or atypical Burkitt lymphoma diagnosed by expert hematologists do not show the molecular signature of Burkitt lymphoma, whereas some cases considered to be definitely not Burkitt or atypical Burkitt lymphoma turn out to show the molecular signature of Burkitt lymphoma. These findings suggest that molecular diagnosis of Burkitt lymphoma may be more accurate and more consistent with the expected clinical outcome than conventional diagnosis based on morphology and immunohistochemistry, noting that the diagnostic criteria of this entity were originally derived from the latter.[37] Currently, the major types of lymphoma recognized by the WHO classification can be distinguished from one another by their gene expression profiles. A custom DNA microarray, LymphDx, constructed using approximately 2653 genes claims to be able to distinguish various lymphoma types and subgroups with a concordance of 95% to 100% to the diagnosis based on current methodology.[38]

Gene expression profiling can potentially subclassify the existing heterogeneous diagnostic categories (e.g. DLBCL) into more homogeneous subgroups, and provide prognostically relevant parameters.

Molecular technology and the practice of pathology

The world of pathology has witnessed several waves of technological advancement, e.g., the electron microscope and immunohistochemistry, that had profound impact in its practice.[39] At the early period, molecular technique represented no more than a supplement to the existing armamentarium of diagnostic aids in confirming the clonal nature of the tumor and putting the tumor into the existing categories of classification system. As the technology advances, the target of interest expands from an individual gene, chromosomal translocation, to the entire genome. The microarray findings not only purify various categories in the existing classification systems, but also refine and redefine new entities. The findings also evolve from diagnosis-oriented to individual patient-oriented, providing biological parameters that are relevant to prognosis, predicting response to certain therapy, and even identifying potential therapeutic targets in the future. The new information will undoubtedly be incorporated into the definition and diagnostic criteria in the future tumor classifications, similar to what immunohistochemistry has done to expedite adoption of REAL classification to replace the Working Formulation.[5, 40]

Conclusions

As the impact of diagnosis based on genomic features is beginning to be recognized, a post-genomic era has been proclaimed by some investigators.[41] This post-genomic era focuses on the epigenetic aspects of genome, that is, modulation of gene expression without changes in DNA sequence, such as DNA methylation, non-coding RNA, histone modification and chromatin remodeling. Their influence in our understanding of diseases is still limited, but the potential cannot be underestimated as epigenetic control sits in between the genotype governed by DNA sequence and phenotypes dictated by the pattern of gene expression. It appears that epigenetic alterations occur more readily in response to environmental factors than its genetic counterparts, with profound biological consequences.[42] The practice of pathology has been changing since the very beginning of this specialty, and is bound to evolve along the advancement in medicine. The role of the pathologist, however, remains unchanged if not becoming more and more important in the future, as there are no medical professionals who are more capable and appropriate than a pathologist to preside at this strategic position from the bench to the bedside in patient care.

The potential in the study of the epigenetic aspects of genomes cannot be underestimated.

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Out of the Whitecoat:

Veteran Scales New Heights in China

I drove my car, an SUV, starting from home in Hongkong all the way to Shangri-la (香格理拉) in Yunnan (雲南) in last September, a to and fro journey of some 5,000km in 14 days amongst a convoy of 60 cars. This had always been my ambition and joy of driving on the motherland. We took the Lok Ma Chau Crossing (落馬州) into Shenzhen (深圳), by-passed Guangzhou (廣州), turned west to Guangxi (廣西), Guizhou (貴州) and arriving at our destination, the beautiful Shangri-la along the Lei River (漓江) valley. The drive had been a most memorable journey in my over-10-years driving experiences on the Mainland with most awesome scenery snapshots all the way climbing from sea-level to the Yalong Snow Mountains (玉龍雪山) at 3600 metres. I can testify that even at over 3000m when the oxygen saturation is much reduced and with petrol at Octane value of 93 (not the 98 we are enjoying in HK), my car, fully loaded with 4 passengers and all the luggage, could continue to climb the hilly roads at over 120kph!

This year I should have set off driving to Nei Mongol (內蒙) for a 14-day drive to Hohhot (呼和浩特) as originally planned, but due to some technical reasons, I missed the occasion. I am eagerly anticipating my annual drive on the Mainland to Tibet in 2008 or beyond – the ultimate challenge of a life-time dream.

Dr. H.K. Mong

The arduous trip evidently took no toll whatever on the wonderful vehicle

The inscription aptly spells out the vigour of this couple

All set to embark on the next leg of the long march

The vehicles neatly lined up against a backdrop of imposing terrain

A group photo commemorating a successful journey

A posh vehicle outshining the crowd

The maestro of motoring with the automobile that served him splendidly

The perfect companion to share the breathtaking scenery

Trek for Charity Brings Insight

In April 2007, we participated in the fund-raising walk along the "Ancient Tea Horse Route" (茶馬古道) organized by Sowers Action (苗圃行動), a charitable organization that aims to provide basic education to underprivileged children in Mainland China. The "Ancient Tea Horse Route" originated in the Tang Dynasty when traders, travellers, mules and horses with their goods walked on this mountainous path from Yunnan (雲南) to Tibet, on into Nepal and India. The route also passes through Dali (大理), Lijiang (麗江) and Shangri-la (香格里拉) where a variety of colourful ethnic minorities live.

While some took the challenge to complete the full 4000 km journey on foot, we walked for about 70 km along the first section of the ancient route in Xishuangbanna (西雙版納). We visited a primary school for the Hani people (哈尼族) in rural Yunnan. We were moved to see their physical hardship and abject poverty. But through the cheerful and spirited faces on those little children, we saw hope in their future and we reflected on the contrast of their simple rural lives with our hectic city lifestyle. Unexpectedly, we ended up gaining more than we gave in the journey.

Lastly we would like to thank all those colleagues for their kind donations.

Dr. Tony W.H. Shek and Dr. Ivy S.C. Luk (=Mrs. Shek)

The authors with a statue of the late Premier Chou Enlai in the background

Mixed facial expressions of Hani school-children in rural Yunnan

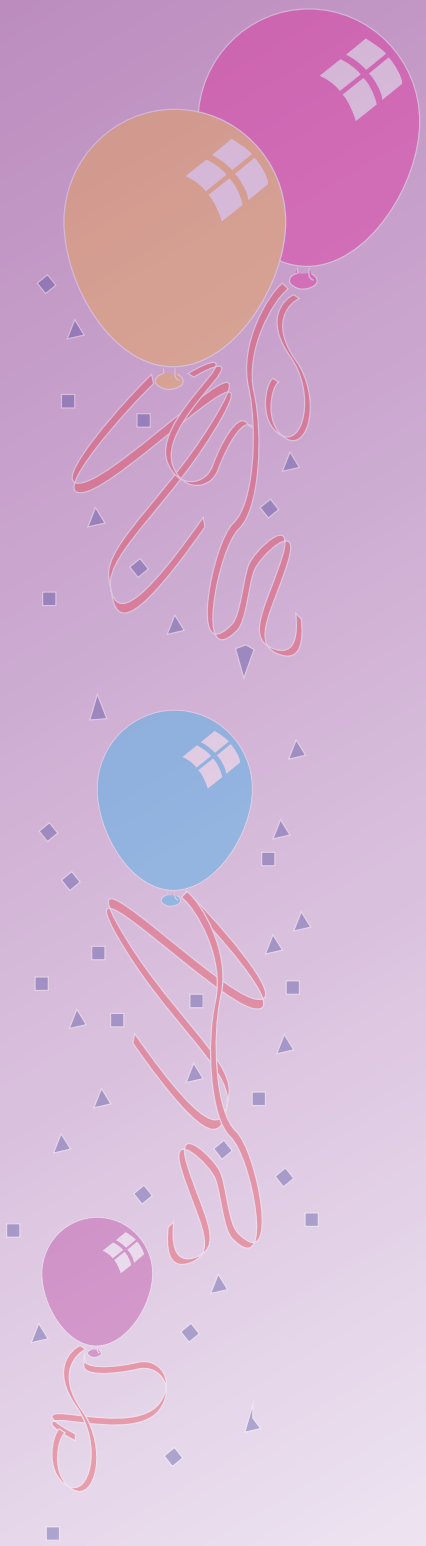
HKCPath Presentation Session for Pathologists in Training:

3rd Trainee Presentation Session on AGM day

The Education Committee would like to announce that the oral presentation session for trainees will be held on the day of the Annual General Meeting on 24 November 2007. This is a good opportunity for our trainees to share experience and to practise presentation skills. A prize will be given for the best presentation.

Please support this meaningful activity of our College and take part in the presentation or support your trainee to take part. An abstract of not more than 300 words can be submitted to Dr WK Luk through e-mail (lukwk@ha.org.hk). Confirmation letter for acknowledgement of receipt will be issued. The deadline of submission is 31 October 2007.

CONGRATULATIONS!!



We are pleased to announce that the following candidates have passed the membership examination/fellowship assessment. Please join us to congratulate them on their success.

Dr. LEE Kin Ping
(Fellowship Assessment in Clinical Microbiology and Infection)

Dr. CHAN Pui Ha, Natalie
(Fellowship Assessment in Haematology)

Dr. LEUNG Yuk Yan, Rock
(Fellowship Assessment in Haematology)

Dr. MAK Siu Ming
(Fellowship Assessment in Anatomical Pathology)

Dr. Cherry WU
(Fellowship Assessment in Anatomical Pathology)

Dr. CHAN Siu Ki
(Membership Examination in Anatomical Pathology)

Dr. CHAN Wing Hung, Anthony
(Membership Examination in Anatomical Pathology)

Dr. IP Yiu Tung
(Membership Examination in Anatomical Pathology)

Dr. LO Wing Ip, Anthony
(Membership Examination in Anatomical Pathology)

INCREASE IN EXAMINATION FEE STARTING FROM 2008

Please note that there will be an increase in the examination fees for membership examination (HK$10,000) and fellowship assessment (HK$14,000) starting from 2008. Accordingly, the fee for membership exemption will be increased to HK$10,000 in line with the membership examination fee.

NEW GUIDELINES FOR TRAINEES

The Council has recently passed two new guidelines that affect both existing and newly registered trainees.

New Guideline for Trainee Registration Within 6 Months of Training

In order to better monitor the training progress of trainees, the Council has decided to encourage the registration of new trainees with the Training and Examinations Committee (TEC) within 6 months from the first day of career development in pathology.

Applications for retrospective recognition of laboratory training period will NOT be considered unless a sound reason is provided and accepted only at the discretion of the TEC with an administrative fee of HK$2,000 for recognition of the whole or part of the whole year of laboratory training period. Please be informed that there will be a grace period until 31st December 2007 for applications for retrospective recognition of laboratory training for existing trainees without the need to pay for this administrative fee. You are advised to submit applications before this deadline.

Applications for retrospective recognition of relevant clinical training prior to the first day of career development in pathology will NOT be affected. However, relevant supporting documents certified by Educational Supervisor are required during new trainee registration.

New Guideline on Trainee Status After Completion of 72 Months of Recognised Training

In order to better monitor the training progress of trainees, the Council has decided to encourage trainees to attempt for College Examinations once they are eligible, that is, after completion of 36 months and 60 months of recognised training (counted up to 30th June of the same calendar year of examination) for Membership Examination and Fellowship Assessment, respectively. However, there are a number of trainees who have completed 72 months of recognised training without attempting any College Examinations due to various reasons. Since their training in pathology has considered to be completed, the Council has endorsed that their trainee status will be rendered inactive automatically after completed 72 months of recognised training. Please note that there will 36 months of grace period after completion of 72 months recognised training applicable to all existing and newly registered trainees. There is no need for inactive trainees to further submit their annual return via their Educational Supervisor as well as the annual trainee subscription fee.

The main effect for the inactive trainee is that the College does not have the obligation to arrange the examination for them if the inactive trainee is the sole applicant for that specialty for that year. The inactive trainee will ONLY be able to sit for examination if there is another active trainee in that specialty who has successfully applied for examination in that year.

If you have any query about the newly endorsed regulations, please contact the Secretary of the Training and Examinations Committee.

NEW EDITION OF THE REGULATIONS ON POSTGRADUATE TRAINING AND EXAMINATIONS (2007)

A new edition of the Regulations on Postgraduate Training and Examination (2007) has just been published. Please note that the new regulations will only be applicable to all new trainees registered on or after 1 July 2007. Hard copies have been sent to all Educational Supervisors. The electronic version is also available at the College website (http://www.hkcpath.org).

ADMINISTRATIVE FEE FOR RETROSPECTIVE ADJUSTMENT OF CME/CPD ACTIVITIES

The Education Committee handles requests from Fellows regarding retrospective adjustment of annual CME/CPD return. Please note that an administrative fee of HK$500 will be charged for request of retrospective reporting of activities that have not been reported in the submitted annual return. This administrative charge does not apply to retrospective adjustment of CME/CPD points for activities that have already been reported in the annual return.

NEW CONTINUING MEDICAL EDUCATION / CONTINUOUS PROFESSIONAL DEVELOPMENT (CME/CPD) SCHEME

To tie in with the revision of the Principles and Guidelines on Continuing Medical Education (CME) and Continuous Professional Development (CPD) issued by the Hong Kong Academy of Medicine, the College CME/CPD scheme has been revised and will be effective in the next CME/CPD cycle starting on 1 January 2008. Please visit the College website (http://www.hkcpath.org) for the complete document. Some of the major changes are highlighted below:-

- Two new categories of CME/CPD activities are introduced in the new scheme.

  5.7 Mortality/Morbidity Meetings and Clinicopathological Conferences: Participation in mortality/morbidity meetings and clinicopathological conferences is separated out from the categories of Passive Participation and Active Participation to form a new category of CME/CPD activities to more accurately reflect the mode of participation of pathologists in these activities.

  5.8 Activities for Improvement of Patient Care: This new category embraces learning/activities that enhances the ability of Fellows to practice medicine both as an individual doctor and as part of the health care team eventually leading to improvement of patient management and care, e.g. information technology, interpersonal and communication skill training, clinical and other skills laboratory learning, simulator and virtual reality learning.

- A maximum of 30 CME/CPD points will be accredited for a Formal College Approved Activity.

MEETING ANNOUNCEMENT

Annual Scientific Meeting 2007 of the HKIAP

20-21 October 2007

Shaw Auditorium, Prince of Wales Hospital,

Dermatopathology by Dr. B. Smoller and

Gynaecological Pathology by Dr. J. Prat.

http://www.hkiap.org

Malaria Laboratory Workshop 2007
(Refesher Training Course)

co-organized by the Hong Kong College of Pathologists and
Public Health Laboratory Centre of the Department of Health.

20 November 2007

1/F Lecture Theatre, Public Health Laboratory Centre.

http://www.hkcpath.org

16th Annual General Meeting of the Hong Kong College of Pathologists

with the **T.B. Teoh Foundation Lecture** entitled

'*H. pylori* and its related diseases: 25 years after the discovery'

by **Prof. Joseph Sung,** and the **3rd Trainee Presentation Session.**

24 November 2007, the HKAM Jockey Club Building

http://www.hkcpath.org