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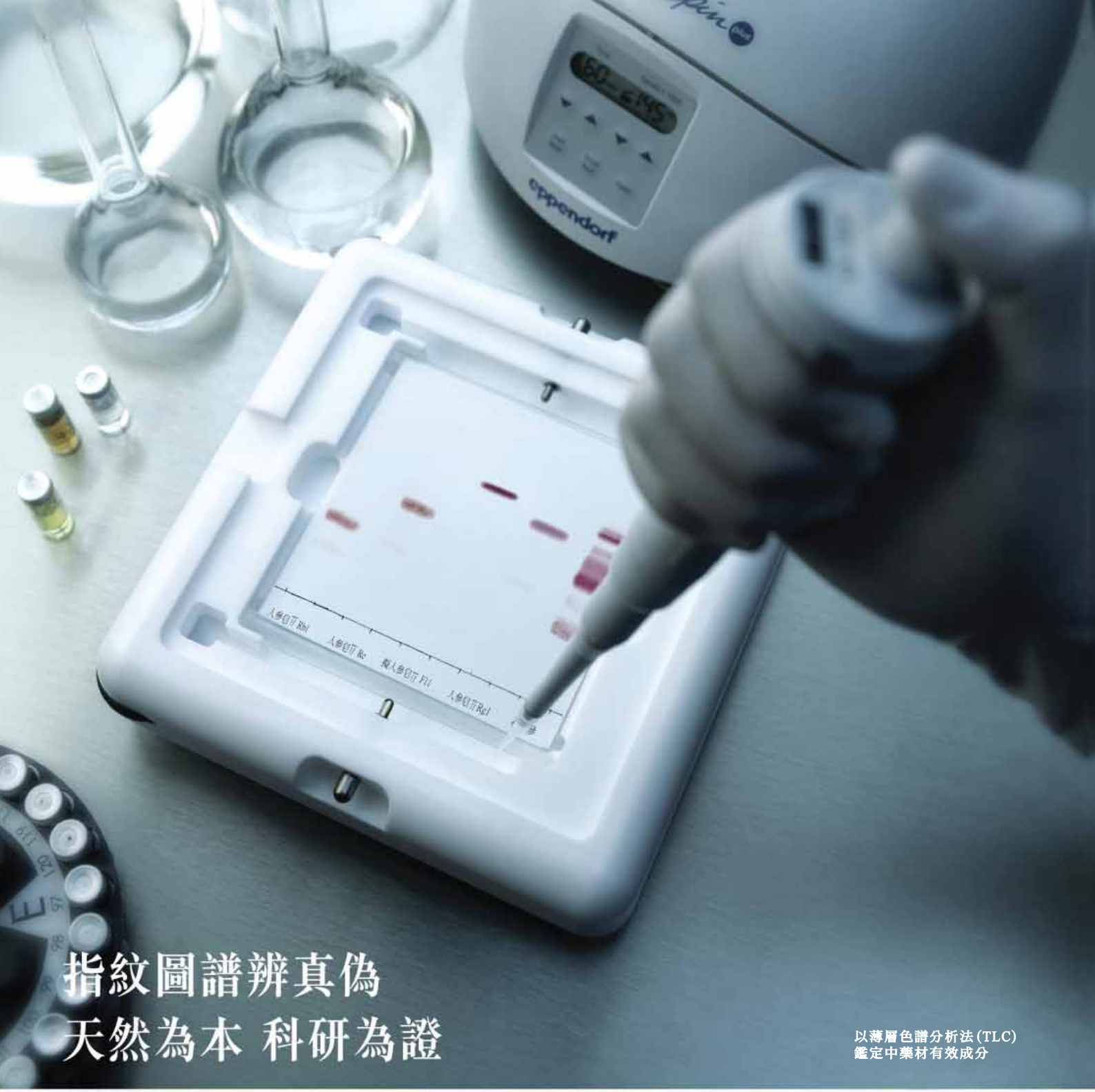
The Pharmaceutical Society of Hong Kong
The Practising Pharmacists Association of Hong Kong
The Society of Hospital Pharmacists of Hong Kong



指紋圖譜辨真偽
天然為本 科研為證

以薄層色譜分析法(TLC)
鑑定中藥材有效成分

率先採用 發揚傳統

作為業界先驅之一，余仁生一直堅持仁澤眾生之理念，憑藉先進科技，致力帶動中藥現代化，以造福社群為己任。

2006年，我們投入龐大資源，於元朗興建符合優良藥品生產作業規範的余仁生中心廠房，進一步拓展中藥研發及品質保證基地設施。

在鑑定中藥材及產品品質方面，余仁生率先引進中藥指紋圖譜，全面加強鑑定的精確性，進一步提升廠房質量管理體系，對品質監控程序起了重要之作用。

我們對品質的堅持，令余仁生成為百多年來至可信賴的名字。

余仁生
Eu Yan Sang
關懷始於1879

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Ms Ivy Chan (Tel. 6082 6338) or ***Ms Gloria Yung (Tel. 9552 2458)*** at the following email address: ***ad@hkpj.org***

INSTRUCTIONS FOR AUTHORS

The Hong Kong Pharmaceutical Journal is a journal of the pharmacists, for the pharmacists and by the pharmacists. Submissions are welcome for the following sections:

- Pharmacy Practice
- OTC & Health
- Medication Safety
- Society Activities
- Drug & Therapeutics
- Pharmaceutical Technology
- Herbal Medicines & Nutraceuticals
- New Products

Comments on any aspects of the profession are also welcome as Letters to the Editor.

There is no restriction on the length of the articles to be submitted. They can be written in English or Chinese. The Editorial Committee may make editorial changes to the articles but major amendments will be communicated with the authors prior to publishing.

It is preferable to have original articles submitted as an electronic file, in Microsoft Word, typed in Arial 9pt. Files can be sent to the following address:

e-mail: ***editor@hkpj.org***

address: ***G.P.O. Box No. 3274, General Post Office, Hong Kong***

For any queries on submission, please feel free to contact the Editorial Committee through mail or by the e-mail address.

Editorial

"Knowing but do not take the right action is no use; delegating but not properly monitored will promote corruption"

You may notice that the name of managing editor of this journal has been changed starting from this issue. Although it is an honor to me, I was so hesitated to take up this post initially as my workload in City University and other organizations is already overflow that I have no more time and energy to look after the interest of a professional body, like Pharmaceutical Society of Hong Kong. However, from the very first day since I gave up my chance forty years ago to become a basic life-science student in one of the local University and chose a pharmacy course in Taiwan, I already committed myself to this profession and have been feeling proud of being part of it throughout the rest of my career life. Although I haven't practiced pharmacy in Hong Kong since my graduation, my research and academic works have not been segregated from my professional trainings. I regard promoting the career of pharmacy practices and education as my mission and personal interest. I could still remember sixteen years ago when I was approached by my NDMC alumni, Mr Chan Wing Ki to contribute an article to the then newly launched journal published by the Society, I was so excited to accept his invitation without any reservation. This was the beginning of my affiliation with the journal. Two years later, i.e. 1995, I was invited to join the editorial board to look after the pharmaceutical technology section and subsequently, also sections of herbal medicines and nutraceutical. Since then, together with other board members, we have devoted a lot of our time and efforts to promote the journal, which has been published so far quarterly of, for and by the pharmacist in Hong Kong. However, I always have a view to make it beyond this horizon and want it to be international.

It is no doubt that to build a good fame always takes a long time and a lot of efforts. But to turn it to ill fame, it merely needs a small fault or scandal. For the Chinese, this year is supposed a time for celebration as it marks the 30th anniversary of open door policy that really changes the whole country tremendously. During this period of time, China has emerged as an advanced country and given people all over the world an impression that we have become a great nation. Although early this year, some of our constructions and facilities were severely destroyed and paralyzed by two natural disasters, i.e. spring snow storm in January and a 8.6 scale earthquake in May, which caused lost of billion dollars of assets and many ten thousand life, people all over the world were yet sympathetic and supportive. More recently, when people all over the world were still surprised and amazed by the splendid and fantastic performance combined with digital-technology in the opening and closing ceremony of the Olympic Game held in Beijing, everybody was almost completely forget those miserable disasters happened not long ago. But suddenly, this astonishment and admiration were vanished because of a cup of tainted milk. After the exposure of death in infants due to intake of melamine tainted milk by media on September 11, we have witnessed many products being rejected or pulled down from the shelves in the last few weeks; all because of deliberate contamination of the milk with this industrial compound which is supposed a raw material for use in the manufacture of plastics and resins. Why this compound was added to make such a big fear among people and how it affects people's health are reviewed in an article written by Zhang et al of this issue. The underlying causes of the problem are addressed from both biochemical and toxicological points of view and it is an up-to-date report of the whole scandal.

The disclosure of milk scandal not only reveals the need to introduce quality assurance in food manufacturing but also reminds us that the importance to implement the adverse reporting system promoted not long ago by FDA. Because some unaware adverse interactions between foods and drugs may take place even though they have passed the clinical trial, it is necessary and important to report such adverse effects to a monitoring unit and make it immediately available to both professional and the public. An article written by Donnelly and Cheung on pharmacovigilance and adverse event reporting is a timely article. The article explains how importance of this practice for safe-guard of people's health. If the tainted pet food containing melamine were reported and taken seriously by the government officers with this reporting system in April 2007, death of 4 infants and many thousands of suffered babies consuming milk could be avoided. Nevertheless, it is always not too late if human being can learn from their mistakes. Sometime we can also learn from others' practice to make improvement of our own practices. In this issue, there is a Chinese article on the regulatory aspects of drugs and Chinese medicines in Macau. Although it is only a very brief account, it does give us a glimpse of drug control and education in our neighbor.

Prevention is always better than curing. To maintain a healthy life, we need the knowledge of a disease. For those who don't know much about the etiology of hypertension, the article on "Pulmonary Arterial Hypertension" written by Mok perhaps is a good material for your continue education. It explains how this disease is evolved and its possible consequence if it is ignored.

By the time when this issue reaches your hand, I believe the big man-made storms, whether they are belonged to social, financial or health problems may not be over. But let bear in mind "Knowing is not enough, we must take the right actions; Delegating is not enough, everything should be properly monitored" if repeated mistakes should be avoided.

Cheung Hon-Yeung
Managing Editor
30th September, 2008

Leadership Encounters of Another Kind*

Ms S C Chiang, BPharm.(Hons), MRPS, MHA, FACHSE, FHKCHSE

The day soldiers stop bringing you their problems is the day you have stopped leading them. They have either lost confidence that you can help them or concluded that you do not care.
Either case is a failure of leadership.

Source : General Colin Powell's Leadership Primer

About a year ago, the Hospital Authority (HA) Hong Kong commissioned a special consultancy leadership training course to train a group of senior executives who must gain their entrance after undergoing a vigorous process of nomination and selection interviews. This group has included some doctors, nurses, administrators and managers from HR, Finance, IT as well as a pharmacist. I was somehow able to join the twenty odd participants to receive this so called Executive Leadership Program (ELP) training.

To me and may be many others in the ELP group, training on leadership and management is nothing new or special. I recalled back in 1991 when HA was first established taking over the management of about 40 odd ex-government and ex-subvented hospitals, many clinicians, nurses and allied health staff, having undertaken some kind of intensified health management training either slightly before or after their appointments into the new positions, were turned into managers overnight. At that time, I was also newly promoted to the senior pharmacist position and I was similarly enrolled in a 3 week Senior Executive Management (SEM) training course. As I remembered, I felt rather thrilled at that time because the entire organization was a new set up and one could hardly catch up with the drastic and rapid changes happening daily at every level of the organisation. So the SEM course was very useful and timely as we were made aware of how hospitals should be run, what were the issues in areas like people management, resource management, financial budgeting, service development, service standards, performance indicators, communication skills, team spirits, etc, etc. We were taught the different leadership and management skills and were given thick binders fully packed with handouts of articles and success stories written by different management gurus sharing their theories, concepts and application experience. We were getting acquainted with all those top-notch management principles and jargons and so it was full of fun as we learned, discussed, mingled, role played and networked.

**Disclaimer :* *this is not an article about leadership nor management. It is a simple and honest account of the reflections from the author about how she felt the different leadership and management approaches have resulted in different effects in her work environment. This is intended for sharing rather than preaching.*

So everything was not only interesting but also exciting. All these proved to be relevant somehow somewhere sometime when we returned to our work place. This was because our hospitals were so poorly run at that time and any system, if in existence at all, was so bureaucratic and antiquated. The organization was therefore desperately in need of massive improvements everywhere to make up for the time lost. Also, staff had felt frustrated for a long time attributable to the many constraints that have existed to discourage staff's potential contribution to their professional practice. It was as if everybody was hungry and deprived and all of a sudden we were relieved from our poverty, not only in terms of financial resource support alone but more so in terms of the freedom to stretch our imagination. So, with the establishment of HA, we were, in some ways, competing to see who could turn around the fastest to come up with the most innovative ideas in order to be the first to make the best improvement seen. The training course was thus very stimulating and we were so enthusiastic and everybody felt motivated, inspired and we found lots of satisfaction making things happened, including new systems, more efficient workflow, etc., etc.. Looking back, those 3 weeks of training were very precious to me and the timing was right as it had tied in with my promotion, enabling me to assume greater roles and responsibilities as I made progress in my work introducing the various kinds of changes to the pharmacy service throughout all these years. I think the same would be felt by many of those who were with the organization at that time doing simultaneous improvements of some kind in other units, sections and services.

So, what is the big deal about another Executive Leadership Program, now 16 years after HA was set up? After all, during the aforementioned years, the senior management level must have received and completed countless other training courses, whether local and overseas and would have gained the necessary exposure to the latest kinds of most prestigious training. Some, including me, have also acquired the formal management qualification e.g. master degrees in Public Health Administration. Besides, after almost two decades, the internal and the external environment have changed in HA. At one time, HA was said to be a victim of its own success, because by offering the "peng, leng and zeng" service, we become overloaded and our service is overstretched and everybody thinks the senior management are overpaid whilst the frontline are overworked. So, the problems that we have today in HA were so different from those of the early HA days. Apparently, many of our today's problems could not

be solved any longer with the traditional management approaches. So I was rather skeptical at the initial stage of the ELP enrolment or rather I was definitely much less enthusiastic than I was compared to the SEM training.

But I was wrong; this ELP was really something different. First, there was only minimal amount of handouts and we were spared from the traditional management brainwash stuff. Instead, we had some unique experiences, e.g. we had the opportunities to spend half a day meeting the CEOs and their teams at Ocean Park and Mass Transit Railway Corporation to see how these public and commercial organizations were run, what were their mission, vision and values, their cultures and what were their challenges and how did they engage their staff to come up with innovative ways to keep their staff and customers happy daily in their organizations.

In fact, for a large and substantial part of the ELP course which went on and off intermittently for about a year, it was focused on self awareness and relationship awareness. Time was spent on self reflection and inner self exploration e.g. it has included a 360-degree feedback at the commencement of the course followed by another one a year later prior to completion of the training course. Then, at one time we had to tell our life line, we had to share stories with the group on our past, e.g. how and where we were brought up, where did we receive our education, what are our family members, why and how did we choose what we are doing now, what are our interests, what and who have made significant impacts on our lives, what are these impacts, what has shaped our values and beliefs, etc.. Another time, we were given a stack of cards each of which had a leadership principle written on it and we were asked to indicate and explain our personal choices of our leadership principles. Whilst we tell our own stories, we had to listen to others in the group. Even Mr Shane Solomon, the Chief Executive of Hospital Authority was invited to do this together with us and so in the process we had learned more about our own selves and also about the others in the group most of whom including CE are people we actually do not have much understanding of. Further more, we were asked to form support learning groups amongst ourselves and after a few times of group sharing, we had developed some close bonding within the groups and we were able to share some deep inner concerns about ourselves.

Lastly, we also had some learning on coaching. Through various games and role plays, we were shown why coaching is so important in our day to day work and what the long term positive impacts this coaching can make in most modern work place. We were encouraged how we shall refrain from continuing to keep telling others what to do, how to do and when to do things. Instead, how we should learn the skills on coaching by asking all the relevant questions so that our staff can find out for themselves about what needs to be done, how best to do things. Thus, our staff will unleash their own potentials to maximize their own performance. In this way, our staff will in turn believe in their own capabilities, feel the confidence and find the satisfaction to continue to excel.

All these learning and sharing experience seem common sense but were new to a lot of us in the ELP course. Too often, we would choose to hide our feelings, wear the protective masks and not speaking up to share our true opinions. Attempts to address the deep rooted issues were superficial and as a result, were often uneventful. Also, we are so used to be told what to do and in turn telling others what to do that most of the times, we merely delegate the task; we do not delegate the responsibility. We become so busy and preoccupied that we as leaders lose sight of our primary goal. We fill our schedules with repeated extraneous events that we forget about our people. We were reminded that we need to serve those who serve our patients. We were made aware that to lead in the next generation we need new authentic leadership approaches. “I am your boss and so do as I told” type of leadership no longer works. But rather, a good leader influence others to do what needs to be done not because of his or her rank but because of the trust and confidence their subordinates, peers and superiors have in them. That process of influencing will always lead to more enthusiastic mission accomplishing than just telling someone what to do.

Throughout the course, the emphasis was on people, not tasks; on dealing with emotions and feelings not on things because we were made aware that leading means taking care of the people that take care of the organization and if we lose sight of this fact, then we as a leader have lost. These sounded so simple but I am not sure if this is commonly practiced. Fundamentally, the clear and loud message is if we do not win the hearts of our people, all things fall apart. I am particularly, struck by the quote from General Colin Powell - “the day soldiers stop bringing you their problems is the day you have stopped leading them. They have either lost confidence that you can help them or concluded that you do not care. Either case is a failure of leadership”.

It is obvious that the Hospital Authority is undergoing a new chapter of leadership. Mr Shane Solomon is now the third Chief Executive in the organization and he is the first non doctor CEO of HA, which is second largest organization in Hong Kong. He believes that public accountability, patient service and future sustainability are the three most fundamental bottom lines for Hospital Chiefs in managing public hospitals. He, being new not only to the organization but also to Hong Kong, has brought in new ideas and new approaches. It is of course not for me or for the few of us to make the judgment on how these would ultimately impact the delivery of the local public health service. But one thing I know for sure is that he has changed the paradigm of many of the ELP participants. It is clear that conventional management methods do not work any more in our organization. With time, I believe that there would be more and more adopting and applying what we have learned in our work place. I believe that with the right leadership, we can build a better tomorrow in the pharmacy service and the profession as well as in the Hospital Authority and the public health system in Hong Kong.

Ms S C Chiang is a very experienced pharmacist working in the Hospital Authority Hong Kong. Readers are welcomed to share comments and opinion with her. She can be contacted at email: *scchiang@ha.org.hk*

Pharmacovigilance & adverse event reporting – why bother? A pharma company's perspective

Emma Donnelly, Karen Cheung

Like healthcare professionals, pharmaceutical companies are committed to and passionate about improving the health outcome of patients. Pharmacovigilance (PV) or Adverse Event (AE) reporting is an important part of this.

The World Health Organisation (WHO) defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems. The primary aim of pharmacovigilance is to improve patient care and safety in relation to the use of medicines. Information collected contributes to the assessment of risk/benefit and effectiveness of medicines, as well as encouraging their safe, rational and more effective use.[1] Initial safety data for a medicine is obtained from clinical trials. However, trials have a number of limitations, one of which is strict eligibility criteria, so only a specific and relatively small group of patients receive the study medicine. As a result, not all AEs are identified.

So, how do we overcome this to add to the safety profile of a medicine? Post marketing surveillance and spontaneous AE reporting.

A spontaneous AE is defined in Volume 9A of the rules governing medicinal products in the European Union as "an unsolicited communication by a healthcare professional or consumer to a company, regulatory authority or other organisation"[2] Volume 9A defines an AE as "any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment".[2]

All information collected during the spontaneous reporting process remains confidential and is only used for the purpose of safety reporting.

Improving the safety profile of a medicine

Spontaneous AE reports add valuable information to the safety profile of a medicine – they have become an essential tool for gathering safety information and help the manufacturer build a better picture of the effects of a medicine.

Spontaneous AE reports are often identified as part of a medical information question. They may come from consumers or healthcare professionals. In addition, companies also search literature for published case reports which may contain AEs.

Data collected from spontaneous AE reports is added to the company's global safety database. The pharmaceutical company assesses the AE for causality (that is did the medicine cause the AE?), safety flags may then be identified – if a trend becomes apparent, further investigation may be required. Global safety databases monitor all of a medicine's events for trends or safety flags. When a certain number of cases have occurred, it causes a trigger – further investigation will then begin. The number of case required for this trigger varies depending on what the event is, ie, a fatal AE would require less events to be reported than for example fatigue.

If it is confirmed there is a causal relationship between the event and the medicine, appropriate action will then be taken. Examples of actions include:

- A change in the prescribing information (Data Sheet)
- A market advisement / dear healthcare professional letter
- Or in a more serious situation, withdrawal of the product from the market.

Pharmaceutical companies must report spontaneous AEs to health authorities. The European and US health authorities receive spontaneous AE reports from all countries. The Hong Kong Department of Health also requests that pharmaceutical companies report all local and overseas spontaneous AE report for products which fall into the category of New Chemical Entry (NCE) and if approved after March 2005.

Responsibilities of the pharmaceutical companies

Many pharmaceutical companies that operate within Hong Kong are part of a global organisation. This means that global procedures and overseas health authority legislation influence local procedures, in addition to the local legislation.

Not only do companies have to endeavour to adhere to PV requirements mandated by Hong Kong Department of Health, they must also adhere to PV requirements mandated by the European and US health authorities (Volume 9A and 21 CRF requirements) and the ICH guidelines (the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use).

These requirements essentially state pharmaceutical companies (or the marketing authorisation/ product license holder) must have a PV system to collect, collate and evaluate information about suspected AEs. To ensure pharmaceutical companies meet PV requirements, they employ staff that have dedicated drug

safety responsibilities. In addition, pharmaceutical companies are required to ensure all staff employed receive AE training, so they are aware of what an AE is and what they must do when they hear of one. Pharmaceutical companies have 15 days within which an AE report needs to be turned around. This is the time from when the company first hears about it, to reporting it to the health authority. Global health authorities have little tolerance for cases that get reported late therefore, – reporting on time to the global health authorities is very important.

If a serious or unexpected AE is reported to a pharmaceutical company, they have a responsibility to try to gather further information (follow-up) from the healthcare professional. Although the healthcare professional is not required to provide the follow-up information requested, it is most useful and always appreciated, as it helps the safety specialists determine if a causal relationship exists between the AE and the medicine.

To ensure companies are fulfilling their obligations, audits may be conducted internally or by the health authority. A global pharmaceutical company could also be subject to audits by health authorities from other countries (such as the FDA).

Our request

When you hear about an AE a patient has experienced while being treated with a medicine, take the time to report it to the relevant company, as it adds to the safety profile of the medicine which ultimately benefits patients.

General/background information

An AE can present itself as one of many things – some examples include:

- Symptom (diarrhoea, headache, fatigue, myalgia etc)
- Disease (progression of disease, worsening of an underlying disease, development of new disease)
- Pregnancy (both maternal & paternal exposure even in the absence of congenital abnormality)
- Allergic reaction
- Lack of efficacy
- Death
- Abuse, misuse and overdose (both intentional and unintentional)
- Drug Interactions

Emma is the Local Safety Responsible for the Roche New Zealand Affiliate and also has medical information responsibilities for a portfolio of Roche products. Emma graduated for the University of Otago with a BSc (Hons) degree and her research dissertation looked at possible pharmacogenetic factors responsible for some of the adverse drug reactions that occur in patients prescribed COX-2 inhibitors.

References

1) The importance of pharmacovigilance: Safety monitoring of medicinal products. World Health Organisation; 2002. http://www.who.int/medicinedocs/collect/edmweb/pdf/s4893e/s4893e.pdf <Accessed 3 October 2007>

2) Volume 9A of the rules governing medicinal products in the European Union œguidelines on pharmacovigilance for medicinal products for human use. April 2007. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol9/pdf/vol9_2007-07_upd07.pdf <Accessed 3 April 2008>

Guidance Notes for ADR Reporting

Department of Health, HKSAR

Introduction

The World Health Organization defines Adverse Drug Reaction (ADR) as "a reaction to drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function." ADR reporting/ monitoring is important for post-marketing drug safety surveillance.

Doctors, Chinese medicine practitioners, dentists and pharmacists are encouraged to report suspected ADR of their patients to the ADR Monitoring Unit voluntarily. ADR reports can be submitted for all western and Chinese medicines (including Chinese herbs, proprietary Chinese medicines and vaccines). For suspected Chinese medicine poisoning cases that require investigation, please use the form "DH 1B", which can be downloaded at http://www.chp.gov.hk/files/pdf/hpf-form3-en-20070214.pdf.

To facilitate the assessment process, please provide the following information when reporting ADR: (i) name of the suspected drug including the brand name (for vaccine, please also provide batch/lot number), (ii) description of the reaction, (iii) information of the patient and (iv) contact telephone number of the person who submits the report. All reports are reviewed by professional staff of the Unit and safety alerts will be issued when new hazards are found.

What to report

Please report any of the following types of adverse reactions:

1. Suspected serious *ADR, even if the reactions are well known;
2. Suspected drug interactions;
3. Non-serious ADR but the reactions are deemed medically significant by the healthcare professional;
4. Unexpected ADR, i.e. the reactions are not consistent with product information or labeling.

*Note: Serious ADR is defined as an adverse reaction which:

- is fatal;
- is life-threatening;
- results in or prolongs hospitalisation;
- causes persistent incapacity or disability;
- causes birth defects

In addition, ADR related to vaccine can be classified under one of the following categories:

	Descriptions
Allergic reactions	Anaphylaxis is the severe reaction that characteristically evolves rapidly towards cardiovascular collapse requiring resuscitative therapy. Other examples of severe allergic reactions are wheezing or shortness of breath due to bronchospasm, swelling of mouth or throat, skin manifestation (e.g. hives, eczema, pruritis); or facial or generalised edema. Allergic reactions usually occur within 24 hours of immunisation.
Local reaction	Local reactions, usually occurs within 5 days of immunisation, of concern may include abscess (sterile or infected), or other severe local reactions, such as redness and swelling, that extend beyond the nearest joint or last 4 days or more.
Systemic reaction	Systemic reactions usually occur within 5 days but may occur up to 3 months after immunisation. Early onset ones include toxic shock syndrome, hypotonic-hyporesponsive episode, persistent crying or screaming episodes, high fever (greater than 39°C or 102.2°F), sepsis, or rash (especially those lasts for 4 days or more or requires hospitalisation). Thrombocytopaenia (with platelet < 50,000/mm^3) may have a delayed onset.
Neurological disorders	Some neurological adverse reactions may be related to vaccination. Seizures (usually generalized convulsion), encephalopathy, meningitis or encephalitis may have an onset within 15 days of immunisation. Brachial neuritis or Guillain-Barré Syndrome, if occurred within 3 months of immunisation, may be related to the immunisation.

If in doult, please report.

You do not need to be certain that the suspected drug is related to the ADR before making the report

How to report

Download an ADR report form (available at http://www.psdh.gov.hk/eps/eng/html/ adrform-20.jsp) and return the completed report by:

1. mail using the self-addressed ADR report form or send to the ADR Monitoring Unit, Pharmaceutical Service, Department of Health at 3/F, Public Health Lab. Centre, 382 Nam Cheong Street, Kowloon; or
2. fax to 2572 4570; or
3. email (please refer to the following instructions).

Reporting by email

1. Access to the electronic ADR report form,
2. Complete the report form,
3. Save the completed report in the computer,
4. Email the file to adr@dh.gov.hk

What information should be included in a report

An ADR report should contain all the essential information to assist assessment. Please try and provide the following information as far as possible:

1. patient information (no need for full name of the patient; initials/ref. no. will be sufficient);
2. adverse reaction description (including the date of onset of reaction and, if related to a vaccine, adverse reaction category);
3. drug therapy or vaccine including name of the suspected and concomitant drug(s), dosage, route, dates of starting and stopping drug therapy, reason for use;
4. treatment of ADR;
5. outcome of the reaction;
6. sequelae of the reaction;
7. comments (e.g. allergies, relevant information - hepatic and renal functions, alcohol use, smoking);
8. reporter details (daytime contact telephone number must be provided for necessary follow-up).

Follow up of a report

Acknowledgment with a unique reference number will be issued to each report received. Please quote this number when sending in follow up information of previously submitted ADR report.

What happens to the report

- All ADR reports are reviewed by professional staff;
- Serious ADR reports may be reviewed by expert advisors if indicated;
- Information of the report will be entered into the ADR database system for analysis.

What regulatory actions can be taken

The ADR reports may identify some unexpected ADR, or indicate that certain ADR occur more commonly than previously expected, or that some patients are more susceptible to certain problems than others. Such findings can lead to the following changes to the products, for example: restrictions in use, refinement of dose instructions or introduction of specific warnings in the product literature. Rarely when a hazard is considered as unacceptable, a medicine may have to be withdrawn from the market.

Contact for further information

ADR Monitoring Unit
Pharmaceutical Service, Department of Health
3/F, Public Health Laboratory Centre
382 Nam Cheong Street, Kowloon

Phone : 2319 8482
Fax : 2572 4570
Email : adr@dh.gov.hk

(Revised 7/2008)

Report can be returned by fax to 2572 4570
For follow-up report (see Guidance Notes), please provide ADRMU Ref. No.: _____

Department of Health
Adverse Drug Reactions (ADR) Report Form

Please read the following instructions:

1. Please read the Guidance Notes for ADR Reporting before completing the ADR report form.
2. This report form is used for voluntary report of all suspected ADR. There is no need to put down the full name of the patient.
3. ADR can be briefly described as a noxious and unintended response to a drug or vaccine when the normal dose is used.
4. Please provide information to every section. Information of individual reporter will be treated in strict confidence.
5. For further enquires, please contact the ADR Monitoring Unit of Pharmaceutical Service of the DH at 2319 8482.

Section (A): Patient Information

Patient initials or ref. no.: _____ Weight (if known): _____ kg

Sex: M/F* Date of birth: (dd/mm/yyyy) / / or age (at last birthday): _____

For female: Is she pregnant? Yes/No*

Section (B): About the Adverse Drug Reaction

Date of onset of ADR: (dd/mm/yyyy) / /

Description: _____

_____

ADR category (for vaccine related ADR only):

❑ Allergic reaction ❑ Local reaction ❑ Systemic reaction ❑ Neurological disorders

Severity:

❑ Life threatening ❑ Hospitalised on: (dd/mm/yyyy) / / ❑ Hospitalisation NOT required

All Drug Therapies/Vaccines Prior to ADR (Please use trade names and, for vaccine, indicate batch number. Please circle the suspected drug.)	**Daily Dosage** (dose number for vaccines e.g. 1st DTP)	**Route**	**Date Begun**	**Date Stopped**	**Reason for Use**

Section (C): Treatment & Outcome

Treatment of ADR : ❑ No ❑ Yes. Details: _____

Outcome: ❑ Recovered ❑ Not yet recovered ❑ Unknown ❑ Died on: (dd/mm/yyyy) / /

Sequelae: ❑ No ❑ Yes: ❑ Persistent disability ❑ Birth defect ❑ Medically significant events

Details: _____

Remarks (allergies or other relevant history): _____

_____

Section (D): Reporter Details

Name of Doctor/Chinese medicine practitioner/Dentist/Pharmacist*: _____

in private/public* service.

Correspondence Address _____

Date: _____ Tel. no.: _____ Fax. no.: _____ Email: _____

* delete whichever inappropriate

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To: ADR Monitoring Unit
Pharmaceutical Service
Department of Health
3/F, Public Health Laboratory Centre
382 Nam Cheong Street, Kowloon

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Why Melamine (三聚氰胺, 蛋白精) in Adulterated Milk Powder Causes Fatal Kidney Failure in Pet and Baby?

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I ABSTRACT

In September 11, 2008 the disclosure of toxic milk powder produced by Sanlu stirred up a storm in food consumption. Twenty two brands of infant formula were confirmed to contain a substance called melamine, making 53,000 infants ills and hospitalized within ten days. What is the physicochemical property of this compound and how does it affect the health of a baby and small animal. In this reviewed article, the toxicological mechanism of melamine is described.

II INTRODUCTION

Recently, people worldwide are giving attention to the "Storm of Toxic Milk Powder" in China because of more than six thousands babies among those given formula milk are suffered from acute kidney failure, with several fatalities. Contamination of the milk with an industrial chemical, melamine, has been confirmed to be responsible for the sickness of those babies. Although the manufacturer Sanlu, partly-owned by New Zealand's Fonterra Cooperative, has recalled all of its powdered milk products, a growing number of babies have been diagnosed with kidney problem after drinking the problem adulterated milk powder for a few days up to a few years in different provinces of China. Today, twenty one more brands of milk powder products, including famous dairy enterprises Inner Mongolia Mengniu Dairy Co., Ltd. and Inner Mongolia Yili Industrial Group Co., Ltd. have been identified to contain melamine by China's General Administration of Quality Supervision, Inspection and Quarantine (GAQSIQ). Moreover, other dairy products, such as instant drinks, ice creams, and yogurt manufactured by Yili have been found to contain the industrial chemical by Hong Kong Food and Environmental Hygiene Department and been recalled, which caused a "Toxic Milk Panic" among Hong Kong people. Ever since the official disclosure of the adulterated milk on September 11, it has caused panic and fear among people in different countries.

In spite of the commonly used word "toxic" to describe melamine, it is not very toxic by itself according to the sources of molecular toxicology. Actually, it has been suggested about the same level of toxicity as table salt by some chemists. Then, why melamine present in adulterated milk powder could lead to kidney failure in infants whoever consumed it? What is the rationale to add this industrial chemical to formula milk powder by so many dairy manufactories? We should firstly know more about the physicochemical properties of this chemical.

III WHAT IS MELAMINE?

Melamine, as its chemical structure shown in Figure 1, is an organic base with the IUPAC name 1,3,5-triazine-2,4,6-triamine and a chemical formula of $C_3H_6N_6$. It is colorless, tasteless, non-toxic (as an industrial material) and only slightly soluble in water.

Melamine was first artificially synthesized in 1834 by the German chemist Justus von Liebig, who also discovered that nitrogen was an essential plant nutrient hence came to be known as the "father of the fertilizer industry". In early production, melamine was prepared from calcium cyanamide through conversion to dicyandiamide followed by heating above its melting temperature. Thus, until the mid-1990s, melamine was still an extremely expensive compound in demand for its satisfied performance in the chemical industry yet difficult to manufacture. However, today melamine is cheap and generally produced from urea in the industrial manufactory. There are mainly two steps contained in the process. First, urea decomposes into cyanic acid, and then cyanic acid polymerizes to form melamine and carbon dioxide. The overall reaction is:

$$6(NH_2)_2CO \rightarrow C_3H_6N_6 + 6NH_3 + 3CO_2.$$

Generally, two technologies, namely catalyzed gas-phase production or high pressure liquid-phase production have been adopted to carry out the reaction [1,2]. Because of these breakthroughs, the reaction is much easier to proceed. Hence cost of melamine production become much more inexpensive. According to Fang Zhouzi, a Chinese science writer, the chemical can now be purchased on the market for a mere 300 yuan per ton.

Melamine is used to synthesize melamine resin, a hard, thermosetting plastic material, by polymerization with formaldehyde; and to synthesize melamine foam consisting of a formaldehyde-melamine-sodium bisulfate copolymer, which is able to remove external markings from relatively smooth surfaces based on its microporous properties. The major end products are countertops, fabrics, glues, flame retardants, and houseware items such as cups, plats, mugs, etc. Melamine is also used to make fertilizers [2].

IV WHY MELAMINE IS ADDED INTO DAIRY PRODUCTS?

As mentioned above, melamine is a common industrial chemical closely related to our daily lives. It is of course not a food ingredient or additive and supposed not easy to contaminate in the dairy products; at least not in such a high content in a variety of brands of milk powder and other dairy products. It is quite obvious that melamine has been deliberately but not accidentally added into the food throughout the whole producing process. What's this for?

Above all, let us look back at the chemical formula and structure of melamine (Figure 1). Melamine is a trimer of cyanamide. Like cyanamide, it has high nitrogen level, 66% nitrogen by mass. Addition of melamine is done to artificially inflate the reading for protein levels of the protein-containing goods. Standard test such as the Kjeldahl and

the Dumas test are used to determine protein content in food. These methods, in fact, work by quantitative determination of nitrogen in chemical substances to estimate the protein content. In Kjeldahl method, when protein is digested, nitrogen is released and converted to ammonia. The amount of ammonia is determined by titration and is correlated to the amount of protein. As for Dumas, the nitrogen content is measured directly after sample is combusted in a high temperature. Both methods yield falsely high value when nonprotein nitrogen present in the sample, so the test result can be misled by adding nitrogen-rich compounds. Melamine has very high nitrogen content, it is tasteless, colorless (forms a white, crystalline powder), which make it ideal as a nonprotein nitrogen source chosen by the unprincipled manufacturers. In addition, the melamine production byproducts contain not only melamine, but also its analogues cyanuric acid, ammeline, and ammelide, which structures are similar to melamine; nitrogen rich and can also contribute to a fake higher protein level (Figure 1).

V HOW TOXIC IS MELAMINE?

Numerous acute toxicology studies on melamine have shown that it has very low toxicity. According to an acute toxicology experiment results, $LD50_{oral, rat}$ (amount of a material, given all at once by mouth, which causes the death of 50% of a group of test rats) of melamine was 3161 mg/kg (3161 milligrams of that chemical for every 1 kilogram body weight of the rat); $LD50_{oral, mice}$ was 3296 mg/kg; and $LD50_{dermal, rabbit}$ (applied to the skin) was higher than 1000 mg/kg [3,4,5]. These values are much higher (low toxic) compared to the value of a toxicant in our common sense, such as daily used insecticide dichlorvos, whose $LD50_{oral, rat}$ is lower than 100 mg/kg [6]. This explains why melamine is suggested with comparable toxicity level to sodium chloride. On the other hand, chronic toxicity studies of melamine reveal that ingestion of melamine might lead to reproductive damage or bladder or kidney stones which subsequently may lead to bladder cancer [5, 7, 8]. However, it is definitely not reasonable that chronic toxicity properties of melamine resulted in such a large number of infant kidney failures happening simultaneously. Hence, other factors are very likely to contribute to the misfortunes.

Although the acute toxicology of melamine is quite low, unfortunately, the industrial chemical is of course not pure, the melamine production byproducts will be synthesized together with melamine in the manufacturing process. One of the byproducts, cyanuric acid, is believed to bring serious problems. It does not mean that cyanuric acid is a highly toxic chemical, to the contrary, the toxicity of cyanuric acid is even lower, with $LD50_{oral, rat}$ higher than 10000 mg/kg and $LD50_{dermal, rabbit}$ higher than 7940 mg/kg [5]. However, a salt will be formed between melamine and cyanuric acid named melamine cyanurate. As the structure shown in Figure 2, triple hydrogen bonding will form between melamine and cyanuric acid molecules, so the salt formed is very stable and almost insoluble in an aqueous environment. The water solubility of melamine and cyanuric acid is 3240 mg/L and 2000 mg/L respectively; while that of melamine cyanurate is only 2.2 mg/L. Furthermore, as one cyanuric acid molecule can bind to two melamine molecules, and the melamine can bind to another two cyanuric acid molecules simultaneously, melamine cyanurte crystal is likely to self-assembly to become a polymer with lattice-like structure and precipitate out [9, 10, 11]. The theoretical schematic of the hydrogen bonding that occurs between melamine and cyanuric acid is shown in Figure 3. Once melamine and cyanuric acid or their salt are ingested into human body, the salt molecular will be broken down by digestive juice; and the melamine and its production byproducts will be aborted within the gastrointestinal tract and enter the circulatory system. Because these two compounds are metabolically inactive or inert in human body, after systemic distribution throughout the body, they are transported to kidney through blood ready to be expelled from the body with urine. Whereas, these two substances meet again inside kidney structure; and perhaps largely because of the high concentration, they re-form an insoluble complex in the kidney tubules and block the discharge of urine finally resulting in kidney failure. Researches have also suggested that the compounds possibly interfere with uric acid metabolism, which may precipitate in kidney tubules, providing a seed for melamine and cyanuric acid crystallization [12]. Probably for this reason, melamine and cyanuric acid do not re-form a crystalline structure during their distribution in body water.

Animal toxicity experiments were carried out after the public began to account for melamine / cyanuric acid problem. Mixture containing melamine and cyanuric acid in a 1 / 1 ratio was fed to rats (400/400 mg/kg/day). After three day treatment, compared with the control groups, initially diuresis occurred in most animals, but close to the end of the dosing period the majority of them were oliguric (urine output < 0.5 ml/kg/h). Some of these animals in test groups were also hematuric. Decreasing of food consumption and body weight also occurred variably among the treated animals. Clinical chemistry test showed a marked increase in blood urea nitrogen level and decrease in creatinine clearance, both of which indicated renal

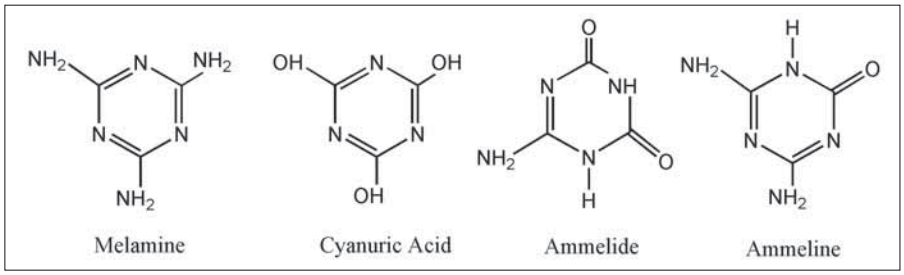


Figure 1. Chemical structures of melamine and its analogues: cyanuric acid, ammelide and ammeline.

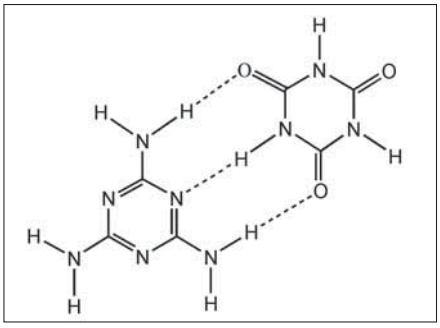


Figure 2. Hydrogen bonds formed between one melamine molecule (left) and one cyanuric acid molecule.

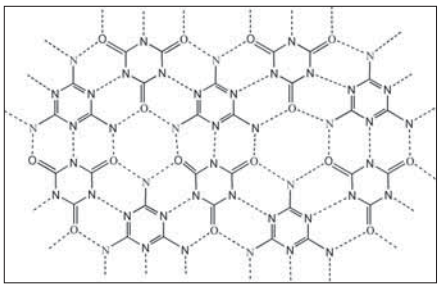


Figure 3. Schematic of the hydrogen bonding that occurs between melamine and cyanuric acid.

damage. It was found that the kidneys of the treated groups were edematous and weight was significantly higher than that of the control groups. Numerous gold-brown granules were visible with naked eye in the kidney tubules (Figure 4). Microscopy examination of frozen sections revealed these granules were crystalline structures and presented in renal tubules particularly in medulla (Figure 5) [12]. Similar results were obtained after the animals were treated with mixture of melamine, cyanuric acid, ammeline and ammelide in a 10 / 1 / 1 / 1 ratio, whereas the situation of four triazines mixture groups seemed less serious than the melamine / cyanuric acid mixture groups [12]. The animal experiments have clearly revealed that melamine together with its production by-products is highly harmful to mammal kidney function, much more toxic than pure melamine.

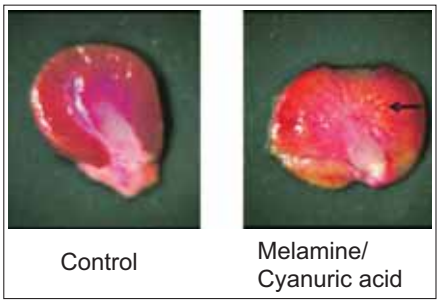


Figure 4. Gross morphology of rat kidney after three days of treatment with a melamine and cyanuric acid mixture. The arrow indicates numerous gold-brown precipitates could be visible with the naked eye.

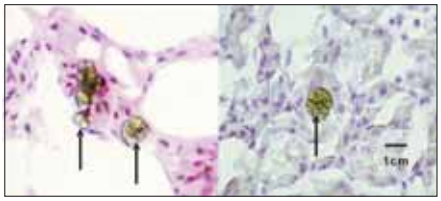


Figure 5. Frozen sections of cat and rat (right) kidneys with the presence of crystals within tubules.

VI PET FOOD RECALLS IN YEAR 2007

It is worth mentioning the pet food toxicity outbreak related to melamine last year, which may still remain in our memory. In the spring of 2007, a large number of animal deaths as a result of renal failure suddenly occurred in the United States. By the end of March, The U.S. Food and Drug Administration (FDA) had received reports of at least 1950 cats and 2200 dogs that might have died after consuming contaminated pet food, but most of the cases were not confirmed as lack of centralized government records database. Therefore, the actual number of affected pets remained unknown, while experts were concerned that the death toll could potentially reach into the thousands. At first, the recalls were associated with the wet pet food made with wheat gluten form a single Chinese company; with the enlargement of the influence, additional recalls were announced by other companies expanded throughout North America and to Europe and South Africa.

It was quickly found that the common factor of problem pet foods was in the wheat gluten used to thicken the gravy in the wet pet foods. Subsequently, Cornell researchers had confirmed the presence of melamine in the originally recalled pet foods, the wheat gluten used in manufacture, in urine of affected pets, and in the kidney of one cat that had died after eating the contaminated pet food (Figure 6) [13]. According to the FDA, a second contaminant might be responsible for the ill effects of pets since melamine was believed not very toxic as a chemical. Researchers began to focus on the role of melamine and related compounds in causing renal failure. Current research has focused on the synergistic toxicity of melamine and cyanuric acid.

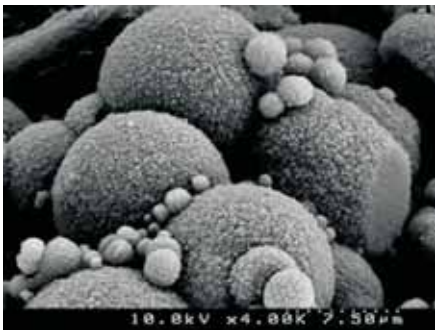


Figure 6. Electron microscope image of melamine crystal found in the urinary tracts of cats affected by pet food contaminants.

VII SAFETY LIMIT OF MELAMINE

Melamine was once used as non-protein nitrogen for cattle in their feedstuff [14]. In 1978, however, a study concluded that melamine might not be an acceptable non-protein source for ruminants, because the hydrolysis in cattle gastrointestinal tract is slower and less complete than other nitrogen sources such as cottonseed meal and urea [15]. Melamine did not make apparent harm to domestic animals, however, was blamed for killing thousands of cats and dogs in the U.S [16]. Besides the variety in total applying content need concerning, one of the main reason is the size difference between cattle and pets such as cats and dogs. Cattle is much lager than cats or dogs, more accurately speaking, has much higher body weight, larger volume of total body water, and larger organs. It is reasonable to think cattle can withstand more melamine distributed through their larger body and successfully expel it out of body based on their higher metabolic capability.

Same principle applies to the different situation between infants and adults. For newborn babies, the average body weight of them is 3.5 kg; so the total body water volume is estimated as approximately 2.1 L, among which extracellular fluid volume (contributing to systemic circulation) is 0.7 L. However, for a normal weight adult (60 kg), the total body water volume and extracellular fluid volume should be about 36.0 and 12.0 L respectively. Apparently, the endurable quantity of melamine of babies is not comparable to that of adults. Moreover, dairy products only take up a very small portion in the daily diet of an adult; on the other hand, formula milk is the sole diet for an infant (if he or she is not fed with maternal breast milk). No mentioning that the urinary and other systems of infant are not annealed and more protection is needed. Therefore, the risk of kidney failure for adults is significantly lower than for infants. Of course, the newborn babies are the most delicate and the formula milk they drink should be produced under the most severe standard. For this reason, adults really do not need to worry too much about development of melamine kidney stone, though some instant drinks, ice creams, and yogurt have been identified with low level of melamine. Still the chronic harm of melamine is another thing for concerning.

Referring to the Interim Melamine and Analogues Safety/Risk Assessment released by U.S. FDA in May 2007, the NOAEL (no-observed-adverse-effect-levels) of melamine is 63 mg/kg bw/day (13 weeks, oral feed, in rat). In terms of the commonly applied 100 times standard for estimation of human NOAEL from animal experiments, the NOAEL of melamine for human should be 0.63 mg/kg bw/day that is the value GAQSIQ announced after outbreak of “Storm of Toxic Milk Powder”. Thus, the safety limit of melamine content in formula milk powder can be calculated base on the NOAEL value. Concerning some babies are fed with formula milk immediately after birth, the data of newborns should be use to calculate the safe limit, whose body weight is 3.5 kg. Normally, the daily ingestion quantity is

at most 150 g for an infant. Hence the safety limit of melamine content can be calculated as:

(0.63 mg/kg bw/day × 3.5 kg) / 0.15 kg/day = 14.7 mg/kg

This result checks up with the safety limit suggested by expert in Chinese Academy of Sciences, which is 15 mg/kg.

Nevertheless, it should be mentioned that the NOAEL is worked out based on the assumption that melamine and melamine analogues (cyanuric acid, ammelide and ammeline) are of equal toxic potency and they are referred to collectively in assessment as melamine compounds. In spite of the works suggesting that melamine may interact synergistically with its analogues, particularly with cyanuricacid at high dose levels [9, 12, 16], no available publications has systematically tested the phenomenon. As a result, the situation of melamine cyanurate has not been taken into consideration. Therefore, the NOAEL announced by FDA is very likely to be under estimated, and the safety limit for melamine in formula milk powder for infants may be actually much lower than 15 mg/kg. With proceeding of further studies on synergistic toxicity of melamine and its analogues, it is undoubtedly the risk assessment of melamine need to be updated.

In fact, according to the recent report GAQSIO has identified melamine in 69 batches of baby formula from 22 dairy producers. Among all the samples, the Sanlu brand has the highest melamine content, up to 2563 mg/kg; in other brands, the melamine content ranged from 0.09 mg/kg to 619 mg/kg. Even the estimated value is used as safety limit without further consideration about synergistic toxicity problem, the melamine content in some brands is significantly higher than the suggested value by expert. No wander suddenly so many babies got sick after being fed the tainted baby formula milk powder.

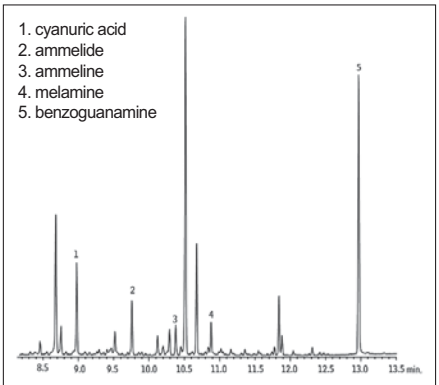
VIII DETECTION OF MELAMINE IN FOOD

Melamine is not a food additive and does not involve in the dairy manufactory. Formula milk products were not until now tested for melamine, because regulators never suspect this ingredient might be added. Actually, until the 2007 pet food recalls, melamine had not routinely been monitored in food, except in the context of plastic safety or insecticide residue. After the investigation of pet food recalls, concerns about the safety of the human food supply related to melamine had been raised. Because melamine at ppm level in food and beverage had been reported due to migration from melamine-containing resins which was often used in food packaging [17]; and contamination of fish with melamine had been reported, which was the potential sources of human exposure to melamine. Suffering from the current "Storm of Toxic Milk Powder", people surely begin to care more about accurate determination and quantitative analysis of the chemical melamine in food.

Melamine at even very low levels can be detected through chromatography, or chromatography coupled to mass spectroscopy (Figure 7) [18]. The analytes have been proved easily identified by reliable retention time matching the mass spectra. In addition, rapid melamine test kit is offered on the market based on ELISA reaction for melamine molecules.

IX CONCLUSION

Nowadays, people pay more and more attention to food health, which is necessary for a healthy life. In the quality tests, presence of some toxic substances in food always hit turbulence among the public. However, Paraceisus have said that "All substances are poisons. The right dose differentiates a poison from a remedy." So actually, the content of a substance decides its effect on human body; and as long as the toxicant content is below the standard safety limit, it will not harm us. Even the content exceeds the limit a little bit, it does not necessarily harmful since the safety limit standardized is usually set much lower than the real adverse-effect level for safety consideration. Besides, in the "Storm of Toxic Milk Powder" case, we should learn a lesson that a low toxic chemical can be extremely harmful depending on other substances whenever they interact. Anyway, the unscrupulous manufactures who added melamine into formula milk powder for fake protein level are immoral and they should be blamed. Although they might just add a substance that is low toxicity by itself, their practice has ended up with a disaster which makes them to pay a big price.



Column:	**Rtx®-5MS, 30m, 0.25mm ID, 0.25µm (cat. # 12623)**
Sample:	melamine, cyanuric acid, ammelide, ammeline, benzoguanamine (10µg/mL prederivatized)
Inj.:	1µL, splitless (hold 1 min.), 3.5mm splitless inlet liner (cat.# 22286)
Inj. temp.:	280°C
Carrier gas:	helium, constant flow
Flow rate:	1mL/min.
Oven temp.:	75°C to 320°C @ 15°C/min. (hold 4 min.)
Det.:	MS
Transfer Line Temp.:	290°C
Ionization:	EI
Mode:	SIM

Figure 7. Spectrum from GC/MS analysis of cat food sample containing cyanuric acid, ammelide, ammeline, melamine and benzoguanamine.

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Dry Eye Disease (DED)

Ms Elfie Yiu

People come to pharmacy more often than the past for advice on eye problems. Pharmacists are the most obvious readily healthcare professionals available to them and it is common for pharmacists to encounter patients with DED who have questions about treatment and appropriate product selection. Although common in elderly of both sexes, DED impairs the ability to perform common activities (such as using a computer, reading or driving) and hence may deteriorate the quality of life.

Symptoms associated with DED may include any of the following:

- Stinging or burning of the eye
- Sandy or gritty feeling as if something is in the eye
- Watery eyes following extended periods of DED
- Uncomfortable when wearing contact lenses
- Decreased tolerance of reading, working on the computer, or any activity that requires sustained visual attention
- A stringy discharge from the eye, Eye fatigue
- Pain and redness of the eye
- Episodes of blurred vision
- Heavy eyelids, Inability to cry when emotionally stressed

Some may even have photophobia. If left untreated, corneal ulceration may occur which eventually leading to loss of sight.

Role of Tear

The outer layer of the tear film is made up of a lipid layer (secreted by the meibomian and a few minor accessory glands) that prevents evaporation of the tear film from the ocular surface. The lacrimal gland and accessory glands produce the aqueous component consisting of a complex mixture of proteins, mucins, electrolytes, cytokines, and growth factors (Table 1 &.2). Finally, the mucin layer provides stability and an interface between the corneal and conjunctival epithelium and the tear film during the normal blink cycle. This layer promotes even distribution of tear film across the corneal surface. Since the cornea is an vascular tissue, the slightly alkaline tear film which is spread across eye by blinking and lost via the lachrymal ducts and/or by evaporation, provides critical lubrication and optical qualities, nutrients, foreign body and microbe removal, and antibacterial and wound healing substances for homeostasis.

Pathophysiology

Dry eye may arise from a variety of conditions, including an abnormality of any of the three (lipid, aqueous and mucin) layers of the tear film; unequal distribution of the tear film due to corneal scarring and/or surface irregularities; and blink abnormalities. Dry eye may also be caused by damage or destruction of the lacrimal tissues or blockage of the secretion ducts, e.g., following infection, chemical burns, or chronic conjunctivitis. The core mechanisms of dry eye are driven by tear film instability and tear hyperosmolarity. Often the tear film becomes hyperos-molar, which can occur from low aqueous flow or excessive tear evaporation (Table 3) or due to exposure to environmental (such as low humidity) or occupational factors. This hyperosmolarity may lead to an inflammatory condition on the ocular surface and produce tear film instability. The instable tear film breaks up into dry spots rather than being maintained between blinks. Such underlying inflammation is a key consideration regardless of the inciting factors. Increased T-cell infiltration of the lacrimal gland and production of inflammatory cytokines, which are then released onto the ocular surface, are main contributors to this inflammatory cascade (Figure 1). It may be a combination of various factors that tips the balance from minor symptoms to more moderate-to-severe dry eye complaints.

Table 1:
Human Tear Film Characteristics

Thickness	6–7 μm
Volume	7–7.5 μL
Osmolarity	296–308mOsm /L
pH	6.5–7.6
Turnover rate	12%–16% /min (normal)

Table 2:
Composition of the Tear Film

I) Oily (lipid) layer (0.1 μm thick) : Cholesterol esters/ Waxy esters/ Phospholipids/ Free fatty acids/ Triglycerides
II) Aqueous layer (7 μm thick) : Glucose/ Urea/ Lactate/ Citrate/ Mucopolysaccharides/ Na^+, K^+, Ca^{++}, Mg^{++} ions/ Cl^-, HCO_3^-, HPO_4^{2-} ions/ Amino acids/ Albumin/ Lysozyme/ Glycoproteins
III) Mucus layer (0.02–0.04 μm thick): Mucopolysaccharides/ Sialomucin/ Glycoproteins

Tear substitutes

Tear insufficiency can be treated with OTC products such as artificial tear solutions, and/or ointments. Artificial tear solutions may also be used in the normal eye for temporary relief of discomfort and dryness caused by exposure to wind, heat, or irritants such as smog or foreign objects and they may be used as often as necessary to keep the corneal surface and conjunctiva moist. Currently commercially available tear substitutes in Hong Kong include solutions and gel/ointments. These products differ in vehicles, preservatives and formulations. The comfort of an artificial tear preparation is influenced by various factors, including choice of viscosity building agent, pH, tonicity, and preservative.

Viscosity-inducing agents are the

Table 3: Main DED etiology	
Aqueous-Deficient Causes (reduced tear production)	**Evaporative Causes**
Sjögren-Related	***Intrinsic***
• Auto-immune disease such as rheumatoid arthritis or systemic lupus erythematosus	• Meibomian gland dysfunction (MGD) (e.g., ocular rosacea and use of isotretinoin)
Non-Sjögren-Related	• Eyelid disorders (e.g., blepharitis, thyrotoxicosis and poor lid apposition often noted in the elderly)
• Age-related causes (Elderly)	• Low blink rate or blink disorders (e.g., Parkinson's disease and stroke)
• Secondary to lacrimal gland infiltration associated with various diseases including AIDS, sarcoidosis, and lymphoma	***Extrinsic***
• Sensory block causes such as refractive surgery, diabetes, or herpes simplex keratitis	• Vitamin A deficiency
• Motor block causes by drugs (such as antimuscarinics or tricyclic antidepressants) or damage to cranial nerve VII	• Contact lens wear
	• Topical drug preservatives
	• Ocular surface disease (e.g., allergic conjunctivitis)

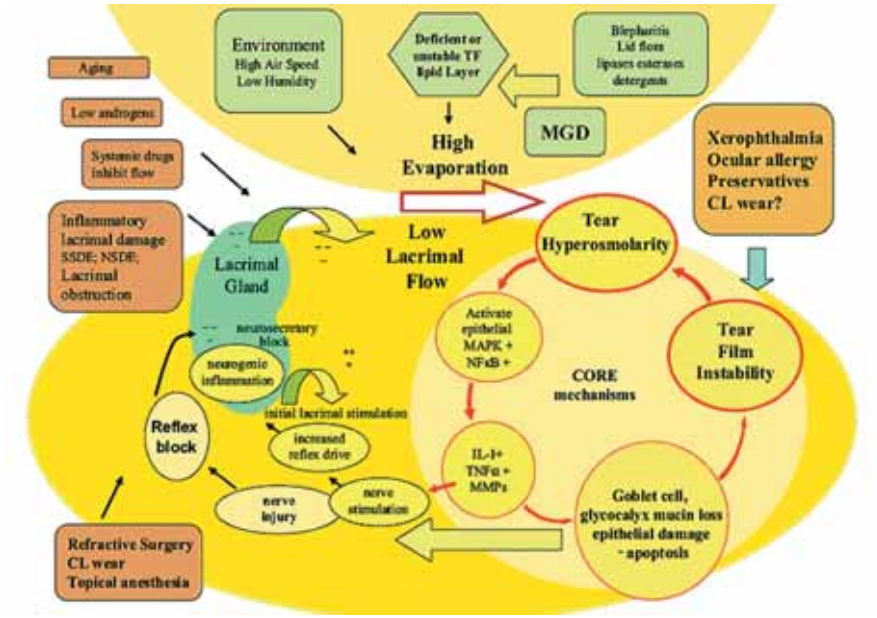

Figure 1 Mechanism of Dry Eye (adapted from ref.1)

main ingredient of artificial tear substitutes. Functionally, these agents adsorb at the cornea-aqueous layer interface, providing relief from dry eye symptoms by stabilizing the tear film and by preventing tear evaporation. The main ingredients include cellulose derivatives such as carboxymethylcellulose (CMC), hydroxymethylcellulose (HMC), hydroxypropylmethylcellulose (HPMC), polyvinyl alcohol, povidone, dextran, glycerine, polyethylene or propylene glycol. Most commercially available artificial tear products have a combination of these ingredients. Product containing a hydroxypropyl-guar combination (Systane® Lubricant Eye Drops) is thought to help supplement the mucin layer by forming a bioadhesive gel on the tear film, creating an ocular shield for a longer period of time. In addition, a combination product containing CMC and glycerin (Moisture Eye®) is believed to provide protection against osmotic stress to the corneal surface.

The excipients used in artificial tear substitutes should mimic the physiological and biochemical properties of the tear film without affecting the clarity of the aqueous layer. The ideal artificial tear product, however, should be slightly hypotonic or isotonic with tears (when applied to the hypertonic tear film will help the tear film become isotonic), be slightly alkaline (in the pH range of 7–8), have mucomimetic properties to facilitate epithelial wetting, should enhance tear volume when necessary, and be preservative-free or contain preservatives that are nontoxic or non-irritating to the corneal epithelium. In addition, they should not alter the functions of the outermost lipid layer.

Preservative-free or not?

The preservative content is important because some preservatives are known to cause toxic or allergic reactions including stinging, burning, and red eyes. The commonly used preservatives, such as benzalkonium chloride (such as in Visine® and Murine®), chlorobutanol (as in Rohto V®), and thimerosal, have been reported to cause allergic reactions. Polyquad (as in Tear Naturale Forte®) , a quaternary ammonium preservative, has been shown to be less sensitizing than benzalkonium chloride or thimerosal. Purite® (as in various Refresh® eye products), a stabilized oxy-chloro complex, is an oxidative preservative that breaks down to sodium chloride and water when exposed to UV light. It is a very well tolerated preservative even in patients with severe DED. Another preservative, sodium perborate (as in GenTeal®), is converted to sodium hydroxide and water and is believed to be less toxic to the ocular surface. Preservative-free artificial tears should be recommended for patients allergic to preservatives or patients who have more frequent need for artificial tears. In addition, there is multi-dose artificial tear product that is preservative-free in a special dispensing system that is designed to prevent contamination (such as Larmabak®).

Eye gel/ointments

Ophthalmic ointments are sterile, bland semisolid dosage forms that usually contain white petrolatum, mineral oil, and lanolin derivatives. The addition of mineral oil allows the vehicle to melt at body temperature, and the presence of lanolin enhances water absorbability. Ophthalmic ointments may or may not contain preservative(s). Ointments form an occlusive film on the surface when applied to the precorneal area where they melt at physiological temperature of the ocular surface and mix with the tear film. When compared to solutions, ointments are retained longer on the corneal surface. Clinical uses of ointments include lubrication and protection of the eye from drying during and after surgery, protection from wind or sun, or foreign body removal.

Ophthalmic ointments may also be useful in protecting the cornea of patients with dry eye syndrome. They are best employed at night, as they may cause temporary blurring of vision. Some products contain carbomers in gel formulations that cause less blurry vision than petrolatum ointments and are better tolerated.

Eyelid care

Proper lid function is vital too, especially in patients with meibomian gland dysfunction (MGD). Patients can be advised to apply warm compresses, perform lid massage, and clean the lids with non-irritating soaps or other commercially available preparations such as Blephagel® Duo or Lid-care® to help restore more normal lid function.

Physicians Referal

For moderate to severe DED patients who do not respond well to artificial tear replacement, other treatment options (such as punctual plugs, corticosteroids or cyclosporine) which address the underlying pathophysiology of DED may also be employed by physicians based on international treatment guidelines (ITF, Delphi approach)

Patient education

Avoidance of wind, drafts, smoky environments, and dry air are recommended for patients with DED. Preventative measures include moving desks away from air vents, use of humidifiers in the workplace, taking breaks while working on computers, and placing drops from artificial tear products prior to onset of symptoms can be beneficial in conserving the moisture in corneal surface.

There are a number of areas that pharmacists should consider before making a recommendation of an artificial tear product to a patient. It would be reasonable to ask patients about their symptoms, assessing why they are considering use of or are currently using an artificial tear product. Another consideration when choosing a dry eye product formulation is whether the patient wears contact lenses. Contact lens wearers should remove them prior to instilling artificial tears or ointments. However, there are products specifically formulated to use with contact lens. They provide added moisture to the ocular surface and remove any debris that could be irritating to the eye. If patients are using an artificial tear product more than four times daily, it may be time to refer them to their eye care professional for further evaluation. Patients with concurrent ocular allergies may benefit from OTC antihistamines eye drops to reduce symptoms of itching and redness. However, OTC decongestant eye drops used to "get the red out" are usually detrimental to DED because these products often cause ocular drying and rebound hyperemia.

Pharmacists may also intervene when patients are improperly using eye preparations or medications (antihistamines used for managing allergy or sleep, topical decongestants, or prescription items that have antimuscarinic activity) that may actually cause an increase in symptoms of DED and may exacerbate it. Pharmacists are in an ideal position to be able to provide excellent education, recommendations and reinforce adherence for patients with DED. Pharmacists should advise patients regarding shelf-life of eye preparations after opening, proper self-administration procedure of eye drops/ eye ointments (Table 4) and to discontinue the use of tear substitutes if persistent discomfort, pain, or blurred vision is experience and when to consult physicians.

Table 4: Self-administration Procedure

Eye Drops:	Eye Ointments:
1 Wash hands.	1 Wash hands.
2 Tilt the head back lightly.	2 Remove cap from tube.
3 Pull lower eyelid down and away from eyeball to create a pocket.	3 Tilt the head back lightly.
4 Drop medicine inside the pocket while looking up and without touching ocular or periocular tissues. The drop should fall on the conjunctiva and not on the cornea.	4 Pull lower eyelid down and away from eyeball to create a pocket.
5 Release lower eyelid and close eye for 1-2 minutes	5 Squeeze a small amount of ointment inside the pocket while looking up and without touching ocular or periocular tissues (i.e., do not touch tip of tube to eye, eyelids, or fingers).
6 With closed eyelids, eyes are rolled to spread the solution on the surface of the eye.	6 Release lower eye lid, close eye gently for 1-2 minutes and roll the eyeball in all directions.
7 Secondary to lacrimal gland infiltration associated with various diseases including AIDS, sarcoidosis, and lymphoma	7 The closed eyelid may be rubbed very gently by a finger to distribute the drug on the surface of the eye.
8 Sensory block causes such as refractive surgery, diabetes, or herpes simplex keratitis	8 Wipe off any excess ointment from the eyelids and lashes.
9 Motor block causes by drugs (such as antimuscarinics or tricyclic antidepressants) or damage to cranial nerve VII	

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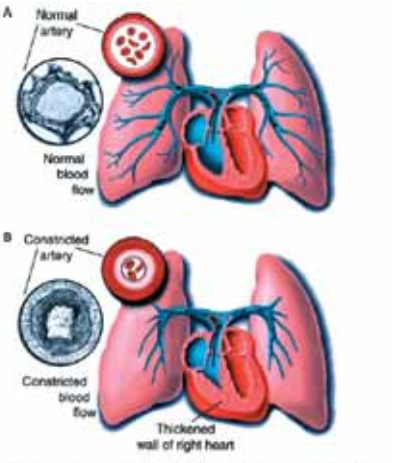
Pulmonary Arterial Hypertension

Mr. Cedric Mok

Definition:

Pulmonary arterial hypertension (PAH, named as pulmonary hypertension PH in short) is a complex problem characterized by nonspecific signs and symptoms and having multiple potential causes. Normal pulmonary artery systolic pressure at rest is 18 to 25mmHg, with a mean pulmonary pressure ranging from 12 to 16mmHg. This low pressure is due to the large cross-sectional area of the pulmonary circulation, which results in low resistance. An increase in pulmonary vascular resistance or pulmonary blood flow results in pulmonary hypertension. Pulmonary arterial hypertension may be defined as a sustained elevation of pulmonary arterial pressure to more than 25mmHg at rest [2] or to more than 30mmHg with exercise [1].

PH is usually classified into 1) Primary pulmonary hypertension, which is a rare disease of unknown etiology and 2) Secondary pulmonary hypertension, [1,2] which is a complication of many pulmonary, cardiac and extrathoracic conditions. However, due to the confused histopathological features and the response to treatment within the category of secondary pulmonary hypertension that resembles primary pulmonary hypertension, the World Health Organization (WHO) classified PH into five groups on the basis of mechanisms, rather than associated conditions.[3] This article would focus on Group I PH.



A, Diagram of the heart and lungs. This illustration shows a normal heart and lung vessels. B, Diagram of an abnormal heart and lungs as would occur in pulmonary hypertension. Note the loss of vessels in the abnormal lungs and the thickening of the right heart to counteract the rise in pressure in the lung vessels.[8]

Regardless of the underlying cause, the abnormally high pressure strains the right ventricle of the heart, causing it to expand in size. Overworked and enlarged, the right ventricle gradually becomes weaker and loses its ability to pump enough blood to the lungs. This could lead to the development of right heart failure (Cor pulmonale).[2]

Etiology:

PH is caused by many different conditions that damage the lining of the pulmonary arteries OR obstruct the passage of blood through the vessels in lungs.

- Idiopathic (IPAH)
- Genetic abnormalities: individuals with genetic mutation are believed to be pre-disposed to pulmonary hypertension. [1, 4, 5]
  1. Two genes in the ubiquitous TGF-(beta) receptor family have been strongly linked to familial pulmonary arterial hypertension: bone morphogenetic protein receptor type 2 (BMPR2) and activin-receptor-like kinase 1 (AKL1). [4, 5, 6]
  2. Serotoninergic pathway: an increase in the serotonin transporter 5-HTT.

  The mutations of these genes cause the overgrowth of vascular smooth-muscle cells.[1]
- An imbalance of vascular effectors, which control the normal physiologic vasoconstriction, vascular cell proliferation and platelet aggregation [1]; these include:
  1. Prostacyclin and thromboxane A2
  2. Edonthelin-1
  3. Nitric oxide
  4. Serotonin
  5. Adrenomedullin
  6. Vasoactive intestinal peptide
  7. Vascular Endothelial Growth Factor
- The use of appetite-suppressant drugs, fenfluramine and dexfenfluramine [1, 2, 8]
- Congenital heart defects, left ventricular dysfunction, aortic valve disease, mitral valve disease and left heart failure which cause an increase in resistance to pulmonary venous drainage and backward transmission of the elevated left atrial pressure [7, 8]
- Connective tissue disease e.g. scleroderma or lupus erythematous [1, 2, 8]
- Alveolar hypoxia: Chronic mountain sickness, sleep apnea, interstitial lung disease and chronic obstructive pulmonary disease (COPD) cause a reduction in oxygen tension resulting in pulmonary vasoconstriction by a variety of actions on endothelium and smooth muscle.[1, 2, 7, 8]
- Pulmonary embolism / thrombocytosis: pulmonary emboli induces a mild to moderate elevation of pulmonary artery pressure. A chronic massive pulmonary embolus may cause pulmonary hypertension. [1, 2, 7, 8]
- HIV infection [1,2,8]
- Liver disease: e.g. cirrhosis [1,2,8]

Clinical Presentation:

PH often presents with nonspecific symptoms so it is frequently misdiagnosed and has often progressed to late stage by the time it is accurately diagnosed [8]. These symptoms are often difficult to dissociate from those caused by a known underlying pulmonary or cardiac disorder.

The most common symptoms are [2,7,8]:

- exertional dyspnoea, shortness of breath
- fatigue
- ankle swelling
- palpitation
- syncope, which reflects an inability to increase cardiac output during activity
- typical angina, which may occur despite normal coronary arteries. The mechanism is unclear, but anginal chest pain may be due to pulmonary artery stretching or right ventricular ischemia
- Hemoptysis, which is coughing up of blood, resulting from the rupture of distended pulmonary vessels but it is rare

Classification of Pulmonary Hypertension [33]:

Class I: Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope.

Class II: Patients with PH resulting in slight limitation of physical activity. These patients are comfortable at rest, but ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.

Class III: Patients with PH resulting in marked limitation of physical activity. These patients are comfortable at rest, but less than ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.

Class IV: Patients with PH resulting in inability to perform any physical activity without symptoms. These patients manifest with signs of right heart failure. Dyspnoea and/or fatigue may be present at rest, and discomfort is increased by any physical activity.

Diagnosis [2, 8]:

One or more of the following tests may be performed if PH is suspected:

- A *chest x-ray* may show heart enlargement and abnormal lung vessels.
- *Autoantibody blood tests* may be done to look for autoimmune diseases like lupus and scleroderma.
- *Liver function tests* may be done to look for cirrhosis or other forms of liver disease.
- *Echocardiograms* use sound waves to create a sonar-like picture of the heart and measure the heart size, function, and blood flow, and can indirectly estimate the pressure in the lung vessels.
- An *ECG* may be done to record the electrical activity of the heart and show changes in heart rhythm and wall thickness.
- *Heart catheterization*, involving long, thin tubes called catheters inserted into the heart and lung vessels, may be performed to measure pressures and the flow of blood. Sometimes, an x-ray dye may be injected into the lung vessels to look at the type and extent of obstruction.
- *Pulmonary function tests* may be done to look for other lung conditions.
- *Ventilation-perfusion scans* may be done with the use of radioactive tracers to look for certain causes of pulmonary hypertension like blood clots.
- *A CAT scan of the chest* may be done to look for abnormal lung vessels, blood clots, and lung disease outside the blood vessels.
- *HIV tests* may be done to look for HIV infection.

How is pulmonary hypertension treated?

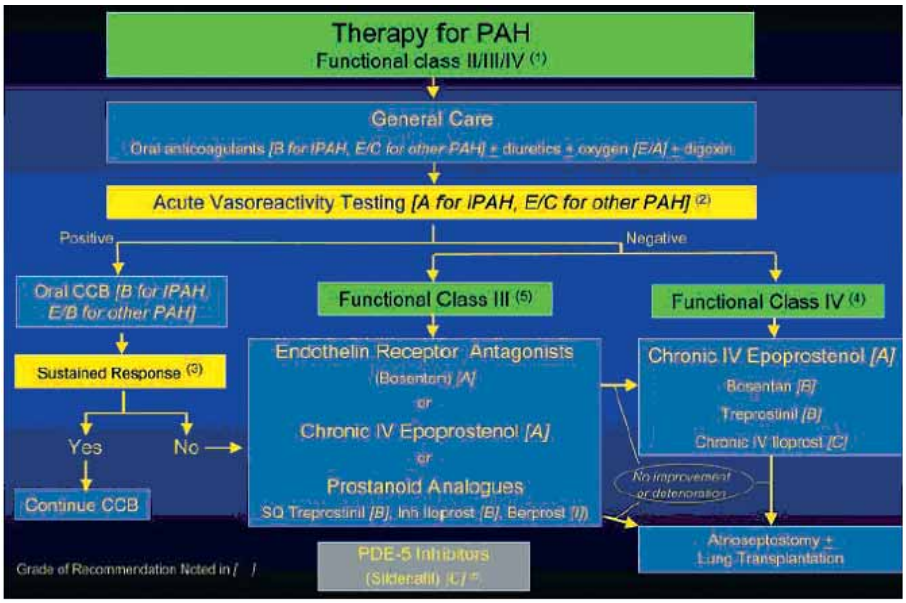


Figure 1. This algorithm is developed at the third World Symposium on Pulmonary Arterial Hypertension, held in Venice, Italy, June 23 to 25, 2003. It has been modified slightly, and the grading of recommendations, based on the system used in this document, is noted in the algorithm in the italicized brackets.

1: The algorithm is focused on patients in functional class III or IV. Patients in functional class II who are not candidates for, or who have failed, CCB therapy may benefit from treatment. However, limited data are available, and no specific drug can be recommended. Therapies in the algorithm have been evaluated mainly in IPAH, and in PAH associated with scleroderma or due to anorexigens. Extrapolation of these recommendations to other PAH subgroups should be done with caution.

2: A positive acute response to vasodilators is defined as a fall in mPAP of at least 10mmHg to 40mmHg, with an increased or unchanged CO during acute challenge with inhaled NO, IV epoprostenol, or IV adenosine.

3: Sustained response to CCBs is defined as patients being in functional class I or II with near-normal hemodynamics after several months of treatment.

4: Most experts recommend that patients in functional class IV in unstable condition be treated with IV epoprostenol.

5: In patients in functional class III, first-line therapy may include oral endothelin-receptor antagonists, long-term IV epoprostenol, or prostanoid analogues.

6: Early reports show promising results regarding the potential therapeutic efficacy of sildenafil in the management of patients with chronic PAH. Despite these promising reports, appropriately designed randomized clinical trials are needed (currently in progress). In patients with PAH who have failed or are not candidates for other available therapy, treatment with sildenafil may be considered. SQ = subcutaneous; Inh = inhaled; PDE = phosphodiesterase. [10]

a) Oxygen:

Oxygen therapy is used to replace oxygen in patients' blood [2, 7].

b) Diuretics:

Diuretics can help remove extra fluid from the tissues and bloodstream to reduce swelling and make breathing easier [2, 7, 8].

c) Digoxin:

Digoxin can be used to make the heart pump more efficiently [7, 8].

d) Inhaled nitric oxide (NO) [10]

NO is a potent pulmonary vasodilator locally produced by the vascular endothelium. It may help to decrease the pulmonary vascular resistance, raise the oxygen levels and rapidly reduce pulmonary pressures. With its vasodilator effect and the recognition of reduced NO production in some PH patients (due to a decreased level of NO synthase), NO was subsequently shown to have selective and potent pulmonary vasodilator effects during brief treatment of adults with IPAH[9].

Subsequent studies demonstrated that inhaled NO is a potent pulmonary vasodilator in multiple settings, including newborns with PH (PPHN), those with pneumonia, children with congenital heart disease, postoperative PH, lung transplantation, and others [11]. It has been shown to be of substantial benefit in PPHN, decreasing the need for support with extracorporeal membrane oxygenation [12, 13]. Although inhaled NO has been used extensively in diverse clinical settings, especially in intensive care medicine, FDA approval for this therapy is exclusively for newborns with hypoxemic respiratory failure at this time [10]. Extensive work is needed to determine whether long-term inhaled NO in the ambulatory setting is safe, acceptable, feasible, and effective.

e) Calcium channel blockers (CCB):

Dihydropyridine CCBs, with the most frequently used being amlodipine, nifedipine and diltiazem [10], can block the peripheral calcium channels in the pulmonary vascular smooth muscle, resulting in vasodilatation and increased supply of blood and oxygen to the heart, while reducing its workload. CCBs are believed to prolong life in about 20% of patients with pulmonary hypertension [8]. However, there is no way to predict which patients will respond to orally administered vasodilators [2]. Patients who demonstrate a significant response to the acute administration of a short-acting vasodilator should be treated cautiously with oral CCBs, and monitored closely to determine both the efficacy and safety of such therapy [10]. The most suitable drugs for testing acute response are potent, short-acting and titratable e.g. nifedipine (half life~3hr), felodipine (half life~10hr), diltiazem (half life~6hr).

f) Prostacyclin and its analogues

Prostacyclin is a naturally occurring prostaglandin produced by the vascular endothelium. It is a potent vasodilator (which inhibits platelet aggregation by elevating platelet cAMP) affecting both the pulmonary and systemic circulation and is the most potent inhibitor of platelet aggregation known.

In two clinical studies, Christman et al [14] and Tuder et al [15] reported a deficiency of prostacyclin and excess of thromboxane in PAH and decreased expression of prostacyclin synthase in lungs from patients with severe PAH respectively. Long-term IV epoprostenol therapy has had a dramatic effect on the symptomatic and hemodynamic improvement, as well as improved survival in patients with severe IPAH in patients with moderately severe-to-severe PAH [16 - 23].

The action of epoprostenol is dose-dependent when the dose is above 2 ng/kg/min, following continuous infusion only (due to its short half life (<6 minutes) and acid instability). Patients are typically begun on a very low dosage of epoprostenol (1 to 2 ng/kg/min), and the dose is gradually titrated upward in increments of 1 to 2 ng/kg/min (for dose of ≥ 4 ng/kg/min, there would be significant inhibition of aggregation induced) based on side effects and tolerance. Many patients seem to eventually reach a “plateau” dose, and may not require continued up-titration from that point. While this dose may be between 20 ng/kg/min and 40 ng/kg/min for many patients, the dose range tends to be quite wide, with considerable interindividual variability [10].

The success of epoprostenol therapy, coupled with the limitations of its delivery system, has led to the development of prostacyclin analogues that allow a subcutaneous delivery. An example is treprostinil, which is a prostacyclin analogue with a half-life of 3 hours [10].

In December 2004, a new form of the drug, iloprost, was approved for the treatment of PAH. This medication can be inhaled through a nebulizer. This makes it more convenient and less painful to take. Also, the medication goes directly to the lungs where it is needed [2].

Common side effects of epoprostenol therapy include headache, flushing, a blotchy erythematous rash, and musculoskeletal aches and pain, and line-related infection.

g) Anticoagulant: warfarin:

Patients with right ventricular failure and resultant venous stasis are likely at increased risk for pulmonary thromboembolism, because of sluggish pulmonary blood flow, dilated right heart chambers, venous insufficiency and relative physical inactivity [10]. Warfarin is used to prevent clot formation in the blood vessels [2, 7, 8]. The target INR of 1.5 to 2.5 is recommended, but varies with different local guidelines [10].

h) Sildenafil (Viagra)

Sildenafil is a phosphodiesterase inhibitor, selective for type 5, which is more strongly expressed in the lung [10], than type 3 and type 6 (involving cAMP, used in asthma and myocardial dysfunction). It inhibits the breakdown of cGMP, which augments the pulmonary vascular response to endogenous or inhaled NO in smooth muscle in models of PH via the regulation of vascular tone, growth and structure [10].

Sildenafil treatment for PH is an unlicensed indication. Nevertheless, several reports suggest that sildenafil combination therapies with NO [24,25], or iloprost [26,27] appear to be significantly superior to either agent alone, in terms of PVR and pulmonary arterial pressure. Other nonrandomized, single-center studies of patients with PAH treated with long-term sildenafil suggested promise for sildenafil as a therapeutic agent [28, 29], in terms of 6-min walk test (distance that a patient can walk within 6 minutes) and dyspnoea index, with decreased echocardiographic estimates of systolic pulmonary arterial pressure.

The usual starting dose of sildenafil is 25 mg TID, which can be titrated up to 100mg 5 times daily but data is limited for this dosage.

i) Bosentan (Tracleer)

Bosentan is a specific and competitive endothelin receptor antagonist for both subtypes, ETa (slightly higher affinity) and ETb [32]. In patients with PH, there is an increased concentration of endothelin, which binds to endothelin receptors in the endothelium and vascular smooth muscle. As endothelin may contribute to the increase in vascular tone and pulmonary vascular hypertrophy, a pathogenic role for endothelin in PAH has been implicated [10].

Bosentan is licensed for the treatment of PH in patients with Class III or IV symptoms [10, 32]. Two clinical trials have shown that, the use of bosentan was associated with a significant increase in exercise capacity, an improved 6-minute walk distance and a decreased pulmonary artery pressure and mean right atrial pressure [30, 31].

Bosentan is available as 62.5mg and 125mg oral tablets. The usual starting dosage is 62.5mg BID or 125mg BID [31,32].

Due to the risk of potential hepatic toxicity, the US FDA requires that liver function tests be performed at least monthly in patients receiving this drug [10]. Teratogenic effects should also be noticed,

especially in women of childbearing age [10,32].

Lung transplantation:

Primary PH is usually progressive and ultimately fatal. Lung transplantation of one or both diseased lungs with healthy lungs is an option in some patients who have PH that does not respond to medical management [2,7]. The immediate reduction in pulmonary artery pressure is associated with an improvement in right ventricular function [7].

Conclusion:

Pulmonary arterial hypertension is often difficult to diagnose and challenging to treat. Untreated PAH can be a life-threatening illness which causes right ventricular failure and even death. With the advance in medicine, the length of survival is improving, from an average survival rate of 2.8 years to about 10 years, with some patients able to manage the disorder for 15 to 20 years or longer.

To achieve a better therapeutic outcome, pharmacists play an important role in the pharmaceutics and therapeutics.

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Questions for Pharmacy Central Continuing Education Committee Program

(Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pccchk.com) to fill in their answers there.)

2 CE Units

Pulmonary Arterial Hypertension

1. Which of the following statement(s) is/are true?

i. Primary PH is of unknown etiology whereas secondary PH is a complication of many conditions

ii. PH may be defined as the elevation of pulmonary venous pressure to more than 25mgHg at rest.

iii. PH may eventually cause heart failure due to continuously straining the left ventricle.

A. i B. ii C. i and ii
D. i and iii E. All of the above

2. Which of the following(s) concerning vascular effectors is/are false?

i. Prostacyclin is an artificial prostaglandin

ii. Endothelin, nitric oxide and prostacyclin are the vascular effectors identified as targets for therapeutic intervention.

iii. Thromboxane plays a role of vasoconstriction, vascular cell proliferation and platelet aggregation.

A. i B. iii C. i and ii
D. i and iii E. All of the above

3. PAH would probably strain the _____of the heart most.

A. Left ventricle B. Right ventricle
C. Left atrium D. Right atrium
E. Aorta

4. Which of the following statement(s) is/are true?

i. PH patients may be genetically pre-disposed.

ii. 6-minute walk test is a tool to determine the effectiveness of a patient's response towards a therapeutic treatment.

iii. Heart problems e.g. congenital heart defects, mitral valve disease, etc. may cause PH due to the increase in vascular resistance towards pulmonary venous drainage.

A. i B. ii C. i and ii
D. i and iii E. All of the above

5) Which of the following(s) concerning Calcium Channel Blocker (CCB) in the treatment of PH is/are true?

i. Non-dihydropyridine CCBs are not recommended due to their limited effect on peripheral calcium channels.

ii. Only those patients who show a positive acute response to inhaled NO, IV epoprostenol, or IV adenosine would be put on a trial of CCB therapy.

iii. Some PH patients may achieve sustainable and acceptable clinical outcome towards CCBs.

A. i B. iii C. i and iii
D. ii and iii E. All of the above

6) Which of the following(s) concerning inhaled Nitric Oxide (NO) in PH management is/ are false?

i. The therapeutic role of inhaled NO is placed in newborns with PH only.

ii. NO is, naturally, produced through enzymatic action of NO transferase in the body.

iii. Inhaled NO was shown, in several studies, to be a selective pulmonary vasodilator.

A. i B. ii C. i and ii
D. i and iii E. All of the above

7) Which of the following(s) concerning Epoprostenol Sodium in PH management is/are true?

i. The dose-effect relationship of epoprostentol follows a linear curve.

ii. In functional class III and IV, epoprostenol could be used as the first-line therapy.

iii. For acute raise in pulmonary blood pressure, a loading bolus dose of epoprostenol may be used.

A. i B. ii C. i and ii
D. ii and iii E. All of the above

8) Which of the following(s) concerning sildenafil in treating PH is/are false?

i. Sildenafil is the second therapeutic agent licensed for treatment of PH.

ii. The usual dosage and frequency of sildenafil in PH treatment is similar to that applied in erectile dysfunction treatment.

iii. Sildenafil, a type 5 phosphodiesterase inhibitor, augments NO in regulating vascular tone, growth and structure.

A. i B. ii C. i and ii
D. ii and iii E. All of the above

9) Which of the following(s) concerning Bosentan in treating PH is/are true?

i. Hepatic toxicity and teratogenicity are the concerns when using Bosenatn.

ii. Bosentan is not licensed for treating PH patients with Class III or IV symptoms.

iii. Bosentan acts on endothelin receptor ETa and ETb rather than acting on endothelin.

A. i B. ii C. i and ii
D. i and iii E. All of the above

10) Which of the following(s) is/are false?

i. Lung transplantation of one or both diseased lungs with healthy lung may be one of the solutions for PH patients who do not respond to medical management.

ii. The immediate reduction in pulmonary artery pressure following lung transplantation is associated with an improvement in right ventricular function.

iii. The advance in medicine has lengthened the survival of PH patients from an average of 2.8 years to 10 years or even longer.

A. i B. ii C. i and ii
D. ii and iii E. All of the above

Answers will be released in the next issue of HKPJ.

Answers for the past issue (Jan-Jun 2008)

Suggested answers:
1)B 2)D 3)E 4)C 5)C 6)D 7)B 8)A 9)B 10)E

Literature Review of Rhizoma Smilacis Glabrae(土茯苓)

Zhang, Qing-Feng; Zhang, Zhongrong; Cheung, Hon-Yeung*

*Research Group for Bioactive Products, Department of Biology & Chemistry, City University of Hong Kong SAR, China (*email: bhhonyun@cityu.edu.hk)*

Botanical Name: Smilax Glabra Roxb.
Plant family: Liliaceae
Part used: Rhizome
Latin Name: Rhizoma Smilacis Glabrae
Chinese Name: Tufuling 土茯苓, 禹餘糧
English Name: Glabrous Greenbrier Rhizome

I ABSTRACT

Rhizoma Smilacis Glabrae, also called Tufuling in Chinese, is commonly used for detoxication, relieving dampness and as a diuretic in traditional Chinese medicine. It is also one of the main ingredients in Guiling gao; an old traditional functional food in Southern China and Hong Kong. To facilitate the research about this herbal medicine, different aspects e.g. confusable species, compounds isolation, quality control and bioactivity of this herb had been reviewed in this article.

II DESCRIPTION AND BACKGROUND

Rhizoma Smilacis Glabrae (RSG), also called Tufuling in Chinese, is the rhizome of the *Smilax Glabra Roxb*. The rhizome is collected in summer or autumn, with the length of 5-22 cm and diameter of 2-5 cm. It is subcylindrical, slightly flattened or irregularly slat-shaped and lump-shaped, with knob-like outgrowths and short branches. Externally yellowish-brown or grayish-brown, uneven, with stiff remains of fibrous roots and the tops of branches possessing rounded bud scars. Some outer bark irregularly fissured and exhibiting remains of scales. After removing from fibrous root, the rhizome was washed clean and dried, or sliced while fresh and dried, and preserve in a ventilated and dry place [1]. Figure 1 showed the photo of *Smilax Glabra Roxb*. and its rhizome. The resource of RSG is abundant, it distributes in almost all provinces of southern china. Sichuan, Guandong and Hubei are the main producing area [2].

Tufuling was first appeared in *Ben cao jing ji zhu* (本草經集注), with the name of *Yuyuling* (禹餘糧), and was eaten as foodstuff when the famine occurred. Many ancient medicinal books had recorded its use and action, such as *The Compendium of Material Medica* (本草綱目), *Ben cao fei pian* (本草彙編) etc [3]. The *Pharmacopoeia of the People's Republic of China 2005* (PPRC2005) record it can be used for detoxication, relieving dampness and as a diuretic. *RSG* can be used to treat leptospirosis, dermatitis, syphilis, brucellosis, acute bacterial dysentery, and acute and chronic nephritis in traditional Chinese medicine [1]. Besides, it is also used for skin problems, such as psoriasis and chronic eczema. It is also one of the main ingredients in Guiling gao; an old traditional functional food in Southern China and Hong Kong. This food is said to help minimize the effects of damp-heat, nourish yin, clear body heat and toxins in the blood. It has also been claimed that the food specifically helps to improve or cure skin disorder.

Figure 1. Photo of Smilax Glabra Roxb.土茯苓 and its rhizome

Contraindications
No contraindication has been reported.

Undesirable Effects
No reports of side-effects or adverse reaction associated with the use of this herb.

Interaction with Conventional Drugs
No interaction with conventional drugs has been reported at the moment of this publication.

II Confusable species and identification

There are more than 60 *Smilax* plant distributing in china. Many of them are alike RSG without careful examination. These include *Smilax glabra var. concolor, Smilax lanceiefolia var. opaca, Smilax China, Heterosmilax japonica, Heterosmilax yunnanensis, Smilax glauco-china, Smilax discotis, etc* [2]. Hence, the PPRC 2005 version demands the microscopic identification of the herb. It is documented that

the powder of RSG is pale brown with abundant starch granules. Raphides of calcium oxalate may exist in mucilage cells as needle crystals with length of 40-144 μm and diameter of 5 μm. Stone cells are subelliptical, subsquare or triangular, 25-128 μm in diameter, with fine and close pit canals; deep brown stone cells are elongated and about 50 μm in diameter. Walls are heavily thickened on three sides and thin on one side. Fibres existed in bundles or scattered, are 22-67 μm in diameter. Bordered pitted vessels and tracheids are more frequent, most bordered pits elongated to be scalariform [1]. Zhang using morphological and microscopic method has successfully identified RSG from its seven confusable species [4]. Chen et al also use microscopic method for the identification of RSG and its eleven confusable species [5]. Li et al investigated the fingerprint of *RSG* by HPLC-method. Ten samples were analysed and their fingerprints were compared to its three confusing species [6]. Li et al used capillary electrophoresis method for the identification of *RSG* from its six confusing species [7]. We also have developed the capillary electrophoresis fingerprint of RSG. 18 samples from different area in china have been tested. As showed in Figure 2, 6 common perks was found in all sample when detected at 214 nm. However, at 325 nm, only five peaks can be found. The most abundant peak 2 was identified as astilbin, peak 4 was taxifolin and peak 6 at 214 nm was shikimic acid.

III BIOACTIVE CONSTITUENTS

Many bioactive compounds, which may be responsible for the pharmacological effects of RSG, have been identified and isolated. These include flavonoids such as taxifolin and four stereoisomeric flavanones of neoastilbin, astilbin, neoisoastilbin, isoastilbin; polyphenols such as *trans*-resveratrol; phenolic acids such as syringic acid, shikimic acid and ferulic acid; etc.

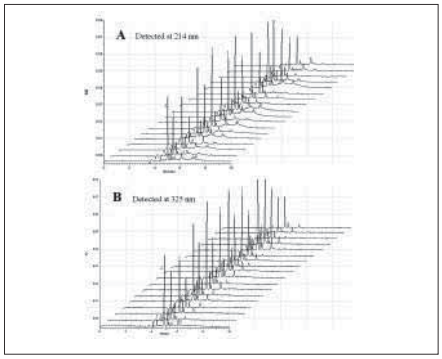

Figure 2. Capillary electrophoresis fingerprint of RSG. Separation condition: 20 mM sodium borate containing 3 mM β-CD at pH 9.4 and 25 kV with an effective length of 50 cm of capillary (total length 60.2 cm) on a Beckman P/ACE MDQ Electrophoresis system. (Unpublished work)

(i) Flavonoids [8-18]

Flavonoids are the main bioactive compounds in *RSG*. By now the 12 flavonoids isolated belong to five types, namely dihydroflavonols, dihydroflavones, flavonols, isoflavones and flavanols.

Dihydroflavonols are the dominant compound. Ten dihydroflavonols have been isolated from RSG, including astilbin (3-O-alpha-L-rhamnoside-5,7,3',4'-tetrahydroxydihydroflavonol (1) and its three stereoisomeric forms, neoastilbin (2), isoastilbin (3) and neoisoastilbin (4), taxifolin (5), taxifoli-3'-o-β-D-pyranglucoside (6), engeletin (7) and stereoisomeride isoengeletin (8), smitilbin (9) and its stereoisomeride neosmitilbin (10). The structures of these compounds are shown in Figure 3.

The other flavonoids are two flavonols, namely quercetin (11) and naringenin (12), the isoflavone, 7,6'-dihydroxy-3'-methoxyisoflavone (13); and the flavanol, (-)-epicatechin (14). The structures of these compounds are shown in Figure 4.

(ii) Phenylpropanoid glycosides [19]

Chen et al isolated seven phenylpropanoid glycosides from the rhizome of *Smilax glabra*, including five new compounds named smiglasides A-E (15-19), together with the previously described closely related analogue helonioside A (20) and (3,6-di-O-feruloyl)-b-D-fructofuranosyl-(3,6-di-O-acetyl)-a-D-glucopyranoside (21). Their structures were elucidated on the basis of spectroscopic studies, including UV, IR, ^{1}H-NMR and ^{13}C-NMR. The structures of these compounds are shown in Figure 5.

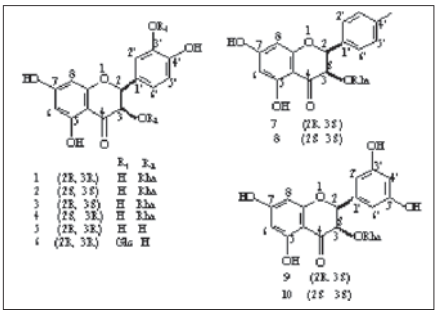

Figure 3. Dihydroflavonol isolated from RSG.

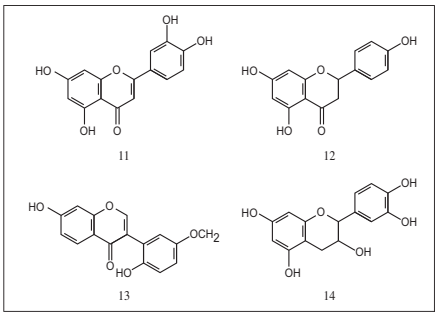

Figure 4. The other flavonoid isolated from RSG

(iii) Lignan glycoside [9]

Yuan et al isolated a new lignan glycoside, (+)-syringaresinol 4-*O*-b-D-glucopyranosyl-(1-6)-b-D-glucopyranoside, together with twelve known compounds from the rhizomes of *Smilax glabra*. The structure of this compound is shown in Figure 6.

(iv) Polyphenol, phenolic acid and their glycosides [12, 13, 20, 21]

The phenolic compounds isolated from the rhizome of *Smilax glabra* include resveratrol, resveratrol-3-O-*β*-D-glucopyranoside, shikimic acid, syringic acid 2,4,6-trihydroxylacetophenone-2,4-di-O-*β*-D-glucopyranoside, 3-O-*β*-D-glucopyranosyl-1-4(4'-hydroxy-3',5'-dimethoxyphenyl)-1-propanone,

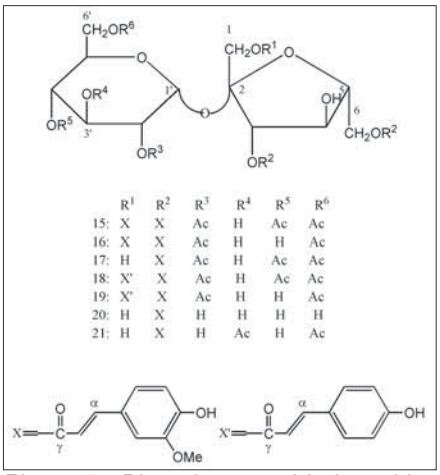

Figure 5. Phenylpropanoid glycosides isolated from RSG

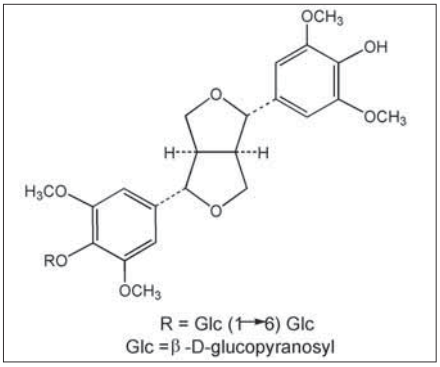

Figure 6. Lignan glycoside isolated from Rhizoma Smilacis Glabra

3,4,5-trimethoxyphenyl-1-O-*β*-D-glucopyranoside,3,4,5-trimethoxyphenyl-1-O-[*β*-D-apifuranosyl-(1-6)]-*β*-D-glucopyranoside and 3,4-dihydroxyphenothyl-3-O-*β*-D-glucopyranoside. The structures of these compounds are shown in Figure 7.

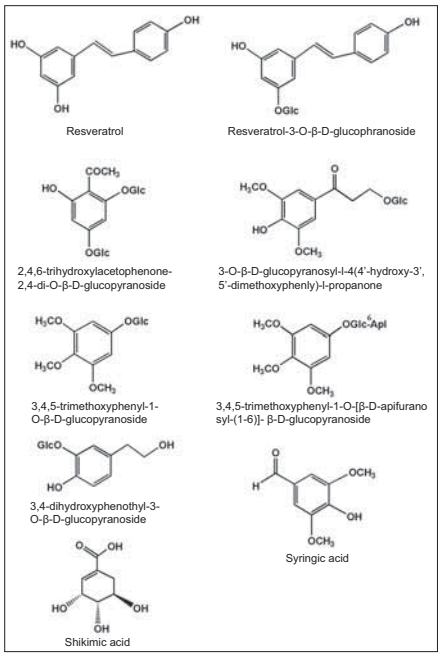

Figure 7. Polyphenol, phenolic acid and their glycosides isolated from Rhizoma Smilacis glabra

(v) Organic acids [13-15, 21]

The organic acids isolated from RSG include butane diacid, palmitic acid and 2,2-dimethylsuccinic acid.

(vi) Sterols [15, 21]

The sterols found in Smilax glabra include beta-sitosterol and stigmasterol.

(vii) Others [21, 22]

Four fructosides including n-butyl-*α*-*D*-fructofuranoside, n-butyl-*β*-*D*- fructofuranoside, n-butyl-*α*-*D*-fructopyranoside and n-butyl-*β*-*D*-fructopyranoside, and two heterocycles namely nicotinamide and 5-hydroxymethylfurfural had been isolated from RSG.

Chu et al purified a protein, with a novel N-terminal amino acid sequence and a molecular mass of 30 kDa from fresh *Smilax glabra* rhizomes. The protein, designated as smilaxin, has immunostimulatory, antiproliferative, and HIV-1-reverse transcriptase inhibitory activities [23]. A heterodimeric agglutinin with a molecular mass of 32 kDa, and comprised of a 15 and a 17 kDa-subunit, was isolated from *Smilax glabra* rhizomes. The hemagglutinating activity of the agglutinin was unstable under acidic and alkaline conditions and when exposed to temperatures at or higher than 50°C. The activity was not altered by a number of monovalent, divalent and trivalent cations, nor by a variety of sugars and glycoproteins [24].

Ooi et al purified a new mannose-binding lectin, designated SGM2, from the rhizome of *Smilax glabra*. SGM2 is shown to have a molecular mass of 37 kDa on gel filtration and 12.5 kDa on SIDS-PAGE, indicating that it is a trimeric protein composed of three identical subunits. When the first 30 amino acid residues at the N-terminal were compared, SGM2 was recorded to have a similarity of about 40% homology with those of some other monocots. SGM2 had the property of hemagglutinating activity toward rabbit erythrocytes, which could be reversed by mannose and mannose polymers. SGM2 exhibited antiviral activities against both herpes simplex virus type 1 (HSV-1) and respiratory syncytial virus (RSV) with the same EC50 of 8.1 μM [25].

IV QUALITY CONTROL OF RSG

PPCR 2005 requires the analysis of water contents, total ash content, acid-insolvable ash content and hot ethanol extract content of RSG for its quality control. The expected ranges are ≤15%, ≤5%, ≤1% and ≥15%, respectively [1]. There are also some reports about the determination of bioactive compounds in *RSG*. Chen et al developed a HPLC-method for the simultaneous determination of five flavonoids, taxifolin, neoastilbin, astilbin, neoisoastilbin and isoastilbin, contained in *RSG* [26]. Li et al had determined astilbin and resveratrol in *RSG* by reverse HPLC-method [27]. Chen et al also determined the content of astilbin in *RSG* by HPLC-method [28]. Our have developed a cyclodextrin-modified capillary zone electrophoretic method for the separation and determination of *trans*-resveratrol, astilbin, taxifolin, shikimic acid, syringic acid and ferulic acid in RSG. 12 samples of RSG collected from different regions in China were analysed. The results reveal that the content of astilbin, which was the most dominant active compound in RSG, ranged from 1-4% while ferulic acid, syringic acid and resveratrol could be absence [29]. The sample electropherograms was showed in Figure 8.

V BIOACTIVITY OF RSG OF ITS DOMINANT CONTITUTE ASTILBIN

Pharmacological studies reveal that the methanol or water extract of RSG have many activity, such as anti-inflammatory, immunomodulatory, protective against hepatocyte damage, insulin sensitivity enhancement, etc. Here, the bioactivity of RSG or its dominant constitute astilbin were reviewed and summarized in 7 aspects.

(1) Anti-cancer property

Sa et al investigated the anti-proliferative and pro-apoptotic effect of methanol extract of SGR on hepatoma cell line HepG2 and Hep3B. Astilbin and smilagenin were identified as the main chemical constituents in the extract by HPLC-MS/MS. They showed that the extract inhibited HepG2 and Hep3B cell growth by causing cell-cycle arrest at either S phase or S/G2 transition and induced apoptosis, as evidenced by a DNA fragmentation assay. SGR-induced apoptosis by alternation of mitochondrial transmembrane depolarization, release of mitochondrial cytochrome c, activation of caspase-3, and cleavage of poly(ADP-ribose) polymerase. The apoptotic pathway also involved activation of p38, INK, and ERK mitogen-activated protein kinase signaling [30]. Thabrew et al studied the cytotoxic effects of individual decoction of *Smilax glabra* and another two herbs on HepG2 cell. The ED50's of the decoction of *Smilax glabra* on HepG2 cell survival was 41 mg/ml as assessed

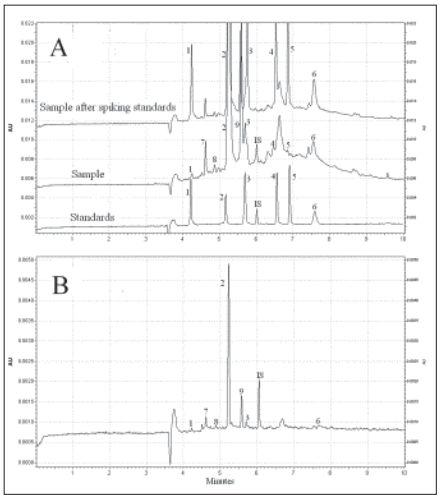

Figure 8. Electropherograms of Rhizoma Smilax Glabra samples and standard markers. (A) original extract of Sample and (B) sample after 20 times diluted. Peaks: 1= trans-resveratrol; 2= astilbin; 3= taxifolin; 4= ferulic acid; 5= syringic acid; 6= shikimic acid ; IS: internal standard [30].

by the SRB assay. The concentration of the *Smilax glabra* decoction required to produce 50% inhibition of DNA synthesis was 29 mg/ml [31].

(2) Hypoglycemic effect

The hypoglycemic effect of RSG was investigated in normal and KK-Ay mice, one of the animal models of non-insulin dependent diabetes mellitus with hyperinsulinemia. The methanol extract of RSG (ME, 100 mg/kg body weight) had been found to reduce the blood glucose of normal mice 4 h after intraperitoneal administration ($p < 0.05$), and also significantly lower the blood glucose of KK-Ay mice under similar conditions ($p < 0.001$). However, ME did not affect the blood glucose in streptozotocin-induced diabetic mice, one of the animal models of insulin-dependent diabetes mellitus with hypoinsulinemia. ME also suppressed epinephrine-induced hyperglycemia in mice. Thus, the authors concluded that ME exhibit the hypoglycemic effect through raising insulin sensitivity [32]. Haraguchi et al investigated the inhibition of aldose reductase and sorbitol accumulation by dihydroflavonol taxifolin and its glycoside, astilbin. Both flavonoids inhibited rat lens and recombinant human aldose reductase. Taxifolin also inhibited sorbitol accumulation in human red blood cells. Furthermore, it can maintain the clarity of rat lens incubated with a high concentration of glucose. These dihydroflavonols may be effective for preventing osmotic stress in hyperglycemia [33].

(3) Hepatoprotective effect

Wang et al evaluated the effect of astilbin on concanavalin A (Con A)-induced hepatitis, a T cell-dependent model of liver injury [34]. Con A administration resulted in a severe liver injury in mice, with a strong increment in spleen cell adhesion and liver infiltration of T cells, as well as in tumor necrosis factor (TNF)-alpha production. Against this liver injury, astilbin significantly inhibited the elevation in transaminase activity, reduced TNF-alpha production, and improved the histological changes, including inflammatory infiltration, hepatocyte necrosis and degeneration and Kupffer cell hyperplasia. In addition, astilbin inhibited the adhesion of spleen cells and purified T lymphocytes isolated from the liver-injured mice to fibronectin, laminin and type IV collagen. Moreover, the adhesion of human Jurkat T cells to endothelial cell line ECV-304 was also inhibited by astilbin. These results suggest that the improvement of the T cell-mediated liver injury by astilbin may be related to the reduction in TNF-a production and in T cell adhesion to extracellular matrices and endothelial cells.

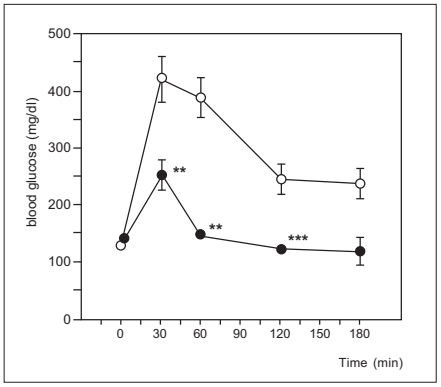

*Figure 9. Effect of methanol extract of RSG on glucose tolerance test in KK-Ay mice. –○–, control; –●– ME 100mg/kg. Each value represents the mean ± SD OF 5 mice. Significantly different from control, **p<0.01,***p<0.001 [32].*

Xu et al found astilbin significantly decreased liver injury induced by delayed-type hypersensitivity to picryl chloride in mice when administered during the effector but not the induction phase. The pretreatment of nonparenchymal cells but not hepatocytes with astilbin in vitro caused a concentration- and time-dependent inhibition against the damage. Nonparenchymal cells isolated from astilbin-administered mice also showed a significant incompetence of hepatotoxicity, correlated with the inhibition of serum transaminase elevation. However, astilbin did not protect from CCl_4-induced liver damage. Nevertheless, the flavanoid markedly promoted the apoptosis of nonparenchymal cells from liver-injured mice, whereas it did not influence those from naive mice. These results suggest that astilbin provides improvement against liver injury through a selective dysfunction of liver-infiltrating cells rather than by protecting the hepatocyte membrane [35]. Closa et al reported the beneficial effect of astilbin in CCl_4-induced hepatoxicity in rats. Histological findings, superoxide dismutase activity, lipoperoxides and prostanoid profiling studies revealed that the hepatoprotective effect of astilbine was higher than that of vitamin E. Astilbin was capable of restoring lipoperoxides and tissue prostanoids to basal values [36].

The structural requirements of RSG,s derivative for preventing immunological hepatocyte damage was studied by Chen et al. through applying 7 compounds to the assay of liver nonparenchymal cells (NPC) against hepatocytes (HC) from mice with an immunological liver damage. The study results suggested that compounds smitilbin-astilbin, eurryphin, and resveratrol could protect the hepatocyte damage from NPC by selectively producing the dysfunction of NPC with an essential requirement of rhamnose; and the chromone part in their structures might be critical for the protective activity [37].

The effects of taxifolin on lipid, apolipoprotein B (apoB), and apolipoprotein A-I (apoA-I) synthesis and secretion were determined in HepG2 cells. Pretreatment of cells with taxifolin led to an inhibition of cholesterol synthesis in a dose and time-dependent manner, with an 86±3% inhibition at 200 μM observed within 24 h. As to the mechanism underlying this inhibitory effect, taxifolin was shown to inhibit the activity of HMG-CoA reductase by 47±7%. In addition, cellular cholesterol esterification, and triacylglycerol and phospholipids syntheses, were also significantly suppressed in the presence of taxifolin [38]. Taxifolin was shown by ELISA to markedly reduce apoB secretion under basal and lipid-rich conditions up to 63% at 200 μmol/L. As to the mechanism underlying this effect, taxifolin was shown to inhibit microsomal TG synthesis by 37% and its subsequent transfer into the lumen (−26%). The reduction in synthesis was due to a decrease in diacylglycerol acyltransferase (DGAT) activity (−35%). Evidence is accumulating that microsomal triglyceride transfer protein (MTP) is also involved in determining the amount of luminal TG available for lipoprotein assembly and secretion. Taxifolin was shown to inhibit this enzyme by 41%. In summary, taxifolin reduced apoB secretion by limiting TG availability via DGAT and MTP activity [39].

(4) Immunosuppressive activity

Fei et al investigated the inhibitory effect of astilbin on contact hypersensitivity and compared its mechanism with cyclosporin A. Astilbin significantly inhibited contact hypersensitivity when given in the elicitation phase but not in the sensitization phase, whereas cyclosporin A inhibited both phases. Lymph node cells from donor mice administered astilbin failed to adoptively

transfer the hypersensitivity. Astilbin in vivo remarkably induced IL-10 expression in lymph node cells at an earlier time and decreased TNF-alpha and IFN-gamma expression at a later time. Furthermore, the in vivo neutralization of IL-10 significantly impaired the effect of astilbin on contact hypersensitivity. In the isolated lymphocytes sensitized with picryl chloride in vivo and challenged with trinitrobenzenesulfonic acid in vitro, astilbin did not affect the cell proliferation but modulated the above cytokine profiles as its in vivo effect in a concentration-dependent manner and furthermore significantly enhanced the expressions of suppressor of cytokine signaling 1 and 3. On the other band, cyclosporin A strongly inhibited proinflammatory cytokine production but influenced neither IL-10 nor downstream suppressor of cytokine signaling 1 and 3 expression. Astilbin alleviates contact hypersensitivity through a unique mechanism involving a negative cytokine regulation through stimulating IL-10, which is distinct from the immunosuppressant cyclosporin A [40].

Further, the authors investigated the metabolite of astilbin and its immunosuppressive activity against contact dermatitis. Astilbin was incubatd with rat liver microsomal/cytosolic fractions, a new metabolite of astilbin identified as 3'-O-methylated astilbin was detected and isolated from the culture solution. The metabolite was detected in both blood and urine samples after oral administration of astilbin, and the metabolite inhibited picryl chloride-induced ear swelling in mice and suppressed the expression of tumor necrosis factor-alpha and interferon-gamma, similarly to astilbin [41].

They also examined the effects of astilbin, on delayed-type hypersensitivity reactions and its mechanisms of action on cell migration. Astilbin significantly inhibited the sheep-red-blood-cell-induced footpad reaction and picryl-chloride-induced ear dermatitis without affecting the organ weights, when administered during the effector phase but not the induction phase. The flavanone also significantly inhibited the migration to gelatin of spleen cells isolated from mice with ear dermatitis in a transwell system. The results suggest that astilbin may inhibit delayed-type hypersensitivity reactions through selectively suppressing the lymphocyte functions, including cell migration, via down-regulating matrix metalloproteinases activity [42].

Yan et al examined the relationship between the activation of T cells and the apoptosis-facilitating effect of astilbin on them. By the stimulation of PHA, a remarkable IL-2 production was detected in the supernatant of Jurkat cells after 120 h among 72-144 h incubation. This kinetic behavior was quite in accordance with that of astilbin-induced apoptosis of Jurkat cells, where 1 h-exposure of the PHA-activated cells to astilbin caused a significantly increased apoptosis in a dose-dependent manner. To the Jurkat cells that had been cultivated for 72-144 h without PHA, however, astilbin did not show any facilitation of the cell apoptosis. These results indicated the dependency of the apoptosis-facilitating effect of astilbin on appropriate status of activated T lymphocytes with a relation to IL-2 production. This characteristic of astilbin may be of great significance for the treatment of a variety of immunologically related diseases [43].

Xu et al has reported that the aqueous extract from RSG (RSG ext) showed a remarkable inhibition on the delayed-type hypersensitivity reactions induced by picryl chloride or sheep red blood cells mainly through affecting the effector phase of DTH with an anti-inflammatory action but without inhibiting humoral immune response. Such selectivity of RSG ext for inhibiting cellular immune response (CIR) is different from that of glucocorticoids and immunosuppressing agents, and may be advantageous to the treatment of CIR-mediated inflammation, such as human hepatitis and rheumatoid arthritis [44].

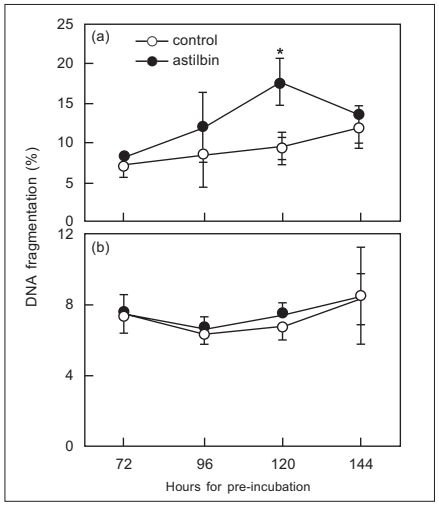

*Figure 10. Effect of astilbin on DNA fragmentation of Jurkat cells using the diphenylamine method. Jurkat cells (1×10^6) were incubated with (a) or without (b) PHA ($1\ \mu g\ ml^{-1}$) for 72, 96, 120, or 144 h respectively. After cultivation in the absence (control) or presence of 1×10^{-6}g ml^{-1} of astilbin for 1h, DNA was extracted and used for diphenylamine assay. Each point represents the mean ± SD of three separate experiments and each experiment included triplicate sets. *P<0:05 vs control [43].*

(5) Anti-inflammatory/anti-rheumatic properties

One of the most widely used models for studying the anti-inflammatory/anti-rheumatic properties of compounds is adjuvant-induced arthritis (AA) in rats. It is an experimental immunopathy that is thought to share many features with human rheumatoid arthritis [45]. It has been accepted that the adjuvant injection to the rat may not only cause arthritic inflammation in the injected site (primary inflammation) but also in the non-injected hind paw (secondary inflammation). In comparison with the primary non-immune inflammation, the secondary reaction usually occurs with an obligate latent interval to reach a peak and has been indicated to be immunologically mediated by a T lymphocyte-mediated delayed-type hypersensitivity (DTH) reaction [46]. Such characteristics of AA are useful for evaluating anti-inflammatory and immunomodulatory remedies for immunologically related inflammations.

By using this model, Jiang et al reported that the administration of the aqueous extract from RSG (RSG ext) remarkably inhibited both primary and secondary inflammations of AA. A remarkable inhibitory activity was exhibited by the extract against both primary and secondary hind paw swelling of adjuvant arthritis in rats. RSG ext also significantly reduced the inflammatory edema induced by carrageenan in either naive or bilaterally adrenalectomized rats, suggesting the independence of the anti-inflammatory action on the function of the pituitary-adrenal axis. Such activity of RSG included a direct anti-inflammatory activity and a selective anti-CIR mechanism, different from the non-selective activity of steroid and immunosuppressors [47].

The authors further examined the activity of RSG ext and its mechanism on the secondary inflammation of AA. The administration of RSG ext (400 and 800 mg/kg) during the later phase significantly inhibited the swelling of the adjuvant-non-injected footpad of AA rats. The lipopolysaccharide-induced production of IL-1, TNF and NO by peritoneal macrophages was significantly reduced. In contrast, the

extract significantly recovered the decrease in weight gain of the AA rats and Concanavalin A-induced T lymphocyte proliferation and IL-2 production by their splenocytes, while prednisolone (10 mg/kg) showed a significant aggravation. Furthermore, RSG significantly recovered the picryl chloride-induced delayed-type hypersensitivity to almost normal levels from the higher or lower levels induced by different treatments of cyclophosphamide with a normalization of CD4/CD8 ratio. These results suggest that RSG exhibit an improvement on AA through down-regulating over-activated macrophages and up-regulating the dysfunctional T lymphocytes during the later phase of arthritis [48].

The authors also further examined the therapeutic effects of astilbin, a main flavanoid isolated from RSG, on arthritis and to compare it with cyclosporine A (CsA). The results found that astilbin dose-dependently inhibited the footpad swelling, arthritic incidence, and clinical scores without influencing the body weights, while CsA showed strong inhibition with a significant weight loss. In isolated spleen cells from arthritic mice, increased potentials in proliferation, NO production, and MMP-2 and 9 activities were suppressed dose-dependently by the oral administration of astilbin. Additionally, astilbin showed neither any cytotoxicity to nor influence on Con A-induced proliferation of spleen cells from naive mice, while CsA showed a dose-dependent cytotoxicity and inhibition of the proliferation. Astilbin may act as an efficient therapeutic agent for arthritis like CsA but with less

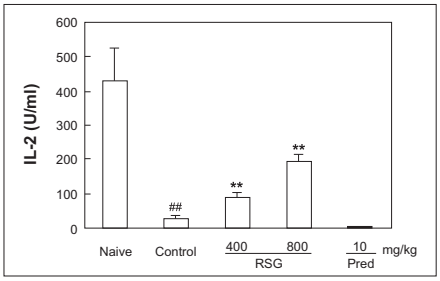

*Figure 11. Effect of RSG and prednisolone (Pred) on Con A-induced IL-2 production by splenocytes from AA rats. The IL-2 production was measured on day 25 of AA induction. Each column represents the mean ± S.D. of three animals and the experiment in each animal included triplicate sets. ##P <0.01 vs. Naive (Student's t-test); one-way ANOVA revealed a significant effect between Control and drug treatment groups (F2,9 = 95.599, P <0.0001), **P <0.01 vs. Control (Dunnett's t-test) [48].*

toxicity. Its mechanism includes a selective suppression on lymphocyte functions via reducing MMP and NO production [49].

(6) Antibacterial and insecticidal properties

Moulari et al investigated the antibacterial properties of extracts of *Harungana madagascariensis* leaves against bacterial strains representative of skin microflora. By isolation and identification of compounds, the authors confirmed that the antibacterial activity of the extract is due to astilbin. The purified astilbin was used to test its inhibitory effects against some bacteria of the cutaneous microflora including *Acinetobacter* sp., *Moraxella* sp., *Micrococcus luteus*, and *Staphylococcus epidermidis*. The minimal inhibitory quantity of astilbin ranged from 25 to 75 µg. The study showed the strong antibacterial activity of astilbin against the Gram-negative bacteria *(Acinetobacter sp., Moraxella sp.)* and Gram-positive bacteria *(M. luteus, S. epidermidis)* tested [50].

Cintra et al tested the toxicity of astilbin on the leaf-cutting ant *Atta sexdens rubropilosa* Forel by ingestion bioassays. Worker ants that were fed an artificial diet daily to which astilbin was added had a higher mortality rate than the controls. All concentrations tested showed toxic effects against ant workers, and the statistical comparison of survivorship rates from control and treated groups was significantly different, confirming the insecticidal properties of the substance astilbin [51].

Pereira et al studied the insecticidal and growth inhibiting activity of astilbin against *Anticarsia gemmatalis* and *Spodoptera frugiperda* by stomach ingestion. A small prolongation of the larval and pupal phase of the insect produced statistically significant increases in the total cycle duration time. A small reduction in the pupal weight of *S. frugiperda* was observed when treated with astilbin. Significant differences were observed for viability (total survival rates) of larvae, pupae and total life cycle for *A. gemmatalis* and *S. frugiperda* by increasing the concentration of astilbin in the diet [52].

(7) Anti-HIV-1 protease- and HIV-1 integrase activities

Tewtrakul et al investigated the inhibitory effects of ethanolic- and water extracts of *Smilax glabra* (and four other herbs) against HIV-1 protease (HIV-PR) and HIV-1 integrase. The result revealed that the ethanolic extract of RSG exhibited anti-HIV-1 IN activity with an IC_{50} value of 6.7 µg/ml, and the water extract of Smilax glabra with IC_{50} of 8.5 µg/ml [53].

VI CONCLUDING HIGHLIGHTS

RSG is a commonly used herbal medicine for detoxication, relieving dampness and as a diuretic in traditional Chinese medicine. It also widely consumed by Southern Chinese and Hong Kong people in functional food. Chemical studies show that it contains high content of polyphenols, especially one dihydroflavonol-astilbin. The modern pharmacological studies reveal the extract of RSG and its dominant constitute astilbin have so many bioactivities. Besides, RSG is a very cheap herbal medicine, its price in Guanzhou market is just around 10 HKD per kilogram. Thus, it is a promising herb (or foodstuff) with high research values.

However, there are also many problems remaining in RSG study. For instance, although there are a few reports on the determination of bioactive compounds in RSG, however, these reports just focus on flavonoids or only one compound determination. No general method for main bioactive compounds in RSG separation and determination has been developed. The *PPRC 2005* still has no fingerprint for RSG quality control. Although there are many papers studied the bioactivity of RSG, however, very litter work related to its chemical constituents. Thus, which compounds play the dominant role in the bioactivity of RSG still unknown. Polysaccharides play important role in bioactivity of herbs, however, no literature study about the polysaccharides in RSG. The reactive oxygen species are well known inducer of cellular and tissue pathogenesis leading to numerous disease states including cardiovascular disease, age-related degenerative conditions, cancer and other disease. RSG contains abundant flavonoid and phenolic acid, however, no literature about its antioxidant property was found. Thus, the researches about RSG on these directions should be further investigated.

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Dr. York Y. N. Chow, SBS JP
Secretary for Food & Health Bureau
19th Floor, Murray Building
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June 10 2008

Dear Dr. Chow,

Health Care Reform Consultation Document -- Your Health Your Life

The Pharmaceutical Society of Hong Kong (PSHK) would like to take this opportunity to congratulate the Bureau of kicking off the consultation on our future health care reform again in which it was stalled after the consultation paper "Building a Healthy Tomorrow" in 2005. We are in no way discouraging the Bureau to pursue this imminent reform but we do have reservation over the proposals & the consultation process logistics with such an emphasis on the financial aspect of the reform at this stage. The PSHK reckons that there is an imminent need to reform our current health care **delivery system** that is not catching up with the advancement and development in the health care arena occurring in the world in the past few decades.

The title of the consultation document this time is "Your Health Your Life" (the document). The Bureau did not hide away this time that the document only touches mainly on reform of the primary medical care sector. But we are not expecting the reform is fragmented and sectorial approach because it is about one's life. We need to address the change of the norm towards the meaning of health which everyone should take an active and responsible role on one's own health. **It is not about treatment alone.**

We are so concerned over such emphasis on medical care & financial reform it ends up with only cost-escalating and unaffordable health care services. In the document, the Government has not indicated whatsoever what Health Policy it holds. We would like to point out that "No one should be denied *adequate* healthcare through lack of means" is only a guiding principle. It cannot be replaced as a policy statement. Be it a national health system nor a private insurance system, the Government should direct the public discussion on what delivery system the society would opt for. Furthermore, the policy should also touch on the roles & responsibilities of each health care provider and the users. It should also govern how the government handles public health issues. Without such policy direction, we believe it is almost impossible to work out a true and sustainable reform on healthcare including health care financing.

If we don't have a Health Policy, how could we define adequate? How could both the public & private healthcare sectors plan for their service provision and business development? How we, as the public, know how much we should contribute? It is very obvious that no one can decide how to pay and what to pay for in such a black hole.

Poor healthcare manpower planning has been witnessed on and off and it is a barrier to the development & advancement of health care services and a waste of resources. Why does such vicious cycle revolving in the last 2 decades? The answer is simple. We don't have a Health Policy and all the expenses spent were piece-meal approach. Such deficiency further damages the already wobbling structure of allied health professionals hence affecting the overall health status of the public. One classic example is there are still many allied health professionals' qualifications are unregistered and the practice standards are unregulated.

Without a Health Policy, who would be the ultimate victim of it? The public at large has all along been the victim of such lack of policy and direction. Take a look at our current situation in air-pollution, nutrition labelling, undesirable medical advertisement, control of health products, **various dispensing standards** etc. Many laws & regulations are out-dated and could not meet the needs of the daily operation of a developed society. For instance, why pharmacists do not have Pharmacist Council to govern the standard and practice of the profession? Why the Pharmacy & Poisons Ordinance is still based on the one enacted in 1968 where in other advanced & well-developed countries the law has been thoroughly revamped at least once or twice to meet the health care system needs.

On health care financing, we were absolutely amazed by the figures and projections stated in the document. We did not quite apprehend how such estimates were projected. On one hand, the document claimed that we would be in big trouble if no supplementary health finance source being identified. But on the contrary, it did not mention at all whether the current expenditure was well spent or not? If the projection was based on something which is not cost-effective, the estimate could be far-fetched. It is historical that our health care system is far too relied on medical treatment. Such situation will only drives the health care cost escalating at a rate which could be out of control particularly in our situation where no health policy is in place.

From our point of views, **splitting up the dispensing and prescribing functions** by allowing 2 different professions to

perform has been proven a useful tool to monitor cost-effective use of drugs and enhance patient's safety in the use of drug. If such system tool does not build in to our future health care system, how could pharmacists agree with the risk pooling theory when such messy operation is not properly addressed? Before we can put our bet in any one of the finance options recommended in this consultation paper, being one of the health care providers, we want to know first the quality assurance mechanism and future service delivery model the government would endorse. Everyone wishes to know the price of the product before deciding to buy it or not.

Our government always prefers little intervention to the market and this worries us most. For health care, even one goes for a complete private market system the government must exercise its control in the accessibility, affordability and quality of all health services. This is particularly true to health insurance model. Otherwise, we will end up with the escalating cost like in the USA. **It is always the middle class who would suffer.** The under-privileged will be taken care of by the government though we don't know how adequately it is. The rich will not bother any way because they can afford it. Always it is the middle class who bears the bulk. And it will be even worst if voluntary insurance option is chosen.

The coverage on the actual reform on the current health care system is minimal except on primary medical care. The PSHK strongly believes that **Primary Medical Care DOES NOT EQUAL to Primary Health Care**. Over emphasis on primary medical care will neither decrease the health care cost, nor will it change the public norm towards health which they should take an active and responsible role on one's own health. How about the other health-related sectors? Does the document imply that they were perfect and reform was unnecessary? For example, the elderly care services provided by the old-aged homes. If all of them could provide an adequate health care standard that includes pharmaceutical care, the current hospital care cost could have been much lowered. We don't quite understand why this document did not mention a single word on allied health professions like pharmacists what they could contribute and provide and what assistance the government would give to develop pharmacist profession like the government proposed to pump in resources to develop Family Physicians? Should we continue this imbalance dependence on medical care, it would only drive up the health care cost up to a level which the insurance industry and the middle class may find it difficult to operate and to afford.

If the government really aims at identifying supplementary funding, we would propose such supplementary funding should be used in primary health care and public health.

To summarise, we, PSHK, would like to see the Bureau to address the following issues in the 2nd consultation document before addressing on the future healthcare finance crisis:

1. What is our Health Policy?
2. Where is the deficiency of our existing system that leads to the anticipated crisis due to aging population?
3. How does the Bureau address healthcare manpower planning?
4. What action plans does the Bureau have in promoting "Be responsible for your Own Health"?
5. Would the Bureau consider incorporating the tool of sharing the responsibility of dispensing and prescribing in the future delivery model?
6. When will our healthcare related out-dated Ordinances & Regulations be revamped as a whole?
7. What reform would the Government take in the provision of elderly care services particularly in old-aged home?
8. Will the government consider increasing the fees and charges of the public system as a source of supplementary fund?
9. What reform would the government take in the provision of safety net to the public?

We are absolutely uncomfortable with this document by being asked **to pay without knowing what we get.** Without such information, it is much better just to revamp the current fee charging of our health care system instead of creating a new supplementary source of health care revenue.

We look forward to seeing those questions mentioned above would be answered in the second consultation document.

Yours sincerely,

Mr Benjamin Kwong
President
The Pharmaceutical Society of Hong Kong

In response to "Healthcare Reform Consultation Document", The Society of Hospital Pharmacists of Hong Kong has the following recommendations:

1. Promoting Preventive Health

Community Pharmacists are a major form of healthcare resource. No other health professionals are so readily available and accessible in the community to help the citizens at large. At present, this kind of resource is underutilized. Pharmacists are in a good position to play an invaluable role in disease prevention through promotion of a healthy lifestyle; for example, conducting smoking cessation campaigns, and introducing blood pressure monitoring.

2. Addressing Primary Healthcare

Community Pharmacists are an untapped resource to facilitate delivery of an effective primary healthcare system. By providing free-of-charge medication review and patient counseling, they are able to minimize patients' medication-related problems and improve therapeutic outcomes. Also, patients having minor ailments can, instead of going to the already overburdened public hospital system, consult pharmacists in their communities for advice and treatment, if necessary, by appropriate over-the-counter medicines.

3. Visiting Old Age Homes

In addition, we recommend every Old Age Home should employ a pharmacist such as Visiting Pharmacist Officer to sort out the complex medication regimens (medication reconciliation) and to maintain updated drug records for elderly residents. Pharmacists should be the professional-in-charge of the drug distribution system in Old Age Homes, with the overall objective of ensuring medication safety and optimal patient care. Standard procedures for drug prescribing, dispensing and administration in Old Age Homes should be clearly defined, established and implemented.

4. Extending the Idea of "Money Follows Patient" to Drug Costs

One of the main reasons why many patients choose the public sector is because they can rely on the public system to provide them with almost free supply of drugs to meet their on-going needs of their chronic illness. Therefore, if the Government intends to introduce any form of subsidy for healthcare services with the aim to give patients more mobility between public and private sectors, such subsidies must cover the cost of drugs in order to have any realistic chance of success. In this way, patients do not need to return to the public system for the medical consultation – they can go to the private sector too if and only if their financial burden on medication costs are catered in the same way as provided by the existing public sector. Hence, the public sector would not be overburdened with the growing number of patients for almost free drug supply.

5. Providing More Information

Patient's choice is an important element in promoting responsible self-care. To empower patients in selecting suitable healthcare services, more disclosure on the qualification of doctors and treatment fees and charges should be encouraged. In particular, drug charges should be distinctly itemized in all medical consultation.

In Conclusion,

We think the Reform is necessary but it is not just about the financial side of the health care system, we need to review the health service structure, look at the possible service providers including doctors, pharmacists, nurses, allied health in both public and private sectors and what are the mechanisms to be put in place to monitor, support the on-going performance of these service providers in order that the public can believe that the Government has true intentions to improve the health system.

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Website: http://www.shphk.org.hk

Great News ....

Continuing Education Units (CEUs) for Authors of Articles in the HKPJ. At the most recent meeting of the Pharmacy Central Continuing-education Committee (PCCC), it was decided that CEU would be awarded to authors of articles published in the HKPJ. For each issue, the Editorial Committee, led by the Managing Editor, will choose an article from all the published articles in that issue, for PCCC to use for CE purposes. The author(s) is(are) responsible for setting questions for the approved CE article. Primary authors are entitled to receive 6 CEUs and other co-authors of the same CE article are entitled for 4 CEUs granted by PCCC. For details on how to get CEU, please refer to the article named "PCCC Continuing Education Units (CEU) Accrediting System" [HKPJ 2002;11(2):79-80] or visit the PCCC Website at www.pccchk.com

Great news to boost the professional standard and recognition of the contributions to the HKPJ!

淺談澳門藥政管理現狀

澳門藥劑師學會
梁國龍

澳門藥事法規背景

澳門從事藥物專業及藥業的活動受相關法令及技術性指示管制。根據現行九月十九日第58/90/M號法令，管制澳門從事藥物活動及專業的法例可以追溯至一九七〇年，而該法令是把當時在葡萄牙實施的原則及解決辦法實施於澳門。由於有關法令只提供了從事藥物活動及專業的大方向，有關技術細則、操作性的定義及補充細則等則由澳門特區衛生局局長透過頒佈技術性指示具體規範及提供相關指引。

澳門衛生系統工作中最重要的環節是要保障公眾的健康。基於此，澳門特區政府透過有關的法令及技術性指示，對澳門從事藥物業的活動及藥物專業的人士作出監管，貫徹保障公眾健康。

澳門藥物的分類

目前澳門西藥大致可分為三大類：包括只供醫院使用藥物(UH)，處方藥物(PMO)及非處方藥物(OTC)。對於所有分類屬處方的藥物，現行法令規定其外包裝上必須標識“PMO醫生處方藥物”的字樣，用以警惕藥房從業員在售賣此類藥物所承擔的法律責任以作為消費者在購買或使用此類藥物時的指引。OTC藥物可於藥房或藥行內自由銷售。除澳門醫院內，其他藥物業商號均不能供應UH藥物。

精神科及麻醉品藥物屬於處方藥物。由於成癮性高，因此有相關法令監管上述藥物的流通。現行七月十九日第34/99/M號法令規定，精神科及麻醉品藥物必須存放於上鎖櫃內，鑰匙只得由具良好品德及專業操守的人士保管。交易精神科及麻醉品藥物時，必須有正確、良好的記錄，保留有關處方，並需於每一季度將有關存貨餘量呈交澳門衛生局，減低不合法供應有關藥物的機會。

根據十一月十四日第53/94/M號法令的規定，中成藥及中藥材只可於獲澳門衛生局發准照的中藥房內出售。毒性及處方中藥材的分類則載於技術性指示第7/SS/2004號。

澳門流通藥物的質量保證

根據衛生局的統計資料，澳門市場上超過99%的藥物是進口藥物。透過由進口、批發、零售及醫療機構所組成的分銷網路供應予市民。藥房、藥行及中藥房為分銷網路的終點。

進口藥物必須在原產國或出口國獲註冊及獲准自由售賣的證明，即有關藥品已通過其他國家評審，其安全性、療效及質量得到基本保證才獲准進口澳門。持牌的藥物產品出入口及批發商號必須依法辦妥進口藥物程序，且獲衛生局預先許可後才可進口藥物供本地區銷售，藉此在源頭上保證了本澳流通藥物的安全性、療效及質量。

在現行九月十九日第58/90/M號法令下，藥物業商號只能透過獲發牌的藥物產品出入口及批發商號採購藥物，同一法令第四十六條明確禁止供應未獲衛生局預先許可進口、來源不合法的藥物；一旦有違反相關規定，衛生局將依法作出行政處罰，確保藥房出售藥物的來源及質量。

澳門衛生局透過定期及不定期的突擊稽查，檢查藥物的來源及質量。透過現行的藥物質量抽檢計劃，對澳門流通的藥物進行抽樣檢查，同時透過市民檢舉，跨部門的合作機制，以及其他國家發佈的藥物資訊等，多渠道收集有關藥物質量安全的訊息，一旦發現本市面上有質量低下的藥物，立即從市場上回收。

市民用藥安全保障

藉著依法管理、公眾監督及業界自律三管齊下的藥政管理方針，進一步完善本澳藥房的管理，確保藥物的質量及保障公眾用藥安全。

現行的法令規定，藥房內必須有藥劑師駐店提供技術指導，以確保市民用藥的安全。

衛生局及澳門藥劑師學會定期有展開加強安全用藥的宣傳教育工作，以提高市民對藥物安全的意識，遇有問題藥物可主動作出檢舉，發揮公眾監督的力量。再者，衛生局及藥劑師學會定期舉辦藥物知識講座，為藥業界舉辦培訓課程，以及定期制作及派發藥物的資訊，包括電視錄播、印製宣傳小冊子、在報章及健康雜誌內發放健康及用藥資訊等，向市民宣傳用藥知識，本澳的藥物監管及投訴/檢舉渠道等，以進一步加強藥物方面的宣傳教育。

澳門藥業將來的發展

隨著澳門藥業市場開放，將有更多藥房開設，澳門藥劑師未來有著持續的需求。藥劑師將抱負著提高本澳市民對藥物的基本安全及認識，減少本澳青年濫藥問題等社會責任，回饋社會，向澳門市民提供正確的專業用藥知識及觀念。同時，澳門藥政部門將完善化現行法令，堵塞法律漏洞，保障公眾健康。

ne Profession

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HONG KONG PHARMACY CONFERENCE

1-2 Nov 2008

Keynote address

Good Medicine - "The Holy Grail":
Finding innovative ways to team up and improve patient care
Dr. Bernard Kong *FRCP (Edin), FRCP (Glasg), FCCP, FHKCP, FHKAM*
Hong Kong Society of Medical Professionals

Theme Speech

Research involving physician/pharmacist collaboration:
Examples and keys to success
Prof Barry Carter *Pharm.D., FCCP, FAHA, BCPS*
Department of Family Medicine, University of Iowa

Education and Healthcare Reform
Prof Vincent Lee *Ph.D., D.Sc.*
School of Pharmacy, The Chinese University of Hong Kong

Generic Drug Substitution: Roles of Pharmacists
Dr Lawrence Yu *Ph.D.*
Food and Drug Administration

Geriatric Specialist Pharmacy Services in the US:
Roles of Pharmacists across Practice Setting
Dr Annie Lam *PharmD, CGP, FASCP*
Department of Pharmacy, University of Washington

The Role of Clinical Pharmacist in Paediatric and Neonatal Servicte
Prof Ian Wong *PhD, MRPharmS, ILTM(HE)*
School of Pharmacy, University of London

Lunch Symposiums & Concurrent Sessions
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- Pharmacogenomics
- Integrative medicines
- Clinical and community practice models and experience sharing
- Clinical pearls
- Generics approval

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Hong Kong Pharmacy Conference 2008 (1 Nov 2008 – 2 Nov 2008)
同一專業同一夢, 推進民康攜手創 One Profession, One Dream — Connect to Advance Health Care

Day 1 (1 Nov 2008)

1:00pm	Registration	
1:30pm – 2:30pm	Lunch	
2:00pm – 3:00pm	Pre-conference Symposium: **Value for Money – Issues around Selection of Antiviral Agents to Treat Chronic Hepatitis B (CHB) Patients by Dr. Hong Li** (sponsor: BMS)	
3:00pm – 3:30pm	Break, Poster and Exhibition	
3:30pm – 3:40pm	**Opening Ceremony** (Room 201)	
3:40pm – 3:50pm	**Welcome Speech by Conference Chairperson**	
Keynote Address 3:50pm – 4:10pm	**Dr. Bernard Kong** **Good Medicine - "The Holy Grail"** **Finding Innovative Ways to Team Up and Improve Patient Care**	
Theme 1 4:10pm – 4:55pm	**Prof. Barry Carter: Research Involving Physician/Pharmacist Collaboration: Examples and Keys to Success**	
4:55pm – 5:15pm	Break, Poster and Exhibition	
Concurrent Theme	**A** (Room 204 + 205)	B (Room 202 + 203)
Theme 2 5:15pm – 6:00pm	**Prof. Vincent Lee: Education and Healthcare Reform**	**Prof. Annie Lam: Geriatric Specialist Pharmacy Services in the US: Roles of Pharmacists across Practice Setting**
Theme 3 6:00pm – 6:45pm	**Dr. Lawrence Yu: Generic Drug Substitution: Roles of Pharmacists**	**Prof. Ian Wong: The Role of Clinical Pharmacist in Paediatric and Neonatal Service**
7:00pm – 10:30pm	Conference Dinner	

Day 2 (2 Nov 2008)

8:00am – 10:00am	Breakfast			
8:30am	Registration			
Concurrent session	**A** (Room 201A)	**B** (Room 204 + 205)	**C** (Room 202 + 203)	
Topics	**Risk Management**	**Clinical: Paediatrics**	**Generics**	
9:00am – 9:20am	**1: Ms. Anna Lee** Medication Safety in HA	**1: Dr. Penny North-Lewis** Paediatric Formulation in Clinical Practice	**1: Mr. Anthony Wong** Using Generic Products - A Perspective from Local Public Hospitals	
9:20am – 10:00am	**2: Dr. Tony Mak** Medication Incidents Resulted in Clinical Poisonings with Public Health Implications	**2: Prof. Ian Wong** Pharmacotherapy in Epileptic and Convulsive Disorders in Children	**2: Dr. Lawrence Yu** Myths and Facts of Generic Drugs	
10:00am – 10:40am	**3: Mr. Michael Ling** Connect to Advance Medication Safety – It's all about Saving Face	**3: Dr. Sara Arenas-Lopez** Drug Dosing in Children	**3: Ms. Audrey Shum** A Brief Guide to Patent Protection in Hong Kong and How it Impacts on the Operation of Pharmacies*	
10:40am – 11:00am	Break, Poster and Exhibition			
Topics	**Sports Medicines**	**Clinical: Geriatrics**	**BABE & EBM**	
11:00am – 11:40am	**4: Dr. Patrick Yung** Sports Injuries Medicine in Primary Healthcare Setting: What pharmacist can help?	**4: Dr. Paul Shea** Medicine in Elderly – Jekyll and Hyde	**4: Prof. Brian Tomlinson** Bioavailability & Bioequivalence Studies in HK - what do we look for?	
11:40am – 12:20pm	**5: Ms. Dora Chan** Pharmacy at the 2008 Olympic Equestrian Games Hong Kong	**5: Prof. Annie Lam** Practice Pearls and Suggestions to Enhance Hand-on Pharmaceutical Care Delivery to Older Adults	**5: Mr. Humphrey Cheng and Mr. Donald Chong** Evidence Based Medicine – the panacea to today's practice	
12:20 pm – 2:00 pm	Lunch & Symposium: **Recent Advances in Diabetes Management by Prof. Alice Kong** (sponsor: MSD)			
Concurrent session	**D** (Room 201A)	**E** (Room 204 + 205)	**F** (Room 202 + 203)	
Topics	**Genomics**	**Integrative Medicines**	**Practice Models / Experience sharing**	
2:00pm – 2:30pm	**1: Dr. Raymond Wong** Pharmacogenetics and Cancer Treatment	**1: Prof. Kelvin Chan** The worldwide development of Chinese medicine in pharmaceutical care	2:00pm – 2:40pm	**1: Prof. Barry Carter** Design of a Health Services Research Study: Important design features and measurement of covariables
2:30pm – 3:00pm	**2: Dr. Patrick Kwan** Genetic Polymorphisms and Efficacy and Safety of Antiepileptic Drugs	**2: Prof. Zhijun Yang** Dynamic Explanation on the Efficacy and Quality of Herb (Chinese Medicine)	2:40pm – 3:00pm	**2: Dr. Wilson Leung** Disease Management in Patients with Type 2 Diabetic Nephropathy – Pharmacist in a Multi-disciplinary Team
3:00pm – 3:30pm	**3: Prof. Joyce You** Clinical Translation of Pharmacogenomics in Anticoagulation Therapy	**3: Prof. Leung Ping Chung** Diabetic Foot Problems – From Standard care to Complementary / Alternative Management	3:00pm – 3:20pm	**3: Mr. Simon So** Specialised Pharmacy Services for Chronic Kidney Disease (CKD) patients: Concept, Design and Experience
3:30pm – 4:00pm	**4: Dr. Siu Wah Tang** Personalized Medicine in Psychiatry	**4: Prof. Joan Zuo** Potential Interaction of Oseltamivir and Chinese Medicine Formulae – Preliminary Investigation in Rats	2:40pm – 3:00pm	**4: Mr. Maxwell Yung** Public Relationship Survey: A Community Pharmacy Based Customer Survey*
			3:40pm – 4:00pm	**5: Mr. Philip Chiu** Image Building for Community Pharmacist*
Evaluation Forms Collection				

Note: Except those marked with asterisk will be delivered in Cantonese, all the presentations will be delivered in English with instant Putonghua translation.*

NEW PRODUCTS

Rasilez
(Novartis)

Active ingredient:
Aliskiren

Presentation:
Available in 150mg and 300mg film-coated tablets

Pharmacological Properties:
Rasilez is an orally active, non-peptide, potent and selective direct inhibitor of human renin. It acts on the RAS by binding to the enzyme rennin, thereby preventing conversion of angiotensinogen to angiotensin I. In this way, it decreases plasma renin activity and levels of angiotensin I and angiotensin II.

Indications:
Treatment of Essential Hypertension

Dosage and Administration:
The recommended starting dose of Rasilez is 150mg once daily. In patients whose blood pressure is not adequately controlled, the dose may be increased to 300mg once daily. It may be used alone or in combination with other antihypertensive agents.

Contraindications:
Hypersensitivity to the active substance or any of the excipients.

Precautions:
Sodium and/or volume-depleted patients
In patients with marked volume depletion and/or massive salt depletion (e.g. those receiving high doses of diuretics) symptomatic hypotension may occur after initiation of treatment with Rasilez. These conditions should therefore be corrected prior to administration.
Renal Impairment
Caution should be exercised when using Rasilez in hypertensive patients with severe renal impairment due to the limited availability of safety information.

Interactions:
Aliskiren has a low potential for interactions with other medicinal products and does not inhibit CYP450 isoenzymes (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A) nor does it induce CYP3A4. It is minimally metabolised by the cytochrome P450 enzymes. The effect of furosemide is reduced therefore it is necessary monitor the effect when initiating therapy and if necessary to adjust the dosage of furosemide to avoid possible underdosage. Co-administration with Ketoconazole increased the plasma levels of Aliskiren by 1.8 fold.

Side Effects:
Common adverse effect was diarrhoea.
Allergic reaction particularly difficulty in breathing or swallowing, or swelling of the face, extremities, eyes, lips or tongue, patients should discontinue treatment and contact their physician.

Forensic Classification:
$P_1S_1S_3$

Myozyme
(Genzyme)

Active Ingredient:
Alglucosidase alfa

Presentation:
Supplied in 50mg vials as a sterile, nonpyrogenic, white to off-white lyophilised cake or powder.

Pharmacological Properties:
Myozyme provides an exogenous source of acid a-glucosidase (GAA). Binding to mannose-6-phosphate receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule, after which it is internalised and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen.

Indications:
Myozyme is indicated for use in patients with Pompe disease an inherited disorder of glycogen metabolism caused by the absence or marked deficiency of the lysosomal enzyme GAA. Myozyme has been shown to improve ventilator-free survival in patients with infantile-onset Pompe disease as compared to an untreated historical control, whereas use in patients with other forms of Pompe disease has not been adequately studied to assure safety and efficacy.

Dosage and Administration:
The recommended dosage regimen is 20mg/kg body weight administered every 2 weeks as an intravenous infusion over approximately 4 hours. Infusion should be administered in a step-wise manner using an infusion pump. The initial infusion rate should be no more than 1mg/kg/hr and may be increased by 2mg/kg/hr every 30mins, after patient tolerance is established until a maximum rate of 7mg/kg/hr is reached.

Precautions:
Patients with an acute underlying illness at the time of Myozyme infusion appear to be at greater risk for infusion reactions. Careful consideration should be given to the patient's clinical status prior to administration.

Contraindications:
None Known

Drug Interactions:
No drug interaction studies have been performed.

Side Effects:
Pyrexia, respiratory distress, respiratory failure, rhinorrhea, tachypnea, pneumonia, otitis media, upper respiratory tract infection, gastroenteritis, pharyngitis, ear infection, oral candidiasis, catheter related infection, bronchiolitis, nasopharyngitis, diarrhoea, vomiting, gastroesophageal reflux disease, constipation, rash, urticaria, diaper dermatitis, tachycardia, bradycardia, post procedural pain, anaemia and flushing

Forensic Classification:
$P_1S_1S_3$

NEW INDICATIONS

Humira
(Abbott)

Active ingredient:
Adalimumab

Presentation:
Each single use pre-filled syringe contains 40 mg Adalimumab per 0.8mL

Pharmacological Properties:
Humira is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab binds specifically to tumor necrosis factor (TNF) and neutralizes its biological function by blocking its interaction with the p55 and p75 cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Adalimumab also induces changes in the levels of adhesion molecules responsible for leukocyte migration.

Indications:
Humira is indicated for treatment of severe, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. For induction treatment, HUMIRA should be given in combination with corticosteroids. HUMIRA can be given as monotherapy in case of intolerance to corticosteroids or when continued treatment with corticosteroids is inappropriate.

Dosage and Administration:
The recommended Humira induction dose regimen for adult patients with severe Crohn's disease is 80mg at week 0 followed by 40mg at week 2. In case there is a need for a more rapid response to therapy, the regimen 160mg at week 0 (dose can be administered as four injections in one day or as two injections per day for two consecutive days), 80 mg at week 2, can be used with the awareness that the risk for adverse events is higher during induction. After induction treatment, the recommended dose is 40mg every other week via subcutaneous injection. Alternatively, if a patient has stopped HUMIRA and signs and symptoms of disease recur. HUMIRA may be re-administered.

Forensic Classification:
$P_1S_1S_3$

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Because it provides well-proven CV mortality and morbidity data[1,2,3]

Because it gets 90% of patients to NCEP LDL-C goal[4]

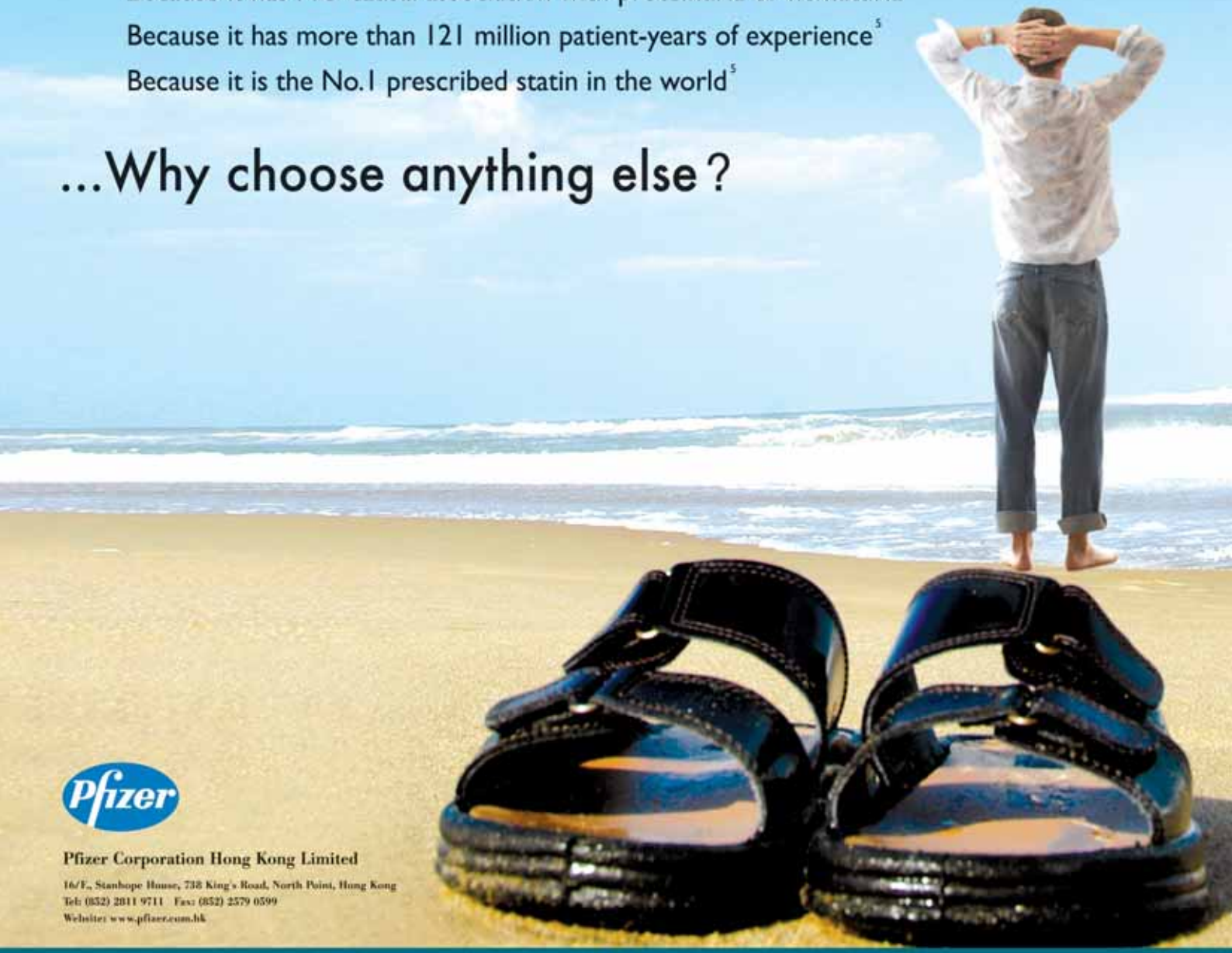
Because it allows you to choose the appropriate start dose (10, 20 and 40mg) to meet your patients' needs[4]

Because it has NO causal association with proteinuria or hematuria[4]

Because it has more than 121 million patient-years of experience[5]

Because it is the No.1 prescribed statin in the world[5]

...Why choose anything else?



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