

HONG KONG PHARMACEUTICAL *JOURNAL*

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News & Short Communications

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The 60th Anniversary Lecture & Dinner of the Pharmaceutical Society of Hong Kong – From Today Onwards

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Reference: 1. Seroquel XR Package Insert Version: Feb 2008.

www.SEROQUEL.info

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

Comments on any aspects of the profession are also welcome as Letter 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:

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For detail instructions for authors, please refer to the first issue of each volume of HKPJ.

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A Journey of Ten Thousand Miles Begins with a Single Step



In the year 2009, many things relevant to the pharmaceutical profession have happened in Hong Kong. All the things that happened, whether good or bad, were due to a decision or action taken or not taken at a critical moment. It is just like a journey of ten thousand miles that begins with a single step but may end up with different consequences.

The year 2009 marked the 60th anniversary commemorating the founding of the Pharmaceutical Society of Hong Kong (PSHK). The society was formed sixty years ago because a group of enthusiastic pharmacists who had professionalism in mind and wanted to excel in their practice. A memorial booklet was published and a series of seminars followed by a banquet that was held on October 31 at the Hong Kong Jockey Club on Hong Kong Island. On that day, pharmaceutical professionals across Hong Kong gathered together to celebrate and to recapture some of the achievements. As recalled by Mary Cheng, over 200 people turned up to celebrate this big occasion. Her report together with a few representative photos gives us a glimpse of some important moments of the celebration (p157).

During the celebration, Mr. Benjamin KWONG, the President of the Pharmaceutical Society, remarked that from today onwards, PSHK would like to see the development of specialized practices of clinical pharmacy in hospitals; penetration of the overseas markets by the local manufacturing industry; more research activities for better and innovative modalities; the expansion of the roles of pharmacists in the society and the revamping of some out-dated Ordinances and Regulations to meet the needs of society.⁽¹⁾ All these wishes can not be fulfilled if the role of prescription and the role of manufacturing and dispensing are not separated. If our healthcare system remains unchanged while all nearby countries and cities have implemented a more professional practice with regard to healthcare, we will be left behind in a manner similar to some other developments for Hong Kong.

On the other hand, the implementation of professional practices requires good education, training and environment. The report by Cheung et al on the centennial development and evolution of the National Defense Medical Center is a good story about how this goal could be met (p.131). Advancement and modernization require a stable environment, a good education system, a prophetic view and a determined mind. Before 1997, Hong Kong people always thought that they have advantages over the mainland China and could help the motherland with their high standard of manpower and management after the return of sovereignty of the territory to the China. However, it turns out to be not the case. Certainly we still have a better system in certain areas, such as the financial sector, but not many matter in the area of high technology, manpower supply and even research, Hong Kong is losing her competitive ground day by day. On the contrary, we have to rely on the supply of high calibre manpower from mainland China. If you calculate the number of good research papers published in recent years, non-local people have been getting a larger share of the contributions. It is an alarming signal for Hong Kong people. Some of our leaders, perhaps, should bear the responsibilities for the consequences of the current situation because they only know how to follow the roadmaps of other countries but don't know what the best solution is for our society; while others may be selfish or short-sighted.

Even in the tertiary education sector, our education is sick. The increasing numbers of accidents in healthcare sectors more recently indicate that the contemporary approach of trainings, in particular the problem-base learning commonly adopted in the last two decades for our younger generation, may be inappropriate at the bachelor level. We have produced more first-class honours students but with lower ability in order to seize a small pool of the research quota. We can not blame our students because it is not their fault. But being an educator and administrator, we do have to ponder whether it is right. We dare not ask the student to repeat a course because we are afraid a bad teaching evaluation may be given to us. We reduce the teaching materials or lower the standard in order to please them. Although the arrival of the digital era suggests that the young generations can have more channels to acquire new knowledge,⁽²⁾ it doesn't mean

that traditional ways of teaching should be replaced. In fact, digitized information could be wrong and unreliable as exemplified by a recent accident that took place in many monographs of the USP (p128). Consequently, an urgent recall of the latest edition had to be announced.

Furthermore, the majority of young people require a systematic and complete training. Conveying a complete but not fragmented knowledge before asking them to do critical thinking and show flexible use of knowledge is necessary and a better approach. It is also the educator's responsibilities to give proper advices, guidance or even implement disciplinary action so that students can become a top class citizen. Unfortunately, we haven't treasured this big pool of assets for our future society.

We are glad, in some ways, to learn that besides the Chinese University of Hong Kong, another local University has recently offered similar courses of pharmacy training. An interview about this new course with Professor Vanhoutte, who is the Head of this new degree programme, can be found in p137. The launch of this new degree programme signifies that young people in our society will have more opportunities to be trained as a pharmacist. However, before it is fully implemented, it is necessary to ask what sort of professional needs in pharmaceutical field are urgently required by the community. Do we really need so many clinical pharmacists in hospital? Is the Health Authority prepared to absorb them after their graduation? Is undergraduate training conformed to the current trend of training for a clinical pharmacist in other advanced country? When are we going to have the separation of prescription and dispensing roles between different healthcare professionals? Without any idea or answer for these questions, it is not really a blessing for the pharmacy profession.

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Cheung Hon-Young
 Editor-in-Chief
 28th January, 2010

Chief Executive's Commendation for Community Service

Date: July 1, 2009

Ms. Dora Chan had been commended by the Chief Executive of HKSAR for Community Service. The Honour List was issued on 1 July 2009. Ms Dora Chan is a pharmacist of the Hospital Authority participated in coordinating the pharmaceutical service for the 2008 Olympic Equestrian Events in Hong Kong. She has successfully established a safe drug dispensing service to safeguard the unintentional use of prohibited drugs by our elite athletes and bring together the pharmacy profession to support, contribute and devote to

the Event. During the Olympic period, she has contributed two articles, "Hong Kong Olympic pharmacy jumps into the final leg of preparation" and "Pharmacy services at the Beijing 2008 Olympic and Paralympic Games" to the renowned British Pharmaceutical Journal. Attached is a photograph of her taken with the Chief Executive and below is the link where her name is listed.

Source: <http://www.info.gov.hk/gia/general/200907/01/P200906300316.htm>



(photo of Ms Dora Chan receiving the award on July 1, 2009)

Miss Janet Wong Wing-Chen Assumed the Post of Commissioner for Innovation and Technology from 14 September

Date: September 14, 2009

Miss Janet Wong Wing-Chen was appointed Commissioner for Innovation and Technology (CIT), with effect 14 September, succeeding Mr. Eddy Chan who retired after 32 years' service in the Government. Miss Wong joined the Civil Service as an Administrative Officer in 1980. Over the years Miss Wong has worked in various Government bureaux

and departments including the Civil Service Branch, Food & Environmental Hygiene Department and Home Affairs Department. She headed the World Trade Organisation Sixth Ministerial Conference Co-ordination Office in 2004 and was Deputy Secretary (Works) in the Development Bureau

before joining the Innovation and Technology Commission (ITC).

Miss Wong will lead ITC in promoting innovation and technology development and ensuring Hong Kong stays ahead as a knowledge-based economy.

Source: Hong Kong Government SAR, China

FDA Issues Proposed Rule on CGMPs for Combination Drug Products

Date: October 1, 2009

The US Food and Drug Administration issued a proposed rule to clarify the current good manufacturing practice (CGMP) requirements applicable to combination products in the Sept. 23, 2009, *Federal Register*. The proposed rule is meant to set forth "a transparent and streamlined regulatory framework for firms to use when demonstrating compliance with CGMP requirements for 'single-entity' and 'co-packaged' combination products," according to the notice.

21 CFR Part 3 defines a combination product as "any combination of a drug and a device; a device and a biological product; a biological product and a drug; or a drug, a device, and a biological product." Approximately 300 manufacturers of combination products will be affected by the proposed rule, says the notice.

"FDA believes that the absence

of clear CGMP requirements for combination products could result in inconsistent or differing application of the various CGMP requirements applicable to the constituent parts, which could affect product safety and the public health," says the notice. According to the proposed rule, combination-product manufacturers would be able to demonstrate compliance with either 1: "the specifics of all CGMP regulations applicable to each of the constituent parts included in the combination product containing," or 2: "the specifics of either the drug or the [quality system] regulation, rather than both, when the combination contains both a drug and a device, under certain conditions."

There are many specific proposals included in the proposed rule depending on the type of combination product manufactured. Of note, the fact that many facilities may be involved in the

manufacture of a combination product, "raises questions about whether and when the proposed streamlined approach to CGMP operating systems could be used," says the notice. The proposed rule would "make clear that when manufacturing of a constituent part does not occur at the same facility as another type of constituent part, the operating system must be shown to comply with all of the CGMP regulations applicable to that constituent part." In the same regard, when two or more types of constituent parts are in the same facility, a streamlined approach may be used, and when "manufacture of a constituent part occurs at a separate facility from all other types of constituent parts, the manufacture of that part must occur under the regulations applicable to that part," says the notice.

Source: <http://www.regulations.gov/search/regs/home.html#documentdetail?r=0900006480a29c7a>

China Launches Biotech VCs, New Tech Stock Market

Date: October 30, 2009

One of China's key economic development groups has spawned 20 new venture capital funds to invest in the country's high tech sector--with biotechnology as a prime focus. The National Reform and Development Commission says the new VC groups will operate in partnership with seven provincial governments.

way soon. The commission's release indicated that these seven provincial governments--Beijing, Jilin, Shanghai, Anhui, Hunan, Chongqing, and Shenzhen--were just the 'first batch' to be selected. The commission did not reveal exactly how much money was involved in each of the new funds.

funds for small and medium-sized tech companies--much like Nasdaq--got started today. All 28 of the tech companies listed saw their share prices soar. And it's a likely spot for the country's emerging biotech companies to make a play in.

Source: <http://www.fiercebiotech.com/story/china-launches-biotech-vc-new-tech-stock-market/>

And more money may be on the

stock market intended to help raise

Tripartite Cooperation in Focus

Date: November 13, 2009

Key officials and experts from Guangdong, Hong Kong and Macao have agreed to step up cooperation and exchanges, and to refine the notification system, to tackle the spread of infectious diseases among the three places. Consensus in this regard was reached at the two-day meeting, the Ninth Tripartite Meeting of Guangdong, Hong Kong and Macao on the Prevention and Control of Communicable Diseases, which ended in Zhuhai today (November 13).

Members discussed in detail contingency plans for public health emergencies such as outbreaks of Influenza A (H1N1) (human swine influenza (HSI)) and other major infectious diseases.

Members signed a memorandum of understanding on cooperation on

HSI prevention was signed and a list of experts on prevention and treatment of HSI was finalized. The new team constituted a cooperation mechanism for prevention and control of HSI.

The following points were agreed: (1) to continue strengthening the response system to for public health incidents and major infectious diseases by implementing the agreement of cooperation on emergency public health incidents in the three places; (2) to continue stepping up communication and cooperation in the preparedness for influenza pandemic to reduce as far as practicable the health, social and economic impacts in case of an influenza pandemic; (3) to continue improving the notification mechanism; (4) to continue cooperation on visits and training of healthcare professionals in surveillance

and outbreak investigations, contingency management, clinical epidemiology, laboratory tests and infection control management; (5) to foster co-operation in scientific researches, including AIDS, influenza and human avian influenza and cooperation on microbial resistance research.

In-depth discussions on a number of public health issues of mutual concern including preparedness for HSI, latest developments in respect of infectious diseases, surveillance and control of major communicable diseases, prevention of enterovirus infection, research on microbial resistance and future directions of infectious diseases prevention and treatment were covered.

Source: Department of Health, Hong Kong Government, SAR

Online Newsletter on Drug Safety News Available Now

Date: December 5, 2009

A drug news bulletin makes its debut online to update healthcare professionals and pharmaceutical traders with drug safety information. The newsletter, entitled "Drug News", is issued by the Pharmaceutical Service of the Department of Health monthly to provide a summary of local and overseas drug safety news. Health professionals

and drug traders can make use of the information and provide corresponding advice and therapeutic measures to patients and customers.

The first issue of "Drug News" highlights drug safety information from overseas drug authorities, recent drug recall, warnings about slimming products

with undeclared drug ingredients as well as medical advice on stopping products containing undeclared steroid.

It is now available at the website of Pharmaceutical Service (<http://www.psdh.gov.hk/eps/DrugNews>).

Source: Department of Health, Hong Kong Government, SAR

Top 10 Layoffs of International Pharmaceutical Companies in 2009

Date: December 9, 2009

With three mega-mergers in 2009, this was a particularly brutal year for job cuts in the pharmaceutical industries of USA. Not surprisingly, Pfizer (which purchased Wyeth for \$68 billion) and Merck (the new owner of Schering-Plough) came out on top of the list, as the drugmakers work to streamline operations and eliminate redundancies. Noticeably absent from this list are Roche and Genentech, which have yet to formally announce any cuts from their joining.

Figuring heavily in many of these companies cuts is the impending patent cliff, which will see some of the industry's most profitable drugs go off patent in the next few years. That's contributed

heavily to a reduction in sales reps jobs, which have disappeared at an alarming rate this year.

The layoffs outlined here are, of course, just the tip of the iceberg. According to staffing firm Challenger, Gray and Christmas, 58,696 pharmaceutical and biotech jobs have been cut through the end of October of this year. That's 15,000 more jobs lost than in all of 2008. The following table shows the figure of layoffs in each drug company in 2009:

1. Pfizer - 19,500
2. Merck - 16,000
3. Johnson & Johnson - 8,900

4. AstraZeneca - 7,400
5. GlaxoSmithKline - 6,000
6. Eli Lilly - 5,500
7. Teva Industries - 1,090
8. Sepracor - 940
9. King Pharmaceuticals - 770
10. Sanofi-Aventis - 750



Source: <http://www.fiercepharma.com>

Man Arrested for Selling Slimming Product with Undeclared Drugs on the Internet

Date: December 16, 2009

A 27-year-old man was arrested for selling a slimming product with undeclared western drug ingredients. The product concerned, which was called "Slimming Beauty", was obtained from an Internet auction website during a surveillance operation.

The department had already issued a warning earlier to remind people not to take the product as laboratory tests on the product showed the presence

of sibutramine and phenolphthalein. The former was a Western medicine used as an appetite suppressant. Its side effects include increased blood pressure and heart rate, psychosis and possibly convulsion. People with heart problems should not take it. The latter was once used for treating constipation but has been banned for its cancer-causing effect.

Any product containing sibutramine

must be registered before it can be sold in Hong Kong. It can only be sold on a doctor's prescription and dispensed under the supervision of a pharmacist. Sale of unregistered pharmaceutical products is an offence under the Pharmacy and Poisons Ordinance. The maximum penalty is a fine of \$100,000 and two years' imprisonment.

Source: Department of Health, Hong Kong Government, SAR

Human Swine Influenza Vaccination Programme Launched

Date: December 21, 2009

The Controller of the Centre for Health Protection (CHP) of the Department of Health (DH), called on parents to take their children aged between six months and less than six years to get vaccinated, joining other target groups. Under the HSI Vaccination Programme, five target groups making up a total of

two million people can receive free or subsidised vaccination on a voluntary basis. They are: healthcare workers; persons with chronic illnesses and pregnant women; children between the age of six months and less than six years; elderly persons aged 65 years or above; and pig farmers and pig-

slaughtering industry personnel. The vaccinations will be given at hospitals, clinics and health centres of the DH and the Hospital Authority (HA) free of charge from December 28 onwards.

Source: Department of Health, Hong Kong Government, SAR

MedImmune Recalls 4.7M Doses of H1N1 Vaccine

Date: December 23, 2009

AstraZeneca's MedImmune unit announced a recall of 4.7 million doses of its nasal spray

version of the swine flu vaccine because tests showed a decline in potency.

Source: <http://www.fiercepharma.com/story/medimmune-recalls-4-7m-doses-h1n1-vaccine/>

Report of the Review Committee on Regulation of Pharmaceutical Products in Hong Kong

Date: December 31, 2009

In early 2009, a number of incidents concerning pharmaceutical products in Hong Kong had caused public concerns on drug safety. A Review Committee on the Regulation of Pharmaceutical Products chaired by the Permanent Secretary for Health with members from the pharmaceutical sector, medical profession, academia, patient groups and consumer representative was thus set up on 24 March 2009. The Review Committee evaluated the existing system for the regulation of pharmaceutical products (western medicines) to find out longer term measures to prevent concerned incidents in the future.

The review completed and a report dated December 2009 was released

to public in early January 2010. The Review Committee has made a total of 75 recommendations covering the following areas:

- Regulation of Drug Manufacturers
- Pre-market Control of Drugs
- Regulation of Importers/Exporters and Wholesalers
- Regulation of Retailers
- Regulation of Drug Procurement
- Pharmacovigilance
- Risk Communication
- Penalty System
- Manpower Requirements

The Government has accepted all the recommendations. In particular, the establishment of a dedicated office

on drugs and the raising of Hong Kong's GMP licensing standards to PIC/S standards will become major milestones in the enhancement of Hong Kong's drug safety standard. The next step is for the Government to implement the recommendations with the pharmaceutical sector.

The full report can be obtained at http://www.fhb.gov.hk/en/press_and_publications/otherinfo/100105_pharm_review/index.html.

Source: "Report of the Review Committee on Regulation of Pharmaceutical Products in Hong Kong", Food and Health Bureau, December 2009

USP Recalls Latest Monographs

Date: January 12, 2009

The US Pharmacopeial Convention (USP) is recalling *USP 33-NF 28* which official date to go into effect is May 1, 2010. According to an USP press release on January 8, 2010, multiple monograph errors have been spotted in the publication when it was converted into a new format and published on November 1, 2009.

Today the Convention further explains that USP's errata process for issuing corrections to *USP-NF* on an ongoing basis is inefficient for the current problem, thus necessitating the recall of *USP 33-NF 28* in its entirety. In the interim, *USP 32-NF 27* remains official, and ***USP 33-NF 28 is not official and should not be used.***

Other official texts related to the recalled publication remain available

and may be used with confidence, including the *USP Dietary Supplement Compendium Food Chemicals Codex*, Sixth Edition, and its supplements; *USP Pharmacists' Pharmacopeia*, Second Edition, and its supplements; and the *2009 USP Dictionary*. In addition, Accelerated Revisions posted on the New Official Text section of the USP website are not affected by the recall and are official as of the dates indicated on *the website*.

USP will reissue the online and CD versions of *USP 33-NF 28* in March 2010 with an official date six months after reissue. Only new and revised monographs available since the *Second Supplement* to *USP 32-NF 27* will be in the redesigned format. The convention will also reissue a print volume of new and revised monographs

and other official text available since the *Second Supplement* to *USP 32-NF 27*. The monographs will appear in the redesigned format. This smaller volume, combined with official text in *USP 32-NF 27* and its supplements without redesign will serve as the print version of *USP 33-NF 28*. Its official date will be the same as the official date of the electronic versions. Finally, USP will release the first supplement to *USP 33-NF 28* at the same time as the reissued *USP 33-NF 28* and with the same official date.

Until the publication and its related supplements are reissued, says USP, industry should continue to use USP 32- NF 27, which remains official.

Source: <http://www.usp.org/USPNF/recall.html>

Publicly Funded Healthcare Programs in the United States of America and the United Kingdom

CHU, Wai Shun Wilson

Pharmacist, United Christian Hospital

ABSTRACT

Both Medicare in the United States and National Health Scheme (NHS) in the United Kingdom are publicly funded health insurance programs. The former is available for citizen aged 65 or above, younger people with disabilities and people with End Stage Renal Disease; while the latter is a nationwide healthcare system for all citizens. These two healthcare systems have their advantages and disadvantages. This article explains how they serve those needed people in these two countries.

Keywords: Public healthcare; Health insurance; USA; UK; Social Security; Medicare; NHS

INTRODUCTION

Both Medicare in the United States and National Health Scheme (NHS) in the United Kingdom are publicly funded health insurance programs. The former is available for citizen aged 65 or above, younger people with disabilities and people with End Stage Renal Disease while the latter is a nationwide healthcare system for all citizens.

Medicare in the United States is a publicly funded health insurance program. It is available for citizen aged 65 or above, younger people with disabilities, and people with End Stage Renal Disease. It is a healthcare program designed to take care of the needy people. People under 65 and the disable covered by this scheme must be receiving disability benefits from either Social Security or the Railroad Retirement Board for at least 24 months before automatic enrollment.

The "Original Medicare" program comprises of two parts: Part A (Hospital

Insurance), and Part B (Medical Insurance). Neither Part A nor Part B pays for all the medical costs. The program contains premiums, deductibles and co-pays (payments due from the covered individual). Only a few special cases exist where prescription drugs are covered by Original Medicare. But as of January 2006, Medicare Part D provides more comprehensive drug coverage. Medicare Advantage plans are another way for beneficiaries to receive their Part A, B and D benefits. At the moment of writing this article, part D has not been activated.

MEDICARE, HOW IT WORKS?

Medicare is partially financed by payroll taxes imposed by the Federal Insurance Contributions Act (FICA) and the Self-Employment Contributions Act of 1954. In the case of employees, the tax is equal to 2.9% (1.45% withheld from the worker and a matching 1.45% paid by the employer) of the wages, salaries and other compensation in connection with employment. The Part A premium is \$216 - \$393 per month. Part B premium is \$88.50 per month.

Part A: Hospital Insurance

Part A covers hospital stays. Medicare Part A coverage is tied to a benefit period of 60 days for a spell of illness. A spell of illness benefit period commences on the first day of your stay in a hospital or in a skilled nursing facility and continues until 60 consecutive days have lapsed and you have received no skilled care. After 60 days, beneficiaries are responsible for coinsurance costs. In 2006, beneficiaries must pay \$238/day (up from \$228/day in 2005).

Part B: Medical Insurance

Part B helps cover doctors' services, outpatient hospital care, and some other medical services that Part A does not cover, such as durable medical equipment (DME). Medicare's DME coverage included payment for canes, walkers, wheelchairs, and mobility scooters for those with mobility impairments, depending on medical necessity. Part B is optional coverage and may be deferred if the beneficiary or their spouse is still actively working. There is a lifetime penalty (10% per year) imposed for not taking Part B if not actively working.

Part C: Medicare Advantage plans

For the last 20 years, the Federal government has offered Medicare beneficiaries the option to receive their Medicare benefit through private health insurance plans, instead of receiving it from the Original Medicare plan (Part A and Part B). At one time the Medicare program called these Medicare + Choice plans, but they have often been colloquially referred to as Part C. In 2003, under the Medicare Prescription Drug, Improvement, and Modernization Act, Medicare Advantage became the new name for Medicare + Choice plans. In addition to offering comparable coverage to Part A and Part B, Medicare Advantage plans may also offer Part D coverage.

Part D: Prescription Drug plans

Medicare Part D went into effect on January 1, 2006. Anyone with Part A or B is eligible for Part D. In order to receive this benefit, a person with Medicare must enroll in a stand-alone Prescription Drug Plan (PDP) or Medicare Advantage plan with prescription drug coverage (MA-PD). These plans are approved and regulated by the Medicare program, but are actually administered by private health insurance companies.

PROS AND CONS OF THE MEDICARE

When Medicare was created in 1965 over 50% of everyone 65 or older had no health insurance while private insurance at that time failed to meet their needs. Medicare is a success. It increased the number of insured older adults to 95%. In 1972 Medicare coverage was extended to people with significant disabilities. But Medicare's success in providing access to health care for millions of people faces continuing financing issues. In its annual report to Congress, the Medicare Board of Trustees stated that the program's hospital insurance trust fund could run out of money before the end of the next decade. Part of the cost of Medicare is fraud, which Medicare estimates costs it billions of dollars a year. In addition, the threat comes from private insurance plans. Funded by taxpayer dollars, privatization is jeopardizing the cost-effective, dependable Medicare program. Since 2003 the number and costs of private Medicare plans have increased exponentially as a result of the design of Medicare Part D and "Medicare Advantage". Medicare privatization costs taxpayers approximately \$15 billion a year, while it hurts many people with Medicare and strangles the traditional Medicare program. On 15 Dec 2009, after meeting with Senate Democrats at the White House in an effort to cement support for his top domestic priority, President Obama said that they were on the verge of passing historic legislation to overhaul the U.S. health care system. The reform may expand coverage with a new requirement for nearly everyone to purchase health insurance, and ban industry practices such as denying coverage on the basis of pre-existing medical conditions. Obama also has urged Congress to slow the growth in health care spending nationally. The biggest problem Washington faces in the future is the hugely growing cost of Social Security, Medicare and Medicaid. We will see how the Healthcare system will be reformed in the near future.

NATIONAL HEALTH SCHEME (NHS) IN THE UK

The NHS in England was set up in 1948. It is changing the way it works to make sure patients always come first, but still need improvements to cope with the demands of the 21st century. NHS is a system which require tax payer to pay certain amount of contributions and in return, citizens are obligated to receive free family General Practitioners (GP), dentists (primary) and hospital (secondary) care. In order to avoid getting too complicated, in general, the National Insurance Contributions rates are 11%. For further information, you may visit the related web site - <http://www.hmrc.gov.uk/rates/nic.htm>

The plan does not include prescription charges. Prescription fee is around £6 (HK\$80) per item.

Advantages of NHS:

1. Patients are making choices about when and where to be treated. They can choose the hospital or place of treatment which is right for them, whether that's the hospital nearest to where they live or the one with the shortest waiting list. Perhaps the one with the most appropriate specialists or the one which has the best patient feedback.
2. Patients are able to manage their own symptoms and medications more effectively.
3. Patients are making decisions about local services through Patient Forums and Foundation Trusts.
4. They are being asked for their views routinely and listened to, as part of every Trust's (hospitals) effort to achieve the best performance ratings. Patients can find detailed local information on the performance of every Trust through www.nhs.uk
5. Primary care services: Primary care is the first point of contact most people have with the NHS and is delivered by a wide range of professionals, including family GPs, nurses, dentists, pharmacists and opticians.

Disadvantages of NHS:

1. The NHS is a politically controlled state monopoly, free at the point of use, funded out of tax, and almost identical to the old health services in the former communist countries of Eastern Europe.
2. High tax:

Taxable Bands in the UK:		
Taxable Bands Allowances	2005-06 (£)	2006-07 (£)
Starting rate 10%	0 - 2,090	0 - 2,150
Basic rate 22%	2,091 - 32,400	2,151 - 33,300
Higher rate 40%	Over 32,400	over 33,300

Reference: HM Revenue & Customs, England (2007)

The NHS tax (National Insurance NI) is 11% on top of your basic tax. For example, if you are single and under 65 and if your annual salary is £30,000 (~HK\$360,000 per year = HK\$30,000 per month). Your Personal allowance will be £5,035. Therefore your taxable income will be about £25,000. Your basic tax will be 22% + 11% (NI) = 33%. Your annual tax will be £8250 (~HK\$ 100,000) per year!

CONCLUSION

This article reviewed the Medicare healthcare system in the US and the National Health Scheme (NHS) in the UK. Both systems have advantages and disadvantages. As a healthcare profession in Hong Kong, understanding the two systems would be beneficial when giving views on the reform of Healthcare system in Hong Kong.

Author's background

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A Century of Rocky Path and Evolution of Modern Pharmacy Education in China

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ABSTRACT

The School of Pharmacy of the National Defense Medical Center (國防醫學院) has been founded for more than a century. It was originally evolved from the Department of Pharmacy of the Beiyang Military Medical School (北洋軍醫學堂) in the Qing Dynasty since 1908. The setup of this first and the earliest pharmacy department eventually led to a far-reaching influence on the developing and modernizing of the pharmaceutical practices in China. Evolved from harsh conditions and frequent interruptions due to chaos caused by wars since its founding and a lasted disturbances about half a century in the mainland, the pharmacy school finally settled down in Taipei and advanced to become a well known school for training pharmacists in the Far East after the 50s. Nowadays students admitted to this school are not only taught and

mentored by prestigious scholastic faculty members but also enjoyed a well equipped learning environment with plenty of chances to practice their learning before graduate.

Keywords: Pharmacy education; China; National Defense Medical Center; Pharmacy trainings; Learning environment

INTRODUCTION

China is currently drawing worldwide attention after its recovery from the frequent invasion by the Western imperialism in the 19 and 20th centuries. Systemization of the stock market, expansion of urbanization, flourishing international trading and industrialization of a variety of manufactures are the significant developments in recent years. Although these are the achievements that the Chinese are proud of, the development of pharmacy education

in China has made some contributions in current prosperity and should not be neglected in modern Chinese history. It has great contributions to the national defense as well as economic growth in China. However, the rooting and development of pharmacy trainings in China is not an easy road. It has to grow under the threaten of warfare, to move around reluctantly due to the tumbling environment, and to struggle with the traditional practices from the old dosage forms to modern concepts and standardized drugs.

In order to understand the path of modernization of pharmacy education in China, we have to study the root and the evolution of a pharmacy school in National Defense Medical Center (NDMC). Figure 1 is a photo showing a gathering of alumni organized by the school in November, 2008 to celebrate the 100th anniversary of its foundation. This school, in fact, could be traced back to the Department of Pharmacy



Figure 1. Gathering of alumni at the 100th Anniversary of the Pharmacy Department in NDMC. Background is some new buildings on the Neiwu Campus, Taipei. (國防藥學百週年慶世界校友大會,背景為臺北內湖新校舍) (Photo taken: November 20, 2008)

established by Tsui Wah Ching (徐華清) more than a century ago in the Army's Military Medical School, also known earlier as Beiyang Military Medical School. Through studying its evolution and development in the past century, we may be able to apprehend the difficulties and pains that our predecessors went through in order to introduce modern pharmacy education to China.

NDMC IN THE EARLY DAYS

NDMC, originated from the Beiyang (Northern Warlords') Military Medical School in Tianjin, was established by the Qing Dynasty in 1902 (Figure 2).⁽¹⁾ The Department of Pharmacy, which was established in 1908 as a branch of the Medical School, was the first modern Chinese pharmaceutical school setup in the mainland. In the early days of its establishment, the teaching contents of pharmacy courses were modified directly from the Japanese pharmaceutical education system, engaging a three-year training to provide advanced knowledge in pharmacy as well as foreign languages for students. Three years later, the first batch of enrolled students graduated from the department. In its early stage of operation, all graduates were assigned to the army to support the need of medical affairs and to assist material production for military purposes. In 1912, the Medical School was managed under the Department of Army after successful overthrow of the Qing Dynasty through National Revolution under the leadership of Dr. Sun Yat Sin. Therefore, it was renamed as the Army Medical School.

Disturbed trainings during the warlord period

In 1918, the campus of the Medical School was relocated to Beijing. A lot of research activities and training programs were conducted in the pharmacy department. Apart from the lectures given in classroom, factory



Figure 2. Beiyang Medical School (Photo taken: 1902)⁽²⁾

for the production of medical products was also constructed adjacent to the department to provide practical trainings for the students. However, as the political situation of China become very volatile due to the warfare between warlords and the deteriorating economy, all types of education were frequently retarded or interrupted by social unrest. Trainings provided by the Army Medical School were also affected. It was not until 1928, when China was totally unified on political ground, that a stable environment for the training of pharmacists was possible.

The period during China's Resistance War against Japanese aggression

Unfortunately, the stable learning environment lasted for only a few years. When the 918 Incident in Shenyang erupted, it incessantly put north-eastern China under the threat of invasion by the militarized Japanese. In order to avoid any casualties due to the warfare and to provide a safe environment for learning, the Medical School was forced to move to Southern China. After serious consideration, it was relocated to Nanjing in 1933 under the leadership of Dr Chang Kin (Figure 3).⁽²⁾ One year after relocation, the school had already achieved some progress in the pharmacy program. The Western educational system and syllabus were adopted. The new syllabus emphasized apprenticeship and on-job trainings. The students were provided with plenty of opportunities to acquire real knowledge and skills via working in the Central Hospital and the Central Research Institution of Hygiene before graduation. In 1936, the predecessor of NDMC was renamed as Medical Officer School.

In 7th July, 1937, the Lugouqiao Incident became a triggering point of the war of resistance against Japanese aggression lasted until 1945. In August of the same year, Japanese armed force attacked Shanghai followed by Nanjing, causing massive destruction of the capital. As the result, operation of NDMC was forced to a halt and inevitably giving up the new campus in Nanjing, and moving to the far southwestern region of China in order to continue the trainings. Educational activities were resumed in Guangzhou in September of the same year. However, as the scale of war further erupted, the affected area increased and



Figure 3. Dr. CHANG Kin (張建), Dean of Student Learning (Middle) taken photo with Dr. YU Siu Hsin (于少卿)(Right), Surgeon Specialist and Mr. CHANG Pang Chung (張鵬翀)(Left), Head of Pharmacy Department (Photo taken in March, 1937 at Central Military Medical School, Nanjing)

the operation of the Medical School, including the pharmacy department had to stop again and move to Guilin in 1938 and subsequently further west to AnShun in Guizhou in 1939 in order to keep it running properly (Figure 4).^(3,4)

To provide adequate support of medicinal experts and better medicines during the period of the Anti-Japanese Aggression War, the Kuo-Min-Tang (KMT) Government setup three research centers, including the Center of Biomedical Products and Manufacturing, the Centre of Sera and Vaccines Production and the Centre of Nutrient in Military, on the campus (Figure 4). These three centers were organized and run by staff from the department alone. In this hard time of China, the department and its staff contributed and dedicated their effort to supporting the Chinese army by improving the quality of drug and medical supplies.⁽⁵⁾

During the period from 1939 to 1945, the Pharmacy School was composed of six departments and one institute, including the Department of Basic Chemistry, the Department of Pharmaceutics, the Department of Pharmaceutical Chemistry, the Department of Pharmacognosy, the Department of Pharmaceutical Analysis, the Department of Chemical Weapons, and the Institute of Pharmaceutical Manufacturing (Figure 4).⁽⁴⁾ Most of the teaching staff at that time were scholars who had studied abroad either in Germany, Japan or the United States of America.

On August 15th, 1945, the surrender of the Japanese gave the KMT government a chance to relocate the School from southwest China to Shanghai and finally rename it as the National Defense Medical Center (NDMC) (Figure 5). According to a plan disclosed, the whole institute was supposed to compose of the Hospital of Shanghai and the Military Hospital; these two hospitals were designed as the main parts of NDMC. Consequently the scale of NDMC was supposed to expand into a beautiful campus of about 1.5M m² in size (Figure 6).⁽⁶⁾ At that time, people were fascinated with the good prospect of NDMC because of favorable factors including advanced facilities, excellent professorial staff, well trained researchers, and last but not least, innovation and reputation established through several generations of difficult periods.

FINAL DESTINATION IN TAIWAN

Despite the end of the Japanese war, the people in China were not able to enjoy peace for too long after 1945. Right after Japanese assault was ceased, Chinese Civil War escalated between the Communist and the Nationalist from north to south. Eventually, the army of Communist, which was backed up by Russia, defeated the army of KMT. The former president of the Republic of China, Lee Zong-Ren (李宗仁), abandoned his moral duty and fled to the United States. At that time Chiang Kai-Shek decided to haul off and the National Government was forced to withdraw from mainland

China to set up a new administration in Taiwan. Because NDMC was a branch of the army belonging to the National Government, NDMC was also moved to Taiwan (Figure 7).⁽⁷⁾ Looking back, the relocation of NDMC to Taiwan was a wise decision. It helped not only the Center to escape from any operational interference by the social turbulences erupted in the subsequent years but also promoted the growth of modern pharmaceutical education and industry in Taiwan. The reckless social movements in mainland China, including the Anti-Rightist and Intellectual Movements a few years later after liberation of the mainland by communists, the Movement of Great Leap Forward initiated by Mao Zedong in the late 50's to accelerate construction of the country and the decade-long Cultural Revolution from the mid-sixties to the mid-seventies by the Gang of Four, were catastrophic to the whole country. They were

source, which is along the bank of Hsintien river in Taipei, the admission policy of NDMC was modified. With approval from the Department of the Ministry of National Defense and the Department of Education, NDMC set up a study program for overseas Chinese student who were self-financed.⁽⁸⁾ Consequently, NDMC produced graduates who significantly impacted the advancement of pharmacy outside the military in Taiwan. One of the most important events was that experts from NDMC dedicated their time and effort to helping the operation of pharmacy schools in other institutes, such as the National Taiwan University; the Chai Nan Pharmaceutical Institute and the Chinese Medical College. However, in the very early days after the relocation, both NDMC and its students were facing various difficulties; e.g. unfavorable learning environment (Figure 8), financial problems, emotional problems due to disconnection with family members in mainland China, etc. Things were gradually improved when the construction of a new campus and new laboratories were completed (Figure 9). Furthermore, the arrival of foreign aids and financial donations from America facilitated its fast growth (Figure 10).

In the 1960s, in order to provide more practical training opportunities to all pharmacy students, the department set up a medicinal manufactory plant. This plant provided large volume injections to support the necessity of all military hospitals and veteran's hospitals as well all around in Taiwan until 1990s. Even by today's standard, the plant possessed the best facilities and highest reputation among pharmaceutical manufacturers in Taiwan. Some breakthroughs and advancements based on scientific research and pharmaceutical technologies, for



Figure 4. The location and operation of Military Medical School at An Shum



Figure 5. The campus of NDMC at Shanghai in 1947.



Figure 6. The West lake besides the nurse dormitory of NDMC in Shanghai. [1947國防醫學院上海校區內,護理宿舍邊之西湖「湖心亭」)(相片由NDMC校友葉續源博士提供)]

human-made disasters that severely stopped the modernization of China for nearly thirty years. The barbarism of these movements also ruined accomplishments that were achieved previously by our predecessors. Advancement of the whole country was completely kaput until the arrival of the open-door policy by Deng Xiaoping in the 80s.

Soon after relocation to Taiwan at Shui-Yuan-Di, the location of water



Figure 7. Unloading stuff from Shanghai after their arrival to Taipei in 1949.

from seaweeds for neurobiological tool as well as an anthelmintic agent were achieved after affiliating with the Veteran Pharmaceutical Plant and the Kingdom (currently Synpac-Kingdom) Pharmaceutical Plant at the late 60's.

MODERNIZATION OF PHARMACY EDUCATION

Nowadays, the School of Pharmacy of NDMC has been well developed into one of the best pharmaceutical research centers and educational institute in Taiwan. By the end of 1999, after the construction lasting more than 10 years, a new campus in Neihu was built and totally completed (Figure 11). The NDMC and the Tri-service General Hospital were combined together in the same building which possessed the largest floor area among the district of Southeastern Asia. Located on the ninth floor of the Medical Center is the pharmacy school that occupies a space more than 3000 square meters. The facilities of the School are



Figure 8. Delivering lecture in an open ground during the early 50s.



Figure 9. Literature search for writing up thesis in the departmental library during the 50s.



Figure 10. The main entrance of Old Campus of NDMC at Shui Yuan Road from the 50s to 90s in Taipei.

composed of study rooms, a conference room, a library, and contain state-of-art instruments to provide ultramodern environments for study (Figure 12,13). Equipments for research projects are versatile with the aim to complement teaching and learning.⁽⁹⁾

Although the principal mission of the School is to provide topnotch medical officers for military services of the Armed Forces of the ROC, students are also trained to advance pharmacy education and the promotion of medical research, equipped with the philosophical and political knowledge, and nurtured with virtue, intelligence, strength, and integration in military sciences (Figure 14).

The teaching and research of the School is highly diversified. Trainings could be divided into five major domains; i.e. medicinal chemistry, pharmacognosy, pharmaceuticals, pharmaceutical analysis and clinical pharmacy (Figure 15). The school also houses the Foundation of Pharmaceutics and the Analytical Center of Tri-Service Medical Supplies. Teaching at the third and fourth year is affiliated with four GMP pharmaceutical plants and four teaching hospitals to provide adequate and balance internship trainings for all students. Hence, the course offered covers the whole range of knowledge required for training pharmacist students for professional practices and for advance learning and studying of pharmaceutical related knowledge.

About a century ago, there were only 9 professionals employed as teaching



Figure 12. Students acquire new knowledge through (A) computer and (B) practicing in pharmaceutical plants or (C) dispensing in hospitals affiliating to the School of Pharmacy, NDMC

staff in the department of pharmacy but in 2000, about 20 famous experts are in services; over half of them possess a PhD degree, which was granted generally by the well known universities in the US and Germany, in different specialized areas. Most of the staffs are recruited to organize the undergraduate program as well as to be in charge of different research activities in the school. Currently the greatest challenge for the School of Pharmacy of the NDMC as well might be the policy of personnel's shrinkage from authorities. The pharmacy school has been threatened occasionally to be dismissed from the Center for more than 20 years under the plane of reducing the armed forces led by the Ministry of National Defense. There are only 11 teaching staffs left at present time.

Apart from the increasing number and quality of the staff, the facilities of the School of pharmacy have been improved tremendously to satisfy the need of modernization of pharmaceutical industry and research. Other than



Figure 11. The modern main building of School of Pharmacy at Neihu, Taipei (Photo taken: 2005)



Figure 13. The herbal garden for learning pharmacognosy outside the classroom. It is located at the back of School of Pharmacy, NDMC at Neihu,.



Figure 14. Small group learning is always the virtue of education offered by NDMC for hundred years

laboratories with advanced equipments, the school has agreements with a few pharmaceutical plants and hospitals to provide hand-on trainings and practices for students.

On top of plenty interactive training opportunities, students are frequently invited to participate in research activities carried out by the staffs. Over 40 research projects, which could be subdivided into (1) pharmaceutical production, (2) activation and synthesis of medicines,

(3) pharmacodynamics investigation of drugs and (4) Chinese medicines studies are the main focus of research activities of this school. The achievement of these research activities has been transformed into reports published in journal or patents to protect the intellectual right.

ROLE PLAYED BY NDMC IN TAIWAN PHARMACEUTICAL SECTOR

Apart from nurturing the professionals in pharmacy, the school of pharmacy of NDMC also plays a vital role on promoting and advancing the pharmaceutical professionals in Taiwan as well as the Great China Region.

First of all, it provides expertise of pharmaceutical knowledge in various fields in Taiwan. Strong connections and mutuality are formed between NDMC and many pharmaceutical companies responsible for medical product production. Therefore, not only can the student in NDMC obtain relatively more training opportunities, but also the companies are able to immerse into an environment with adequate consultative support and supply of advanced and updated information. For example, with the immense support provided from NDMC, Kingdom pharmaceutical company, one of the affiliated pharmaceutical companies of NDMC, has completed the synthesis and production of erythromycin estolate and the extraction of kainic acid, a natural pharmaceutical material as mentioned above. These

discoveries were innovative and original contributions accomplished by the staffs and the students of NDMC. The experts of NDMC also devote their effort to exploring new and valuable processes for the production of active substances and then transferred the related patents and technology to the pharmaceutical industry in Taiwan, such as the synthesis and production of niacinamide, silver sulfadiazine, povidone iodine, l-camphorsulfonic acid, mitoxantrone, etc. Such a kind of corporation and close relationship between academic and industrial field is solely found in Taiwan. In 1990s a project was granted by the National Science Council to build a pilot plant for pharmaceutical study. The School of Pharmacy, NDMC, became the only one who owned his pilot plant and pilot pharmaceutical factory for teaching and studying among the seven Pharmacy Schools in Taiwan.

Apart from above mentioned innovation, from 1985 NDMC has helped some hospitals, such as Tri-service General Hospital, to improve and organize the system of clinical pharmacists by setting up the department of clinical pharmacy, installing the laboratory of clinical pharmacodynamics and providing on-job training courses for pharmacists. Last but not least, some important tasks handled by the NDMC are usually overlooked, such as quality control of medicine production, providing consultative advisory for professional examinations and pharmacopeia editing.



Figure 15. Five Major domains of teaching and research pursued by staff in the School of Pharmacy, NDMC in recent years.



Figure 16. A century of evolution and development of the School of Pharmacy, NDMC (1908-2008)⁽¹⁰⁾

SCOPING AND CONCLUSION

In recent years, due to the fast advancements and breakthrough of biopharmaceuticals, course curriculum and mode of teaching have been restructured extensively. More resources and manpower are being injected into areas such as biotechnology and the clinical aspects of these therapeutics so that students could work proficiently amongst other healthcare professionals. Hence, pharmaceutical biotechnology, recombinant DNA technology, pharmaceutical cares and consultations in hospitals and community are introduced and given more weighting.

After having an exploratory study on the history of NDMC (Figure 16), some conclusions could be drawn about the path of evolution and development of pharmacy education in China in last century. First of all, the development was retarded by social unrest and warfare in the early days. After the Chinese civil war, the development of modern pharmacy education and research advanced very fast in the late 50s onwards because of the political stability and economic growth.

The education of modern pharmacy offered by NDMC was borrowed and modified from the education system developed in Western countries, especially the system in US and Japan. Learning the path of evolution and the development of its pharmacy courses allows people to appreciate a stable and harmonizing environment is critical for training the younger generation. From the history of NDMC, it provides us a picture that successful education requires the commitment and efforts from a lot of people and our predecessors' vision, diligence and persistence. Every time if one has been able to see further, the one should remember that it was only because he stood on the shoulders of giants.

Author's background

Drs CHANG Pong and CHEUNG Hon Yeung are graduates of the School of Pharmacy, NDMC in the mid 70s. Both are working in the tertiary education. Mr LAM Li-Wing Jason is a fresh graduate from City University of Hong Kong. For more information about this article, please contact Dr CHEUNG through the following email address: bhonyun@cityu.edu.hk

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

Department of Pharmacology & Pharmacy at the University of Hong Kong - An interview

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ABSTRACT

This is an article on an interview recently hosted by the reporters of the Hong Kong Pharmaceutical Journal. Its aim is to look into the newly opened department (Department of Pharmacology & Pharmacy) at the University of Hong Kong from myriad perspectives.

Keywords: University of Hong Kong; HKU; Department; Pharmacy courses

INTRODUCTION

One of the missions of a prestigious pharmacy school shall be to graduate pharmacists-to-be who are capable of providing pharmaceutical care to patients in need. He/ she shall also be able to play a pivotal role in public health. For the past 15 years, the School of Pharmacy at the Chinese University of Hong Kong (CUHK) has undertaken the responsibility of training more than 400 pharmacists, many of whom are rendering professional services in the Government, hospitals, community pharmacies and pharmaceutical companies. It is not until this September that we will have the new Bachelor of Pharmacy programme offered by the Department of Pharmacology & Pharmacy at the University of Hong Kong (HKU) to complement each other on this forefront.

THE INTERVIEW

We interviewed Professor Paul M. Vanhoutte, Head of Pharmacology & Pharmacy and Professor George P. H. Leung, Assistant Professor of Pharmacology & Pharmacy at the University of Hong Kong to give us more information on the new pharmacy programme at HKU.

1. Why does HKU, as a University of the longest history in HK, has an interest in opening a School of Pharmacy?

Prof. Vanhoutte: When we look at the Faculty of Medicine in HKU, we will find that we have a strong curriculum of Medicine, Dental as well as Nursing, we also have a Department of Traditional Chinese Medicine. Thus, if there is not a Department of Pharmacy, the structure is not complete as the different professionals are interdependent on each other.

Moreover, when we look at the outside world, it can be seen that the role of clinical pharmacy service is increasing. It is difficult to imagine that the recent health care system is lacking the primary role of pharmacists.

2. As you have mentioned in many western countries, pharmacists play a very dominant role, so how do you see the role of pharmacists in HK right now?

Prof. Vanhoutte: Looking at it from a westerner's eye, I think that the profession of pharmacy is very underdeveloped in Hong Kong.

Prof. George Leung: From my point of view, I feel that pharmacists in Hong Kong are traditionally passive since there is not much interaction between the patients and the pharmacists. Thus the general public does not know the role of pharmacists. However, I think the situation is now better because nowadays pharmacists try to promote their role and let the public know what service they can provide. The image of pharmacists is indeed improving in the recent 10 to 20 years.

However, I think that the clinical pharmacists in Hong Kong are still not enough and the number of clinical pharmacists should be increased. Pharmacists nowadays are trying to make sure the dosage, identity, frequency and the method of administration of the drugs in the prescription are correct and then dispense the drugs to the patients; it seems to have no problem. However, I still think there may be some problems, e.g. the dosage may not be correct if the patient is renally impaired; if the pharmacist only stays in the pharmacy, they will not know that the patient is renally impaired. The only solution is that the pharmacist goes to the ward and looks at the patient's history so as to provide more information for the doctors to prescribe the right dosage.

Prof. Vanhoutte: Moreover, patients in Hong Kong are living in an environment that poly-pharmacy is very common. Patients go to different doctors and get different prescriptions while the only person who can obtain the most accurate drug profile is the pharmacist. On top of it, patients may also be taking traditional Chinese medicine that may have potential interactions with the western drugs.

Back to the question, I think the clinical pharmacy in Hong Kong is still not well perceived and the professional image should be reinforced. Thus, we are very willing to cooperate with the friends and colleagues in the CUHK to improve the image of the pharmacy profession. We don't want to compete with CUHK in any way and we are only providing the best pharmacy program that HKU can offer instead of providing a "better" program than the one already provided by CUHK.

3. So, do you agree that the number of pharmacists in Hong Kong is not enough?

Prof. Vanhoutte: Yes, and one more point is that the number of pharmacists being registered in Hong Kong every year is larger than those who graduate from CUHK. It means that young people are studying abroad and thus there is a need for another pharmacy program in Hong Kong so as to provide an alternative for those young people.

Prof. George Leung: Moreover, according to the recommendation of the World Health Organization (WHO), the adequate ratio between pharmacists to citizens should be around 1: 2300, while in Hong Kong the ratio is 1:4600, in some advance countries like USA, the ratio is even smaller, i.e. 1:1700.

Prof. Vanhoutte: It means that there is a shortage of pharmacists in Hong Kong and our plan is to increase the number of pharmacists in hospital on a 24 hours basis so as to provide a 24-hours clinical pharmacy services. Thus, I am very confident that our graduates can find a job in Hong Kong in the upcoming future.

4. As in the future, there will be an increase in pharmacists in Hong Kong and thus the wages of pharmacists in Hong Kong may be decreased accordingly. What are your comments for the wages of pharmacists in Hong Kong?

Prof. Vanhoutte: I would say that if the society can create more jobs, I don't think the pharmacists will earn less money. Honestly I don't think it is a real problem. It might be a "protective reflex" that pharmacists think that they will earn less if there are more pharmacists. However, we have to look at the problem from a more macro view of the whole society, and not as an individual, and I think this society really needs better pharmacy service.

Prof. George Leung: For the general public, they may think that the wages of pharmacists are relatively high because there is misunderstanding on the role of pharmacists. They think that pharmacists are like dispensers and only focus on dispensing work; instead pharmacists are drug experts who provide drug and health information. If people can fully utilize the service that pharmacists provide, and understand the role of pharmacists and think that it is important, they will realize that pharmacists deserve to have such salary.

5. A lot of graduates will like to join the community and hospital setting but not the industry setting. So what is your opinion towards this, i.e. graduates are not willing to enter the industrial sector?

Prof. George Leung: From my point of view, pharmacy courses in most countries only focus on pharmacy practice, especially clinical pharmacy, thus the graduates will be more familiar with the field and they will prefer to work in a more familiar environment. In addition, students also like to interact with and talk to patients, and they will have the feeling of helping patients. During the curriculum, students may also learn the knowledge on pharmaceutical science and formulation science, e.g. how to make pills in the laboratory, but they are seldom taught about the role of pharmacists in industrial settings. Moreover the structure of a pharmaceutical company is quite complicated and students do not know much about it. Thus they do not have enough confidence to work in such a sector.

Prof. Vanhoutte: Thus, it is all about informing the students about what are the roles and the potential of pharmacists in the pharmaceutical industry. Therefore in our curriculum, there is a subsection which introduces the role of industrial pharmacists and also the various tools for the discovery process of a chemical compound. We also have a strong clinical trial centre which complies with the standards and requirements of conducting clinical trials.

I know the role of pharmacists in the discovery and development process of a new drug is very important. So we are trying to warm up our students so that students can think that being an industrial pharmacist will be one of their future career aspiration other than being a clinical or a community pharmacist. And recently, the Government is going to put Hong Kong in the map of the drug discovery process as one of the six core areas that needs to be developed. In addition, on day one of the curriculum, we will try to show them the role of pharmacists in different aspects, including pharmaceutical industry so that

the student will know that they are not only entering to become a community or clinical pharmacist.

Donald: Yes, actually pharmaceutical industry is not only manufacturing but there are also many aspects that students can develop e.g. registration, medical information and research. You may also contact different companies, e.g. Pfizer or MSD, so that we can introduce the role of pharmacists in medical affairs.

Prof. George Leung: Actually we are now trying to communicate with the Hong Kong Association of Pharmaceutical Industry to arrange a lecture to our students to introduce the pharmaceutical industry.

6. So what are the uniqueness of your curriculum compare with the one of CUHK, or any specific points that you want to tell us?

Prof. George Leung: We never compare with CUHK, we use the program in University of California, San Francisco (UCSF), London University as reference so that we can design our program which can match up with the global trend. In addition, we also interview some frontline pharmacists so that we can know which knowledge is particularly important for their frontline practice. We try to maintain a good balance between different sections. Moreover, we have sections teaching traditional Chinese medicines, herbal products and also health supplements so that our students can become familiar with the knowledge in these areas and also their possible interactions with western medicines.

Another uniqueness is that we have adopted the method of PBL, which is Problem Based Learning. In some topics on clinical pharmacy, we will not give students the lectures. Instead, we will give them clinical cases and let them discuss and solve the problem among themselves. So by using PBL, we hope the students can learn how to self initiate their study, as no one will give them lectures after they have graduated. Nowadays, they need to learn by themselves to get more equipped. The students must have the concept of life-long learning and they have to rely on themselves.

7. Do you think that a three year curriculum is enough to train a student to become a well trained pharmacist?

Prof. Vanhoutte: Actually, the Hong Kong's regulation prevented us from designing a four years program and thus a three year curriculum is our only choice at the moment. However, we are able to organize a four years curriculum in 2012 like most foreign countries nowadays. Therefore, at the moment, we are trying

to provide the best possible pharmacy program and train pharmacists which have a global sense and meet the very specific local situation in Hong Kong. Our goal is to come up with some very well-trained pharmacists.

Going back to a few questions before, one of our uniqueness is to provide opportunities to students according to the three main aspects: clinical pharmacy, community pharmacy and industrial pharmacy. We have very good association with the Queen Mary Hospital so as to let our student know what the real situation of clinical pharmacy is. We also have contacts with community chain pharmacies so as to let our students know more about community pharmacy. And for industrial pharmacy, we can do the same, e.g. contacting different pharmaceutical companies and manufacturers for students' exposure to the role of industrial pharmacist.

In addition, we will look at the program and see if there are areas of expertise that we don't have, so we may invite friends and colleagues in the CUHK to help. We will establish protocols so that our experts can help the CUHK and in return, expert in CUHK may also help us. I think we are not competing but we are complimenting so as to work together to increase the role of pharmacists in Hong Kong.

8. What do you think about the future of pharmacy in Hong Kong?

Bright! We need more pharmacists. we need more well-trained pharmacists, and we would like to cooperate with the CUHK so as to establish a better future for pharmacists in Hong Kong.

CONCLUSION

The new Bachelor of Pharmacy programme offered by the University of Hong Kong tries to cooperate with the existing programme in CUHK to create batches of pharmacists and promote the role of pharmacists. As pharmacists in Hong Kong, we are glad to have more well-trained pharmacists with different talent to provide more extensive services to the Hong Kong citizens, so that the role of pharmacists can be more established in Hong Kong and the pharmacy industry can flourish in the coming future.

Author's background
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Prescribing Pattern of Medicines in a Community Pharmacy in Hong Kong

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ABSTRACT

A study was conducted on the prescribing pattern of a community pharmacy in Hong Kong from January to June 2008 on 70 frequently prescribed medicines. Data were collected manually by reviewing prescriptions dispensed and were recorded using Microsoft Excel 2003 database. During the six-month study period, 11342 prescriptions were reviewed and 17616 items were dispensed. Prescriptions from hospitals accounted for about one-half of total prescriptions and the remaining prescriptions were from private practising doctors. The most frequently dispensed classes of medicines were for the treatment of diabetes, hypertension and hyperlipidaemia. The four most frequently dispensed medicines in descending order were Zocor™, Lipitor™, Norvasc™ and Plavix™ and these four drugs made up about one-fifth of all prescribed items (18.81%). The study concluded that community pharmacist in collaboration with doctors and other health care providers can play a role in patient care.

Keywords: Prescribing pattern; Community Pharmacy; Dispensary; Self-financed items and patient care.

INTRODUCTION

A study was conducted on the prescribing

patterns of a community pharmacy from January to June 2008. The study looked into the prescribing patterns of medicines in a community pharmacy and focused on 70 frequently prescribed medicines. The results showed that a wide variety of classes of drugs were dispensed and the three most frequently dispensed classes of medicines were for the treatment of diabetes, hypertension and hyperlipidaemia. It was concluded that the community pharmacist in collaboration with doctors and other health care providers can play a role in patient care.

The community pharmacy was located in Kowloon and was one of the leading community pharmacies in Hong Kong. It stocked more than 4000 drug items, including brand products and generic drugs, and dispensed a wide range of old and new medicines, from Neupro™ to Januvia™, and from Lugol's solution to Pentrexyl™.

This pharmacy dispensed prescriptions from private and public hospitals, and also those from general practitioners. About half of the prescriptions dispensed every day were from hospitals. Since July 2005, the Hospital Authority has implemented the Hospital Authority Drug Formulary in public hospitals. According to the Hospital Authority homepage, drugs which have preliminary evidence only, and those which have marginal benefits over available alternatives and life-style drugs were regarded as Self-financed Items and hospital outpatients

were required to purchase these items in community pharmacies.⁽¹⁾ These prescriptions were frequently dispensed at this pharmacy.

METHODS

Data was collected by reviewing prescriptions dispensed on the previous day from January to June 2008. Total number of prescriptions, number of hospital prescriptions and number of items were counted manually. The data for the 70 prescribed drug items was recorded using a Microsoft Excel 2003 database. Dangerous drugs were not included for the sake of this study since dangerous drug prescriptions were kept separately in the pharmacy for inspection by the officials of the Department of Health.

All dosages of the same drug were recorded under the same item, for example, Norvasc™ 5mg and 10mg were counted under Norvasc™. Repeat prescriptions were counted as separate prescriptions. Viagra™ repeat prescription, for example, was counted every time the prescription was filled during the study period.

For Self-financed Items from public hospitals, usually one item was printed on one prescription. So for patients who need more than one drug, they could purchase their medicines at different dispensaries, under the circumstances that one dispensary did not stock all the required medicines. In this study,

Table 1. Monthly total number and average number of all prescriptions and hospital prescriptions

	No. of working days	No. of all prescriptions	No. of hospital prescriptions	Average number of prescriptions per day	Average number of hospital prescriptions per day
January	26	2123	964	81.6	37.1
February	15	1208	589	80.5	39.3
March	24	1996	883	83.2	36.8
April	26	2018	950	77.6	36.5
May	27	2044	886	75.7	32.8
June	25	1953	926	78.1	37.0
Total(Mean)	143	11342	5198	(79.3)	(36.3)

when these prescriptions were written by the same doctor and were issued on the same day and for the same patient, these prescriptions were regarded as one prescription.

RESULTS

Eleven thousand three hundred and forty-two prescriptions were reviewed for 143 working days from January to June 2008. There were 17616 items dispensed. On average, there were 79.3 ± 17.6 (15 to 117) prescriptions every day. Almost half (46%) of the prescriptions were from hospitals. The total number of hospital prescriptions was 5198 and on average 36.3 ± 9.2 (6 to 59) hospital prescriptions were received every day.

During the six month period, the 70 selected items accounted for about 1/2 of all prescribed items (49.1%). The top 4 medicines, in descending order, were Zocor™, Lipitor™, Norvasc™ and Plavix™. They made up about 1/5 of all prescribed items (18.81%). Table 2 shows the prescribing pattern of 70 frequently prescribed medicines.

DISCUSSIONS

The author performed a Medline search using the keywords "prescribing pattern" and "community pharmacy". Thirty-four journal articles were found. Prescribing pattern in a single community pharmacy could not be found. Similar studies included anti-diabetic drug use in Hong Kong and Singapore,⁽²⁾ prescribing pattern of general practitioners in Northern Italian region,⁽³⁾ antibiotic use in the Australian community,⁽⁴⁾ antibiotic use in a Mexican city and prescribing patterns of general practitioners in a Swedish city.^(5,6) It is very probable that this is the first report of prescribing patterns in one community pharmacy. This dispensary is very different from most other dispensaries in Hong Kong with respect to the volume of prescriptions. This study highlighted the role of the pharmacist in this community pharmacy.

The number of working days and number of prescriptions were lowest in February because of the long Chinese New Year holiday. The average number of prescriptions per day was highest in January and March. It is because traditionally patients did not visit doctors during Chinese New Year, the month before and after Chinese New Year

Table 2. Prescribing pattern of medicines

Rank	Drug	Frequency	Percentage of total drug dispensed
1.	Zocor™	1317	7.48%
2.	Lipitor™	895	5.08%
3.	Norvasc™	671	3.81%
4.	Plavix™	429	2.44%
5.	Cozaar™	352	2.00%
6.	Betaloc zok™	275	1.56%
7.	Diovan™	273	1.55%
8.	Crestor™	270	1.53%
9.	Glucophage™	266	1.51%
10.	apo-simvastatin (Apotex generic simvastatin)	250	1.42%
11.	Plendil™	235	1.33%
12.	Viagra™	187	1.06%
13.	amitriptyline (generic)	154	0.87%
14.	Viartril™	148	0.84%
15.	Lopid™	143	0.81%
16.	Fosamax™	136	0.77%
17.	Nexium™	131	0.74%
18.	Aprovel™	126	0.72%
19.	Co-Diovan™	120	0.68%
20.	Avandia™	114	0.65%
21.	Micardis™	105	0.60%
22.	Diamicron MR™	103	0.58%
23.	Natrilix SR™	93	0.53%
24.	Acertil™	90	0.51%
25.	Actos™	87	0.49%
26.	Glucobay™	87	0.49%
27.	Fosamax plus™	77	0.44%
28.	Betaloc™	74	0.42%
29.	Zeffix™	74	0.42%
30.	Co-Aprovel™	73	0.41%
31.	warfarin (generic)	72	0.41%
32.	Proscar™	68	0.39%
33.	Deanxit™	60	0.34%
34.	Blopress™	58	0.33%
35.	Hyzaar™	57	0.32%
36.	Micardis plus™	57	0.32%
37.	Daonil™	51	0.29%
38.	Vytorin™	50	0.28%
38.	Olmetec™	50	0.28%
40.	Actonel™	49	0.28%
41.	Diamicron™	48	0.27%
42.	Cardura XL™	46	0.26%
43.	Hytrin™	44	0.25%
44.	Insulin (all preparation)	43	0.24%
45.	Adalat GITS™	43	0.24%
46.	Losec™	41	0.23%
47.	Januvia™	38	0.22%
48.	Celebrex™	37	0.21%
49.	Novonorm™	33	0.19%
50.	Tritace™	32	0.18%
51.	Cialis™	31	0.18%
52.	Seroxat™	30	0.17%
53.	Amaryl™	30	0.17%
54.	Zestril™	27	0.15%
55.	Bonviva™	27	0.15%
56.	Baraclude™	22	0.12%
57.	Glucovance™	20	0.11%
58.	Sporanox™	19	0.11%
59.	Hyzaar plus™	17	0.10%
60.	Caduet™	14	0.08%
61.	Seretide™	14	0.08%
62.	Harnal™ D and OCAS	13	0.07%
63.	Neupro™	11	0.06%
64.	Levitra™	10	0.06%
65.	Hyzaar forte™	9	0.05%
66.	Vesicare™	7	0.04%
67.	Utrogestan™	6	0.03%
68.	Acomplia™	5	0.03%
69.	Dilatrend™	3	0.02%
70.	Exforge™	3	0.02%

49.10%

was the busiest months and number of all prescriptions was highest in these months. Nevertheless, the average number of prescriptions was also high in February. It is because the highest number of hospital prescriptions was recorded in February; the lag time could probably be explained by the fact that prescriptions from public hospitals were valid for one month.

Lipid-lowering agents (16.44%), anti-hypertensives (16.03%) and anti-diabetic drugs (5.16%) were the three most frequently prescribed classes of drugs, account for 41 drugs.

Zocor™ (7.40%) was the most frequently prescribed lipid-lowering agent. Other frequently prescribed lipid-lowering agents included Lipitor™ (5.04%), Crestor™ (1.51%) and arosimvastatin (1.40%).

Norvasc™ (3.79%) was the most commonly prescribed anti-hypertensive drug in this study, followed by Cozaar™ (1.98%), Betaloc zok™ (1.55%) and Diovan™ (1.55%).

For antidiabetic drugs, Glucophage™ (1.49%) was the most frequently prescribed antidiabetic drug. It was followed by Avandia™ (0.64%), Diamicon MR™ (0.58%) and Actos™ (0.49%).

The 41 drugs made up around two-fifth of all dispensed items (37.63%) during the study period and amounted to 6611 drug items dispensed.

These results showed that about two-fifth of medicines dispensed were for the treatment of diabetes, hypertension and hyperlipidaemia. Apart from these medicines, other classes of medicines prescribed frequently included prevention of stroke such as Plavix™ (2.44%), for erectile dysfunction such as Viagra™ (1.06%), Cialis™ (0.18%) and Levitra™ (0.06%) and for osteoarthritis such as Viartril-S™ (0.84%).

High blood pressure, high cholesterol and diabetes mellitus are attributed as the risk factors of coronary sclerosis and stroke. Plavix™ was promoted as an agent to prevent stroke and coronary diseases. Atherothrombosis in heart and brain have been a very expensive disease to treat and also a very disabling disease for patients. Results from this study showed that

two-fifth of all dispensed items are for prevention of atherothrombotic events or for treatment of their risk factors. Community pharmacist was playing a role in dispensing these medicines.

This study did not include patient age and other demographic data, so it is not feasible to determine the relevance of patient age or sex with the pattern of medicines prescribed. Since this is the first prescribing pattern survey of a single community pharmacy, comparison with other similar studies seems not applicable. As of the experience of the author, patients come from all districts of Hong Kong. Therefore, prescriptions were from different private practice doctors and hospitals, geographic factor could not influence the prescribing pattern. Since 46% prescriptions were from a hospital, and the Hospital Authority Drug Formulary, Self-finance Items were substantially dispensed in this dispensary. But data of the proportion of SFI was not available, therefore, no conclusive comment could be made.

CONCLUSIONS

Pharmacists in the Hong Kong community play a role in dispensing medicines. A wide variety of medicines were dispensed and anti-hypertensives, lipid-lowering agents and anti-diabetics are the most commonly prescribed medicines in this study. Plavix as an agent to prevent stroke and coronary events was also commonly dispensed. This community pharmacy was actively taking part in dispensing drugs that treat common chronic diseases in Hong Kong. Pharmacists having access to objective clinical data, and having the necessary knowledge, skills and resources, can play a role in patient care and this study concluded that the community pharmacist in collaboration with doctors and other health care providers can play a role in patient care.⁽⁷⁾

Comparison of prescribing patterns in the community sector and those of government hospitals and private hospitals would be of great value to policy makers and the general public who were concerned about healthcare reform in Hong Kong. The author wishes that the data presented here would provide evidence for the effort of the private sector in healthcare service.⁽⁸⁾ and would strengthen public/private healthcare interface.⁽⁹⁾

Author's background

CHONG KL Candy being a practising pharmacist in Hong Kong furthered her education in the Department of Medicine and Therapeutics, CUHK and graduated as an MPhil in Medical Sciences in 2003. She is now working as a community pharmacist in one of the leading community pharmacies in Hong Kong. E-mail address of the author: candychong1025@yahoo.com.hk

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The Failure of ACAT Inhibitors

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ABSTRACT

Despite landmark clinical trials demonstrating statistically reliable evidence on the benefits of lipid-lowering agents on the reduction of cardiovascular risks, morbidity and mortality rates, as well as improved overall survival rates, deaths caused by cardiovascular diseases (CVD) continue to increase worldwide. In Hong Kong CVD was responsible for over 60,000 episodes of hospitalisation, and more than 6,000 deaths per year in 2008. Acyl-coenzyme A: Cholesterol acyltransferase (ACAT) is an intracellular enzyme involved in the hepatic biosynthesis of cholesterol. Existing in two sub-forms ACAT-1 and ACAT-2, pharmacological models and animal studies suggested a theoretical method through the inhibition of ACAT-1, the intrinsic esterification of cholesterol could be retarded or even halted, resulting in the slowed progression of atheroma/ atherosclerotic plaque formation. In light of further assessing the clinical usefulness of ACAT inhibition as a potential pharmacological strategy in lipid-lowering, the ACTIVATE and CAPTIVATE trials were carried out to evaluate the safety and efficacy of the ACAT inhibiting agent Pactimibe. Study subjects were randomised in either Pactimibe or placebo. Atheroma progression was evaluated using either intravascular ultrasonography (IVUS) in ACTIVATE or carotid intima-media thickness (CIMT) in CAPTIVATE. In ACTIVATE, both the placebo and Pactimibe groups showed statistically significant atheroma volume progression on IVUS, with slightly greater atherosclerotic plaque formation in the Pactimibe group. The CAPTIVATE study found a statistically greater increase in LDL-cholesterol in the Pactimibe group (7.3%) compared with placebo group (1.4%). Statistically insignificant but the researchers observed a greater increase in terms of CIMT in the Pactimibe group. The two studies demonstrated that ACAT inhibition failed to slow atherosclerosis and may even be

pro-atherogenic. Drug treatment with statins and fibric acid derivatives yet remain as the cornerstones in terms of pharmacological interventions against cardiovascular and cerebrovascular diseases.

Keywords: Statins, ACAT inhibitors, lipid-lowering, Cardiovascular Disease, Atherosclerosis

INTRODUCTION

Cardiovascular disease (CVD) secondary to atherosclerosis is the leading cause of morbidity and mortality in the western societies and is rapidly progressing in the developing countries. In Hong Kong, CVD was responsible for more than 64000 episodes of hospitalisation and over 6000 deaths in year 2008.⁽¹⁻²⁾ It was well recognised that there is a trend of CVD becoming decreasingly age-adjusted in recent years. Figure 1 shows the number of mortality due to heart disease, which was only second to malignant disease in year 2008.

Medical management strategies of atherosclerosis as primary and secondary prevention of CVD involve stringent and proactive control of its risk factors, including hyperlipidaemia, hypertension, monitoring for family history that may pre-dispose an individual to the disease, reinforced by smoking cessation and the effective monitoring of other pre-disposing factors such as diabetes or

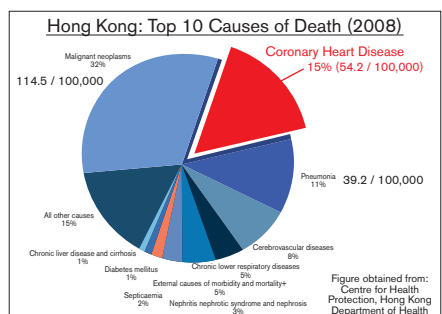


Figure 1. Top 10 Causes of Death in Hong Kong (2008). Figures obtained from the Centre for Health Protection, Department of Health of HKSAR indicated that heart disease accounted for over 50 death per every 100,000 population in the year 2008, made up to 15% of the total age-adjusted deaths.

other metabolic syndromes.⁽³⁾

Early researches on lipid-lowering drugs and cardiovascular disease, such as the Lipid Research Clinics Coronary Primary Prevention Trial in 1984, and the Helsinki Heart Study 1987 demonstrated the use of fibric acid derivatives such as Gemfibrozil and Bezafibrate resulted in a 1 percent reduction in total cholesterol or a 1% elevation in high-density lipoproteins (HDL) and a 2% reduction in cardiovascular events over a 5-year period. The infamous Scandinavian Simvastatin Survival Study (4S) in 1994 hailed the success of lipid-lowering pharmacotherapy with the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (i.e. the statins), followed by the Air Force Coronary Atherosclerosis Prevention Study / Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) (1998), the Cholesterol And Recurrent Events Study (CARE) (1996), the Long-term Intervention with Pravastatin in Ischaemic Heart Disease (LIPID) study (1998), and numerous other megatrials demonstrated some statistically (and arguably clinically) solid evidence on the benefits of statins, in terms of cardiovascular or cerebrovascular outcome reductions, and overall significantly decline in mortality rates. Figure 2 shows the cholesterol biosynthesis pathways and the effect of statins on hepatic cholesterol synthesis.

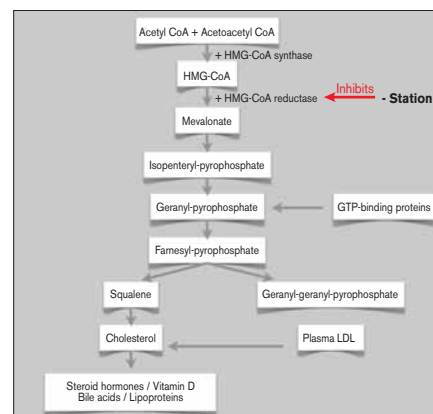


Figure 2. Cholesterol biosynthesis pathways. HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A; GTP: guanosine triphosphate. Inhibition of HMG-CoA reductase leads to the inhibition of the hepatic cholesterol biosynthesis.

Despite these encouraging breakthroughs in the identification of cardiac risk factors, the advancements in increasingly potent lipid-lowering agents based on the statin model, as well as great improvements in highly effective clinical, diagnostic and surgical tools, morbidities and mortalities due to atherosclerotic cardiovascular disease yet remain to be the leading cause of death worldwide and this problem continues to grow. A report published by Libby et al in 2008 suggested that by year 2020, cardiovascular disease will surpass infectious and communicable disease as the leading cause of death worldwide. This implies not only socio-economical impact in terms of national productivity, but also a global health burden. These concerns have fuelled the continuous efforts to search for more effective pharmacological targets.⁽³⁾ Figure 3 shows the top 10 causes of death worldwide in the Global Burden of Diseases Fact Sheet 2008 (2004 update).

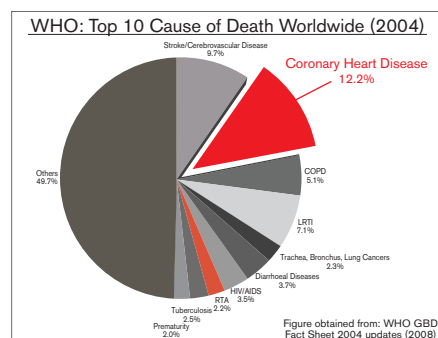


Figure 3. The Global Burden of Diseases (GBD) Fact Sheet (2004 update) published in 2008 reported that coronary heart disease was the number one cause of death worldwide, accounted for over 12% of lost of productive life globally.

ACYL-COENZYME A:CHOLESTEROL ACYLTRANSFERASE (ACAT)

The discovery of acyl-coenzyme A:cholesterol acyltransferase (ACAT) was once seen as a promising pharmacological target, and that inhibition of this enzyme could potentially become a new therapeutic strategy against atherosclerotic cardiovascular diseases. ACAT is an intracellular enzyme involved in cholesterol accumulation. The theoretical model involves two sub-forms of ACAT enzymes: the ACAT1 and ACAT2, presents in intestinal epithelial cells and hepatocytes. By inhibiting ACAT1, the esterification of cholesterol and subsequently the macrophagic foam cells formation could potentially be halted, resulting in the slowed progression of atherosclerotic plaque formation.⁽⁴⁻¹⁷⁾ Figure 4 illustrates the atherogenic mechanisms of ACAT.

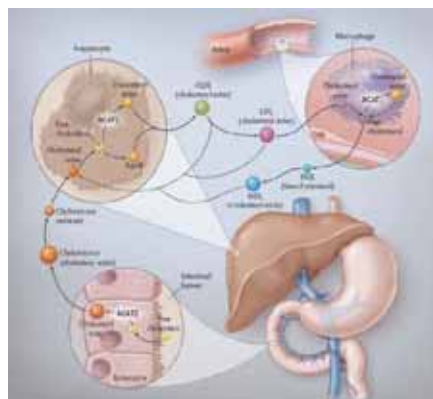


Figure 4. Location and functions of the enzyme acyl-coenzyme A:cholesterol acyltransferase (ACAT). Two forms of ACAT have been identified. ACAT-1 presents in macrophages and ACAT-2 in intestinal mucosal cells and hepatocytes. These enzymes esterify cholesterol in tissues; inhibition of these enzymes could theoretically prevent the transformation of macrophages into foam cells and slow the progression of atherosclerosis. ApoB denotes apolipoprotein B, VLDL stands for very low density lipoprotein, LDL Low-density lipoprotein and HDL high-density-lipoprotein.

Some animal studies done in earlier years of ACAT discovery suggested that the ACAT-inhibitors could result in marked reduction of atheromas formation, while there existed some contradicting results, in which the inhibition of ACAT1 promoted atherosclerosis.

WHAT IS ACAT?

The earliest study on ACAT inhibitors traces back to the 1980s, at which time it was believed that the enzyme ACAT played significant roles in the lipoprotein assembly process and cholesterol absorption. ACAT was described as a membrane-bound protein found in the endoplasmic reticulum, and was activated by the existence of cholesterol.⁽¹⁸⁾ ACAT utilise long chain fatty acid acyl-CoA and cholesterol as substrates, to form cholesteryl esters.

The isolation of this enzyme had not been successful in its early days after discovery, as this enzyme exists in such a minute quantities, and the genetic coding of this enzyme was at that time yet to be isolated. The ACAT gene was first cloned and expressed in 1993 by Chang and colleagues.⁽¹⁸⁾ Who developed a specific enrichment procedures that enabled its isolation and characterisation of mammalian cells.

Acyl-CoA:Cholesterol Acyltransferase Intravascular Atherosclerosis Treatment Evaluation (ACTIVATE) Study

In year 2002, Nicholls S and Nissen et al conducted the ACTIVATE Trial, which was a biphasic randomised controlled trial, with an aim to assess the safety and efficacy of the novel agent Pactimibe in slowing the progression of atherosclerosis.⁽⁵⁾ In ACTIVATE, the researchers assessed the plaque volume, via angiographic information, obtained from intravascular ultrasound (IVUS) on 408 study subjects with angiographically documented coronary disease. Figure 5 describes how intravascular ultrasound images were obtained to assess revascularisation of a target segment.

Study subjects were randomised to receive the study drug Pactimibe 100 mg or Placebo for 18 months, with the IVUS repeated after such period to measure the progression of atherosclerosis. The preliminary result published in October 2005 was unfavourable in terms of risk reduction, in that the baseline in percent atheroma volume, an indicator of atherosclerotic plaque shown on IVUS failed to decrease in the Pactimibe group measured after 18 months. Both the Pactimibe and placebo groups showed statistically significant atheroma volume progression – with a slightly greater increase in the Pactimibe group when compared with placebo. In other words, Pactimibe, not only failed to slow atherosclerotic plaque formation compared with standard therapy, but was shown to have pro-atherosclerotic effects. This important finding concluded that ACAT inhibition failed to slow disease progression. Soon after the publication of the results, the drug company (Daiichi Sankyo) announced that all clinical trials involving Pactimibe had to be discontinued in view of safety. The researchers cautioned that extreme care must be taken in exposing patients in further study on this class of drugs.

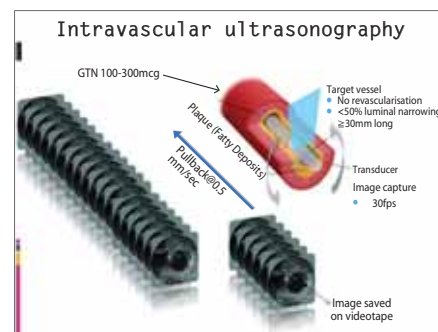


Figure 5. Intravascular Ultrasonography (IVUS) involves the insertion of a 40 MHz intravascular ultrasonographic catheter into the target vessel. Ultrasound images could be obtained at a rate of 30 frames per second and these are recorded on a videotape. After the recording, the transducer would be pulled back at a speed of 0.5 mm per second with the use of a motor drive. The image could then be used as diagnostic purposes.

ACAT INHIBITION AND PROGRESSION OF CAROTID ATHEROSCLEROSIS IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLAEMIA (CAPTIVATE) TRIAL

Between February 2004 to October 2005, Meuwese et al conducted the CAPTIVATE trial with an aim to evaluate the effect of the same study drug Pactivibe on carotid atherosclerosis progression.⁽⁶⁾ The trial was conducted at 40 lipid clinics in various countries and involved 892 patients who were heterozygous for hypercholesterolaemia. These study subjects initially had their baseline carotid atherosclerosis assessed using ultrasound carotid intima-media thickness (CIMT) method. On top of their usual care, the subjects were randomised to receive Pactivibe at 100mg dose or placebo. The researchers also analysed the subjects' lipid profiles including the subjects' LDL cholesterol, triglycerides, apolipoprotein A-1 and apolipoprotein B. Baseline characteristics of the above were compared at various stage of the study. The primary endpoint was the incidence of cardiovascular events such as non-fatal myocardial infarction, stroke, coronary or carotid revascularisation, unstable angina, as well as any cardiovascular-related mortality.

After 6 months of treatment with Pactivibe, it was revealed that the baseline LDL cholesterol significantly increased by 7.3% in the Pactivibe group, compared with 1.4% in the placebo group. This effect on Pactivibe was also seen together with an increase in apolipoprotein B. No statistically significant difference was found in the subjects' CIMT between the two groups, although a greater increase was seen in patients who received Pactivibe. A higher incidence of cardiovascular endpoints was also observed in the Pactivibe group than the placebo group (2.3% vs 0.2%, $p=0.01$).

Summarising the findings of statistically greater increase in LDL cholesterol, the faster progression of atherosclerosis observed on CIMT, as well as observation of higher incidence of cardiovascular outcome, the researchers concluded that ACAT inhibition does not slow the progression atherosclerosis. Once again, this trial concluded with Pactivibe exhibiting no beneficial effect compared with placebo on atherosclerosis, as well as an increase in the incidence of major cardiovascular events.

The release of ACTIVATE trial results led to the premature termination of CAPTIVATE trial and therefore only fairly limited efficacy data were collected based on the CIMT study model.⁽⁶⁾

The A-PLUS trial published in 2004 showed similar results. The double-blinded randomized controlled trial looked at the effects of avasimibe on the reduction of atherosclerosis, assessed by IVUS. Study subjects were randomized to avasimibe dosage at 50, 250, and 750 milligrams daily. In A-PLUS, avasimibe was found to raise LDL cholesterol and that the trial drug failed to slow atherosclerotic plaque formation.

THE VERDICTS: STATINS AND FIBRATES REMAIN AS TREATMENT OF CHOICE

The burden of cardiovascular disease is further increased as a result of the ageing population and the globalization of obesity pandemic in both the developed and the developing worlds. The Global Burden of Disease report (2004 update) by the World Health Organization indicated the fact that coronary heart disease was responsible for 7.2 million mortalities worldwide, accounted for over 12% of total deaths around the world. It was suggested that by year 2020, cardiovascular disease will overtake infectious and communicable diseases as a leading reason for loss of productive life years worldwide.

Statins reduce the risk of cardiac morbidities and mortalities from cardiovascular disease by around 30 percent provided that a sustained and continuous use of the lipid-lowering drugs. There have been numbers of researches on newer lipid-lowering agents, in this article we reviewed several sizable randomised controlled trials on the novel agent acyl-coenzyme A:Cholesterol acyltransferase (ACAT) inhibitors, all of which demonstrated that ACAT inhibition failed to slow atherosclerosis and may even potentially be pro-atherogenic. Thus drug treatment with statins and the fibric acid derivatives remain as the major pharmacological strategies in the primary and secondary prevention of cardiovascular disease.

Author's background

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Immunotherapeutic Vaccines for Treating and Preventing Cancer

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ABSTRACT

A large number of drugs are available for treating particular cancers but the outcomes of treatment with the drugs are not ideal due to poor survival rates. A more satisfactory approach to cancer treatment, as well as to treating chronic infections, is to harness the body's natural defenses through the use of therapeutic vaccines and immunotherapeutic products. Already there are nonspecific immuno-modulation products that are used to treat some cancers. There are no therapeutic vaccines or immunotherapeutic products currently on the market but development is progressing and the launch of the first product may be getting close. The aim here is to discuss current pharmacological options for 12 major cancer conditions that companies are targeting for solutions through immunotherapeutic products or vaccines.

Keywords: Immunotherapy; Vaccines; Cancer; Immuno-modulation products; Adjuvants

INTRODUCTION

The impact of immunological thought on medical practice has been increasing at a steady rate for nearly half a century. There appear to be very few fields to which the immunologist cannot contribute. Initially the immunological approach was limited to assistance in diagnosis and in sera and vaccine production. New approaches in the field of therapy are not only in the use of

vaccines, sera and immunosuppressive agents, but also in the more rational use of conventional therapeutic agents. Immunological knowledge is especially necessary in the field of tumor therapy, particularly in the balanced use of surgery and radiotherapy.

CANCER VACCINES

There are two kinds of cancer vaccines; those called **therapeutic vaccines** that are designed to treat existing cancers and those called **prophylactic vaccines** that are designed to prevent the development of cancer. Therapeutic vaccines are administered to strengthen the body's natural defenses against cancers and so prevent the further growth of cancer cells and the recurrence of treated cancers, or eliminate cancer cells not killed by prior treatments. Prophylactic vaccines are administered to healthy individuals and are designed to target cancer-causing viruses to prevent any viral infection that may lead to cancer.

CANCER-RELATED VACCINES CURRENTLY AVAILABLE IN THE UNITED STATES

Two prophylactic vaccines have been licensed by the U.S. Food and Drug Administration to prevent viral caused cancers. They are the hepatitis B vaccine that targets the hepatitis B virus which is associated with some forms of liver cancer; and Gardasil™ that targets two types of human papillomavirus (HPV) - HPV 16 and 18 - that together cause 70 percent of cervical cancer cases worldwide. Gardasil also protects

against genital warts caused by HPV types 6 and 11 that cause 90 percent of cases of warts.

There are currently no licensed therapeutic vaccines. However in Russia approval has been granted to market Oncophage to treat kidney cancer.

THE DESIGN OF THERAPEUTIC VACCINES TO TREAT CANCER

These vaccines like all vaccines rely on unique protein or carbohydrate molecules on the surface of the cells that are not on non-cancerous cells. These molecules are antigenic so they can stimulate the immune system to cause a specific immune response. The hope is that when a vaccine containing cancer-specific antigens is injected into a patient, they will stimulate the immune system to attack cancer cells only.

WHY DOES THE IMMUNE SYSTEM NEED A VACCINE TO HELP FIGHT CANCER?

The immune system generally does not recognize tumors as foreign so it doesn't mount an attack against them. The reason for this may be that tumor cells are derived from normal cells. Therefore, even though there are many molecular differences between normal cells and tumor cells, cancer antigens are not truly foreign to the body, but are normal molecules, that are either altered in subtle ways or more abundant.

Another reason may be that cancer

cells have developed ways to “escape” the immune system. Some modes of escape include shedding tumor antigens, and reducing the number of molecules and receptors that the body normally relies on to activate T cells and other immune responses. Reducing these molecules makes the immune system less responsive to the cancer cells; the tumor becomes less “visible” to the immune system. It is hoped that with this knowledge more effective vaccines may be designed.

STRATEGIES BEING USED TO DESIGN EFFECTIVE CANCER TREATMENT VACCINES

There are several strategies under study to stimulate an immune response against tumors. Having identified a unique cancer cell antigen the aim is to make the tumor-associated antigen more immunogenic so as to cause an immune response. Approaches include:

- (a) altering slightly the amino acid structure of a protein based antigen,
- (b) placing the gene for the tumor antigen into a viral vector that can deliver genetic material to a targeted cell,
- (c) adding genes for one or more immuno-stimulatory molecules into a viral vector along with the genes for the tumor antigen.
- (e) incorporating tumor molecules with an adjuvant to trick the immune system into attacking both the antigen/adjuvant complex (the vaccine) and the patient’s tumor.

TYPES OF TREATMENT VACCINES CURRENTLY UNDER INVESTIGATION

The types of vaccines listed below show various methods designed to present cancer antigens to the body’s immune system in the hope of stimulating an immune response to a tumour. The list is not comprehensive.

Antigen/adjuvant vaccines

Antigen vaccines, the first types studied,

commonly use specific protein fragments, or peptides, combined with an adjuvant, to stimulate the immune system. One or more cancer cell antigens are combined with an adjuvant and used to vaccinate a patient. It is expected that the immune system will then respond to tumor cells that express that antigen.

Whole cell tumor vaccines

Cells taken either from the patient’s own tumor (autologous) or from one or more other patients (allogeneic) are used to prepare whole cell vaccines in the hope of stimulating an immune response.

Dendritic cell (DC) vaccines

Dendritic cells (DCs), special white blood cells, are taken from a patient’s blood through leukapheresis and stimulated with the patient’s own tumour antigens, grown in Petri dishes, and re-injected into the patient. DC vaccines activate the immune system’s T cells which is expected to cause T cells to multiply and attack the tumor cells.

Viral vectors and DNA vaccines

These depend on antigen-presenting cells (APCs). The nucleic acid sequence (the gene) of the targeted tumor antigen is manipulated in the laboratory so that it will be taken up by the APCs. Part of the antigen together with another molecule are then displayed on the APC cell surface. The hope is that on injection the immune system will respond by attacking not only the APC cells, but also tumor cells containing the same antigen. The advantage of these vaccines is they are easier to manufacture than some other vaccines.

Idiotype vaccines

Antibodies can act as antigens and induce an antibody response. Antibodies produced by certain cancer cells (namely, B-cell lymphomas and myelomas), called idiotype antibodies, are unique to each patient and can be used to trigger an immune response in a manner similar to antigen vaccines.

ANTIGENS COMMONLY FOUND IN STUDIES OF CANCER VACCINES

Cancer cell antigens may be unique to individual tumors, shared by several tumor types, or expressed by the normal tissue from which a tumor grows. In 1991, the first human cancer antigen was discovered in the cells of a patient with melanoma, a potentially lethal form of skin cancer. The discovery sparked intense research on cancer antigens.

Therapeutic Vaccines

Patient-specific vaccines

use a patient’s own tumor cells to stimulate an immune response against the patient’s malignant cells. The therapy is tumor-specific so theoretically non tumor cells should not be affected. There are several kinds of patient-specific vaccines being studied.

Prostate Specific Antigen (PSA) is a prostate-specific protein antigen that is found on the cancer cells and in the blood. However PSA is generally present in small amounts in men who are cancer free, but the quantity generally rises when the cancer develops. Although a high PSA level may indicate cancer, there are many other possible reasons for an elevated PSA level. Patients do mount T-cell responses to PSA.

Sialyl Tn (STn) is a small, synthetic carbohydrate that mimics the mucin molecules (the main molecule in mucus) found on certain cancer cells.

Heat Shock Proteins (HSPs) (e.g., gp96) are produced in cells in response to stresses such as excessive heat, low sugar levels and other signals and protect against the stresses. Further, they are also involved in the proper processing, folding, and assembling of proteins within cells. In laboratory experiments, HSPs from mouse tumors, in combination with small peptides, protected mice from developing cancer. The human vaccine incorporates peptide complexes isolated from a patient’s tumor. Studies with HSPs are targeting liver, skin, colon, lung, lymphoma and prostate cancers.

Ganglioside molecules (e.g., GM2, GD2, and GD3) contain carbohydrates and fats and when incorporated into the cell membrane they make the cell more easily recognized by antibodies. GM2 is found on the cell surface of a number of human cancers. GD2 and GD3 contain carbohydrate antigens expressed by human cancer cells.

Carcinoembryonic antigen (CEA) occurs in high levels on tumor cells from colorectal, lung, breast and pancreatic cancers. CEA may be released into the bloodstream. Patients mount T-cell responses to CEA.

MART-1 (also known as Melan-A) is an antigen expressed by melanocytes, the melanin producing cells that color skin and hair. It is a melanoma cancer marker recognized by T cells and more abundant on melanoma cells.

Tyrosinase is a key enzyme involved in the initial stages of melanin production. Tyrosinase is also a specific marker for melanoma due to its abundance on melanoma cells.

Prophylactic Vaccines

Viral proteins on the outside coat of cancer-causing viruses are commonly used as antigens to stimulate the immune system to prevent infections with the viruses.

THE ADJUVANTS COMMONLY USED

Adjuvants are decoys that consist of weakened proteins or bacteria which "trick" the immune system into mounting an attack on both the decoy and the tumor cells. Antigens from tumor cells are incorporated with the adjuvant. Several adjuvants are described below:

Keyhole limpet hemocyanin (KLH) is a protein produced by keyhole limpets found along the coast of California and Mexico. KLH is a large protein that both causes an immune response and acts as a carrier for cancer cell antigens that are

relatively small. KLH provides additional recognition sites for T-helper-cells and may increase activation of cytotoxic T-lymphocytes (CTLs).

Bacillus Calmette Guerin (BCG) is an inactivated form of the tuberculosis bacterium. BCG is added to some cancer vaccines with the hope that it will boost the immune response to the vaccine antigen. It is not well understood why BCG may be especially effective for eliciting immune response. However, BCG has been used for decades with other vaccines, including the vaccine for tuberculosis.

Interleukin - 2 (IL-2) is a protein made by the body's immune system that may boost the cancer-killing abilities of natural killer cells. Although it can activate the immune system, many researchers believe IL-2 alone is not enough to prevent cancer relapse. Several cancer vaccines use IL-2 to boost immune response to specific cancer antigens.

Granulocyte Monocyte-Colony Stimulating Factor (GM-CSF) is a protein that stimulates the proliferation of antigen-presenting cells.

QS21 is a plant extract that, when added to some vaccines, may improve the body's immune response.

Montanide ISA-51 is an oil-based liquid intended to boost an immune response.

OTHER VACCINES UNDER DEVELOPMENT TO PREVENT CANCER

In addition to the FDA-approved Hepatitis B vaccine and HPV vaccine, there are other vaccines being studied that may reduce the risk of cancer. These vaccines target infectious cancer-causing agents, similar to traditional vaccines that target other disease-causing infectious agents, such as polio or measles viruses. Commonly the viral coat proteins (proteins on the outside of

the virus) are used as the antigens for these vaccines. It is hoped to stimulate the immune system in the future to attack cancer-causing viruses, which should, in turn, reduce the risk of the associated cancer.

Vaccines that have reached Phase III testing

Phase III testing of vaccines for the following cancers are in progress. Cervical Cancer, Follicular B-cell Non-Hodgkin's Lymphoma, Kidney Cancer, Cutaneous Melanoma, Ocular Melanoma, Prostate Cancer and Multiple Myeloma. The names of some of these vaccines include GardasilTM HPV (human papilloma virus) quadrivalent vaccine, CervarixTM HPV bivalent vaccine, Biovaxid®, GTOP-99 MyVax® Personalized Immunotherapy, OncophageTM (HSPPC-96), OncophageTM (HSPPC-96), MDX-1379, GVAX® and Provenge® sipuleucel T.

The results from ongoing or unpublished Phase III trials will determine what role vaccines will play in the treatment and prevention of different cancers. Information about such trials are available from U.S. government databases including the National Cancer Institute's clinical trials database, <http://cancer.gov/clinicaltrials/search> and the National Institutes of Health clinical trials Web site, <http://clinicaltrials.gov>.

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Human Papillomavirus Vaccine: Friend or Foe?

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ABSTRACT

The human papillomavirus (HPV) is confirmed to cause cervical cancer and HPV vaccines have been developed to control the HPV infection. The cases of death after vaccination that have drawn the worldwide attention of women raise concerns about the safety issue of the vaccines. The development of HPV vaccines is still walking stepwise as it shoots for the target of combining both the preventative and therapeutic aspects of a vaccine.

Keywords: Papilloma, Warts, Sexually transmitted disease, Cervical cancer, HPV Vaccine

INTRODUCTION

Papillomas are small tumour of epithelial tissue (skin, mucous membranes, or glandular ducts), caused by a papillomavirus. Papillomas affecting the skin are commonly known as warts or verrucas. Papillomaviruses (HPV) are largely host-specific, and different types of papillomaviruses may cause morphologically distinct types of papilloma in a given host. In man, papillomas are caused by human papillomaviruses, which are small, non-enveloped double stranded DNA viruses. They are one of the common sexually transmitted disease (STD) agents that infect the genital area. Some of them result in papillomas, warty growths in external or internal genitalia and may cause non-warty lesions of mucosal surfaces like uterine cervix and also contribute to the major factor of cervical cancer development.⁽¹⁾ Figure 1 shows the model of human papillomavirus and also the health problems due to the viral infection in different part of human body, including the HPV related cervical cancer in female on the top right corner.

In order to prevent the HPV related cervical cancer in female, HPV vaccine was firstly developed by GSK targeted with HPV 16 and 18. The vaccine is now used worldwide with the intention of preventing cervical cancer. However, injection of this vaccine occasionally

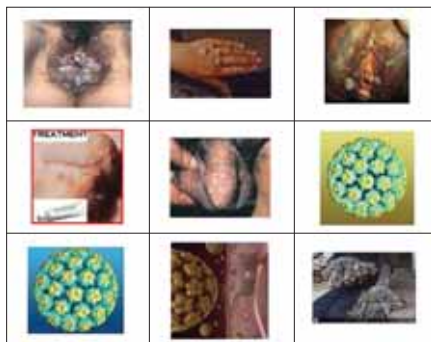


Figure 1. Human Papilloma viruses. The diagram above shows the model of Human papillomavirus and also warts caused on various places of human body. (adapted from <http://www.thetop10.com/>)

results in death for some patients. According to CBC news, a British girl died after receiving injection of the Human Papillomaviral vaccine which caught the attention of the whole world. "HPV vaccine" appeared on the billboard of many internet engines, reflecting the concern about the safety and efficacy of HPV vaccines.⁽²⁾

Further reports on CBC news said that the girl may not have been killed by the vaccination but because of a malignant chest tumor.⁽³⁾ The incident developed into a question of whether HPV vaccines are our friends or foes.

ETIOLOGY OF HUMAN PAPILOMAVIRUS

The name of Human Papillomavirus (HPV) arose because of the papilloma formed after infecting a human. It is known that over 130 types of HPV can cause infection in human bodies.⁽⁴⁾ However, most of them can be ignored due to self immunity and only certain types of HPV, most commonly HPV 16 and 18, are referred to as the high risk HPV because they play a causal role in the development of cervical cancer.⁽⁵⁾

The hypothesis of the HPV causing cervical cancer was first introduced by Prof. Harald Zur Hausen in the year of 2001, who won the 2008 Nobel Prize in physiology and medicine. Hause (2001) provided firm evidences for the HPV causality in cervical cancer and encourages the

development of HPV vaccine.⁽⁶⁾

The route of HPV infection is through microscopic abrasions at the deeper layer of the epithelium. Latent infection may last for several years without any symptoms and evidence shows that 90% of the infection may be totally eliminated in two years. However, mutation process of deeper layer of the epithelial cells could happen during intermittent viral replication and release which result into various types of lesions and eventually cervical cancer.⁽¹⁾

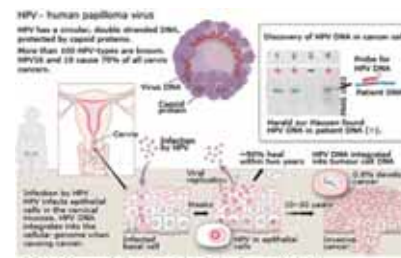


Figure 2. The infection routine of human papilloma virus. The diagram shows the relationship between the general infection and HPV which induce latent infection which potentially develops to cervical cancer. (Adapted from the Nobel Committee for Physiology or Medicine 2008)

Up to date, more than 40 types of HPV are confirmed to be capable of causing the infection of the epithelial and mucosal lining of the anugenital tract and other areas and could result in lesions like genital warts (condylomata) and low-grade squamous intraepithelial lesions of the cervix (LSIL) and vulva, no matter whether the infection was caused by high risk or low risk HPV.⁽⁷⁾

There were suggestions that cervical cancer could only develop in the presence of HPV DNA⁽⁵⁾ and thus HPV infection is considered as the most important risk factor in cervical cancer.⁽⁸⁾ There is evidence indicating that HPV infection causes DNA mutation which turns on the oncogene or turns off the tumor suppression gene in cells.⁽⁷⁾ These tumor suppression genes are called p53 and pRb which are inactivated by E6 and E7 protein of the HPV genome and result in serious intraepithelial neoplasia that can finally develop into cancer.⁽⁹⁾ The expression of the putative tumor suppressor gene *B-cell translocation gene-2 (BTG2)* could be repressed by

oncogenic HPVs and the activities of the viral E6 and E7 oncogenes.⁽¹⁰⁾

TYPE OF HPV VACCINES

Due to the increasing trend of cervical cancer in women related to HPV infection, a safe, effective and long lasting HPV vaccine is now available that has been produced using DNA recombinant technology.⁽¹¹⁾

There are now five approaches to producing HPV antigens, using a harmless virus or bacterium as a vector, using certain proteins and viral proteins (L1, L2 protein with E6 and E7 protein), using virus-like particles (VLPs), and using naked DNA of the virus by inserting HPV genetic material into bacterial plasmids.⁽¹¹⁾

Gardasil is the first HPV vaccine available which aimed at preventing the HPV infection. Nowadays there are two types of HPV prevention vaccine now available on the market that are produced by means of VLPs especially for woman aged 9 to 26, namely Gardasil and Cervarix produced by MSD and GSK, respectively. Besides the variation on the target HPV, the adjuvant used in the two vaccines is different. The VLP of Cervarix is made with AS04 containing 3-O-desacyl-4'-monophosphoryl lipid A (MPL) adsorbed on aluminium hydroxide while the VLP of Gardasil is made by adsorption on amorphous aluminium hydroxyphosphate sulphate adjuvant.⁽¹²⁾

The general mechanism of HPV vaccines is that they contain an attenuated virus-like particle, L1 major capsid protein, that aims in elicit the production of virus-neutralizing antibody.⁽¹³⁾ A comparison of two brands of HPV vaccine is summarized on Table 1.

CLINICAL EFFECT OF HPV VACCINE

According to the CDC's records, the female age group in the US with the highest risk of being infected with HPV is those aged around 20-24 while those aged around 50-59 have the lowest risk. The different risk percentages on prevalence of HPV infection in different age groups is illustrated in Figure 3. Certain studies indicate the effectiveness of the HPV-16/18 vaccine could reduce the lifetime cervical cancer cases by 61.8%. The results obtained are summarized in Figure 4.⁽¹⁶⁾

The result of the reduction in lifetime risk of cervical cancer shows that the vaccine was most effective for females

(Figure 4.) aged 12 or below and which are not yet sexually active, compared with women aged 24 or above.⁽¹⁶⁾

HPV VACCINE

The latest approach to promote an anti-tumor effect focuses on the modification of HPV vaccine. By HPV has early genes (E1 to E7), late genes (L1 to L2)

FUTURE APPROACH: THERAPEUTIC

Table 1. Comparison of two major brands of HPV vaccine. The two brands of HPV vaccine produced by MSD and GSK are compared with major components, adjuvant, and clinical usage. ^(12,14)		
Brand	Gardasil (加護苗)	Cervarix (卉妍康)
Manufacturer	MSD	GSK
Vaccine Type	Virus-like particle prophylactic	Virus-like particle prophylactic
Active Ingredient	L1 protein of target viruses	L1 protein of target viruses
Adjuvant Used	Morphous aluminium hydroxyphosphate sulphate	AS04 containing 3-O-desacyl-4'-monophosphoryl lipid A
Target Virus	HPV 16 HPV 18 HPV 6 HPV 11	HPV 16 HPV 18
Number of Doses and Time	3 doses	3 doses
Interval for Injection	0, 2, 6 months	0, 1, 6 months
Target Group	Women 9 - 26	Women under 25
Common Side Effects	Pain, itchy at injected site Low grade fever(>38)	Pain, itchy at injected site Low grade fever (>38)
Uncommon Serious Effects	Paralysis Convulsions Sight problems Muscle Weakness Bell's palsy Hypoesthesia Guillain-Barré syndrome	Paralysis Convulsions Sight problems Muscle Weakness Bell's palsy Hypoesthesia Guillain-Barré syndrome
Precaution	Pregnant women	Pregnant women
Reported Death	32 reports of death	21 reported deaths

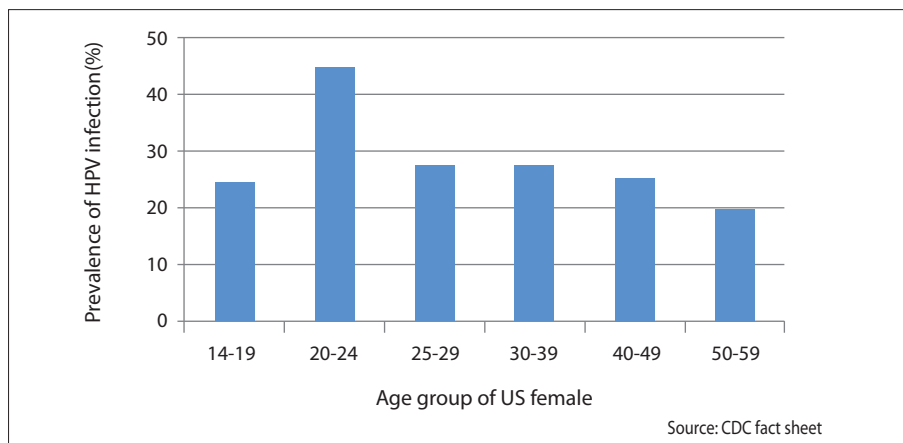


Figure 3. The percentage of US females in different age group with prevalence of HPV infection. The average of prevalence of HPV infection of females in selected age group including 14-19, 20-24, 25-29, 30-39, 40-49, 50-59 in every year in US.⁽¹⁵⁾

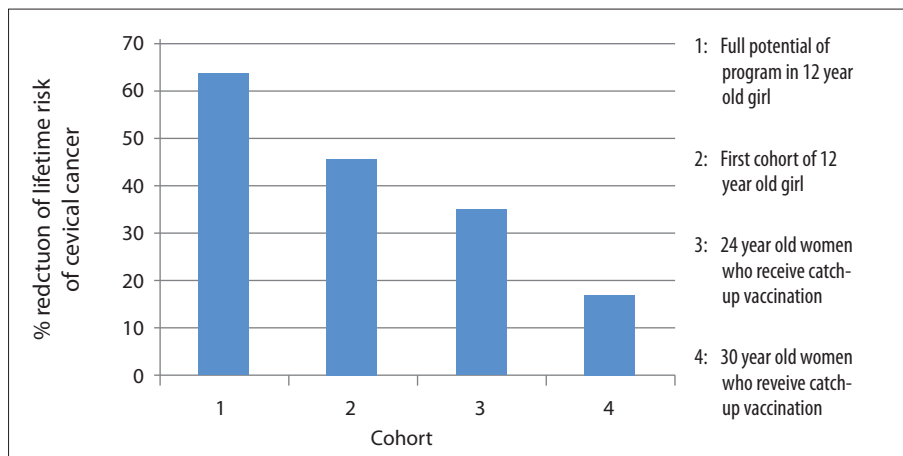


Figure 4. The percentage reduction of lifetime risk of cervical cancer in different cohorts. Highest reduction of lifetime risk of cervical cancer was found in girls who are 12 years old and subject to the full potential program while the lowest reduction is found in women who are aged 30 and receive the catch up vaccination.⁽¹⁶⁾

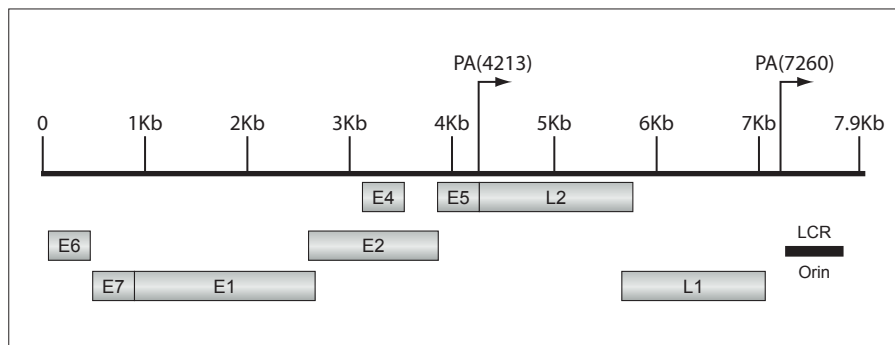


Figure 5. The linear HPV genome structure. The typical HPV genome is composed of early gene and late gene which refers to E1 to E7 protein and L1 to L2, respectively, and also the non coding long control region (LCR) which is responsible for regulating viral replication and gene expression. (Adapted from ref. 17)

and a non-coding long control region, in which the E2 protein expression is the hallmark of HPV associated with cervical carcinoma and also viral helicase E1. The distinct interaction is directly related to viral genome replication and E5 proteins have been confirmed to be a suitable therapeutic target of HPV 16. The latest vaccine is aimed at stimulating a T-cell response to eliminate the infected cells.⁽¹⁷⁾

Another approach is chimeric VLPs that are indistinguishable from the parental VLPs in their morphology and in their ability to agglutinate erythrocytes and elicit high titers of neutralizing

antibodies.⁽¹⁸⁾ Moreover, certain research has suggested that the E6 is a better target gene than other HPV-16 genes for the elimination of tumor cells in the early onset stages of the disease.⁽¹⁷⁾

Also, as shown in Figure 5, there are studies focused on increasing the target antigen by combining the L1 major capsid protein with the non structural papillomavirus protein E7 (11kDa), or E2 (43 kDa) with the L2 major capsid protein in order to increase the potential therapeutic effect of VLP-based prophylactic vaccines of VLP-based prophylactic vaccines.⁽¹⁸⁾ The E7 protein of

HPV 16 can be produced by HPLC purification and good manufacturing practice to enhance the development of immunotherapy to fight against cervical cancer.⁽¹⁹⁾

CONCLUSION

There is no argument that the cost effectiveness of HPV vaccine is quite high with only few side effects. The safety issue is the main concern of the public however according to studies there is evidence showing satisfied effectiveness in female especially those before sexually active stage. Thus the HPV vaccine should be highly promoted to the public so as to allay the fear of HPV vaccine in the mind of the public. HPV vaccines should be the friends of human rather than of foe.

Author's background

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The Mysterious Veil of the Biological Functions of *Panax ginseng* C.A. Meyer (高麗蔘) – What Ginsenosides Can Do for Our Health?

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Botanical Name: *Panax ginseng* C.A. Meyer

Plant Family: Araliaceae

Pharmacopoeia Name: Radix Ginseng

Chinese Name: 高麗蔘

Chinese Phonetic Name:

Other Names: Asian Ginseng, Korean Ginseng, Gao li Shen, Bai Shen, Ye Shan Shen, Ji Ling Shen, Bie Zhi Shen, 人蔘、棒棰、山參、園參、人蔘、鬼蓋、土精、神草、黃參、血參地精、百尺杵、海蔘、金井玉蘭、孩兒參

ABSTRACT

The main medical application of *Panax ginseng* C.A. Meyer is the maintenance of homeostasis of the body. The most important bioactive components that are responsible for the pharmacological effects of *P. ginseng* that have been identified, all belongs to ginseng saponins (GS). Their effects include activities against cancers, enhancement of immune system function and improvement of brain function. Some of the effects are summarized and reviewed in this article. Bioactive substances, such as G-Rb₁, GRG₁ and G-Rg₂ have been successfully isolated and characterized. They are the main pharmacologically-active components responsible for improving the cerebral functions, while G-Rh₂ and G-Rg₁ are ingredients responsible for enhancing the immune system, inflammation and allergy. Studies reveal that the anticancer effects of ginseng are attributed to the presence of G-R₃, G-Rb₂, G-Rg₃, GRh₂, G-Rp₁ and GS. Non-saponin compounds, such as polyacetylene play an important role in the pharmacological function against cancer. The angiogenesis of ginseng is attributed to G-Rg₁ and G-Re. Nevertheless, the exact pharmacological function of GS has not been completely confirmed, and further research is required in order to unveil the complete biological

functions of ginseng.

Keywords: *Panax ginseng*, active components, pharmacological effect, Ginsenosides; Adaptogenic



Figure 1. Photo of *Panax ginseng* C.A. Meyer



Contraindications

Patients with acute illness, cardiovascular disease, diabetes, or blood pressure disorders should use caution when taking ginseng. Pregnant women should not take ginseng because its safety during pregnancy has not been determined.

Undesirable effects

One of *P. ginseng*'s most common side-effects is the inability to sleep after use. However, some sources state that ginseng causes no sleep difficulties. Other side-effects may include nausea, diarrhea, euphoria, headaches, epistaxis, high blood pressure, low blood pressure, and mastalgia.⁽¹⁾

Interactions

Red ginseng may increase the effects of caffeine or other stimulants. Any ginseng product may increase the effects of phenelzine (Nardil) or other antipsychotics, or blood pressure, anti-diabetic or steroidal medications.

INTRODUCTION

Radix Ginseng, which is also called Renshen in Chinese (Fig. 1), is the root of *Panax ginseng*. *Panax*, the genus to which Ginseng belongs, is formed from two Greek words, pan (all) and akos (cure), which indicates it treat all diseases. With thousands of years of history, it has been traditionally known as a medicinal plant with mysterious powers in the Orient. Particularly used in traditional Chinese medicine (TCM), it has been known as the most valuable medicine of all medicinal herbs. Against this background in order to reveal the mysterious veil of *P. ginseng*, a great deal of research is carried out on the active components and their pharmacological effects. In this article, we concentrate mainly on the main potential active constituents of *P. ginseng* and find out their specific effects on the body.

MORPHOLOGICAL DESCRIPTION AND IDENTIFICATION

P. ginseng grows in the Northern Hemisphere in eastern Asia (mostly northern China, Korea, and eastern Siberia), typically in cooler climates. Radix ginseng is the root of *P. ginseng*, and is usually the main medical ingredient. Ginseng leaf, although not as highly prized, is sometimes also used. It is most often available in two forms of radix ginseng: white ginseng and red ginseng (Fig. 2). White ginseng is grown for four to six years, and then peeled and dried to reduce the water content to 12% or less. White Ginseng is air dried in the sun and may contain less of the therapeutic constituents. The form called red ginseng is harvested after six years, is not peeled and is steam-



Figure 2. White (left) and red ginseng (right)

cured, thereby giving the roots a glossy reddish-brown coloring. Steaming the root is thought to change its biochemical composition and also to prevent the breakdown of the active ingredients. The roots are then dried. *P. ginseng* roots are taken orally as adaptogens, aphrodisiacs, nourishing stimulants, and in the treatment of type II diabetes, as well as sexual dysfunction in men.

General appearance

P. ginseng is a slow-growing perennial herb with characteristic branched roots extending from the middle of the main root in the form of a human figure. Stem is erect, simple, and not branching. Leaves verticillate, compound, digitate, leaflets 5, with the 3 terminal leaflets larger than the lateral ones, elliptical or slightly obovate, 4-15 cm long by 2-6.5 cm wide; apex acuminate; margin

serrulate or finely bidentate. In general, one leaf in the first year with one leaflet added annually until the sixth year; inflorescence at small terminal umbel, hemispherical in early summer. Flowers are polygamous, pink. Calyx vaguely 5-toothed Petals 5, stamens 5. Fruit is a small berry, nearly drupaceous, and red when ripe in autumn.

MACROSCOPIC APPEARANCE AND ORGANOTECTIC PROPERTIES OF DRIED GINSENG

The main root is fusiform or cylindrical. 2.5-20 cm long by 0.5-3.0 cm in diameter; externally greyish yellow; upper part or entire root exhibiting sparse, shallow, interrupted, and coarse transverse striations and distinct longitudinal wrinkles; lower part bearing 2-5 branching lateral

roots and numerous slender rootlets with inconspicuous minute tubercles. Rhizomes 1-4 cm long by 0.3-1.5 cm in diameter, mostly constricted and curved, bearing adventitious roots and sparse depressed circular stem scars. Texture relatively hard, fracture yellowish white, cambium ring brownish yellow, starchy. The colour of dried herb is greyish white to amber-yellow; odour, characteristic; taste, slightly sweet at first followed by a slight bitterness.

MICROSCOPIC CHARACTERISTICS

The transverse section of a ginseng shows epidermis consisting of several rows of cells; cortex narrow; phloem showing clefts in the outer part, and parenchymatous cells densely arranged and scattered with resin canals containing yellow secretions in the inner part; cambium in a ring; xylem rays broad, vessels singly scattered or grouped in an interrupted radial arrangement, and occasionally accompanied by non-lignified fibres; parenchyma cells containing abundant starch grains and a few clusters of calcium oxalate.

OTHER IDENTITY TESTS

No reliable method has been developed for the identification of *P. ginseng* C.A. Meyer although FTIR spectroscopy, HPLC and genetic identification have been explored.^(4,5,6)

BIOACTIVE CONSTITUENTS

P. ginseng is known to have kinds of efficacy, and many scientists agree that it acts to normalize the physical condition; that is to say, it maintains homeostasis.⁽⁷⁾ In addition, it is characterized by its fluent action, and nearly no drug dependence or tolerance occurs despite a long intake period. Many researchers have tried to validate past empirical observations of the efficacy of *P. ginseng* on the basis of modern physiological, biochemical and pharmacological knowledge. Phytochemical studies on *Panax* species commenced in 1854 when panquinone was isolated from *P. quinquefolius*. Since the beginning of the year 2000 a number of chemists have been engaged in chemical studies

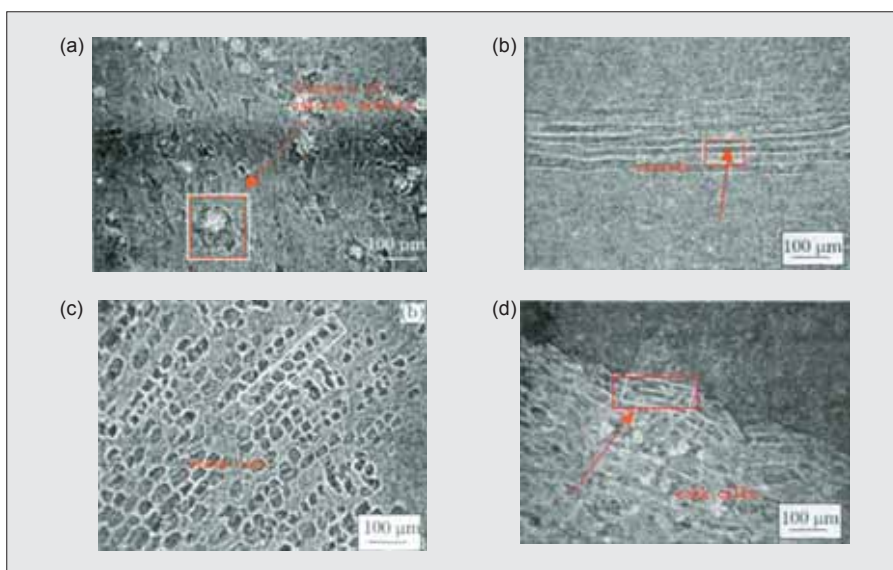


Figure 3. X-ray phase contrast imaging of characteristics section of dried root in *Panax ginseng* C.A.Meyer. (a). Clusters of calcium oxalate; (b). Wessels; (c). Xylem rays; (d). Cork cells.⁽³⁾

of saponins from *Panax* species. The most prominent of the phytochemicals isolated from the various species of *Panax* are the saponin glycosides. Many other classes of compounds have been found as well.⁽²⁾

Saponins of *P. ginseng*

Ginsenosides are triterpenoid saponins found nearly exclusively in ginseng and they have been the target of a lot of research as they are believed to be the main active principles behind the claims of ginseng's efficacy.

The first 6 saponin glycosides isolated from *P. ginseng* were given the names of panaxoside A, B, C, D, E, and F.⁽⁸⁾ More than 60 ginsenosides have subsequently been isolated from various *Panax* species. Based on the triterpene aglycones, the ginsenosides have been classified into 3 major categories, namely, the panaxidiols, panaxatriols, and the oleanolic acid derivatives (Fig. 4). A basic summary of the ginsenosides in each category for *P. ginseng*, and the plant parts from which they were isolated, is shown in Table 2. Although this table does not attempt to present a comprehensive or quantitative analysis of all ginsenosides, it does indicate the diverse and complex nature of the array of saponin glycosides in this species, many of which are biologically active.

Polysaccharides and glycopeptides identified from *P. ginseng*

GS polysaccharides and glycoproteins are the important bioactive components in *P. ginseng* and *P. quinquefolium*. Besides purified polysaccharides GH-1 (MW = 4,500) and G-H-2 (MW = 5,300), 21 panaxan (A-U) compounds with molecular weights (MW) ranging from 2,500 to 1,300,000 have been identified. A glycopeptide named *P. ginseng* P-21 (average MW = 6,000) and glycoproteins PA and PB have been obtained from the root of *P. ginseng*. Polysaccharides from stem (5AUH, 5AUL, 5NUH, 5NUL), leaf (GL-P1, II, IV) and berry (F1-F4) have also been identified from *P. ginseng* by investigators in China.⁽⁹⁾

Other constituents isolated from *P. ginseng*

Other chemical constituents isolated from *P. ginseng* include alkanes, alkynes, sterols, fatty acids, fatty acid esters (lipids), monoterpenes, sesquiterpenes, phenylpropanoids, chromones, amines, flavonoids, organic acids, and vitamins. Amino acids, nucleic acids, various enzymes, and inorganic compounds have also been isolated from ginseng.

FACTORS AFFECTING THE BIOACTIVE

COMPONENTS IN PLANTS

The pharmacological effects of herbal drugs not only depend on the type of bioactive components, but also the quantity that is used. However, many variables such as soil, fertilization, temperature, rainfall, distance between or among the cultured plants and age, will determine the quality of the herb. Again, the contents of bioactive components in leaf, flower, bud, seed, berry, stem, and each part of the root (main root, side root, root let) are different. Of course, the process changes the chemical composition, and the sensitivity of the method, and instruments used are other variables. The total content of ginseng saponins (GS) increase in accordance with the age of *P. ginseng*. In 10-, 6-, or 4-year-old *P. ginseng*, the contents of GS in the main root are 4.99%-5.89%, 3.80%-5.22%, and 2.60%, respectively.⁽¹⁰⁾

QUANTIFICATION ANALYSIS

The approved test for *P. ginseng* is a qualitative analysis described in the Pharmacopoeia of People's Republic of China. Total saponins in terms of ginsenoside-Rg₁ (C₄₂H₇₂O₁₄) and ginsenoside-Re (C₄₈H₈₂O₁₈) should not be less than 0.25% through HPLC determination, calculated on the basis of dry matter contents.⁽¹¹⁾

PHARMACOLOGICAL EFFECTS OF GINSENG

Historically, the efficacy of *P. ginseng* has been recognized based on traditional Chinese medicine where it is regarded as being warm in nature, sweet or slightly bitter in flavor and it is able to restore from collapse, reinforce the lung and spleen, to promote secretion of body fluid and relieve mental stress. It is considered the most effective herbs for reinforcing "Qi" (vital energy) and strengthening the body. Therefore, whoever are deficient in Qi, are fatigued, have poor appetite, suffer diarrhea, shortness of breath, feeble pulse, spontaneous perspiration, diabetes, febrile diseases, amnesia, insomnia and impotence, may find ginseng an effective herb.^(13, 14)

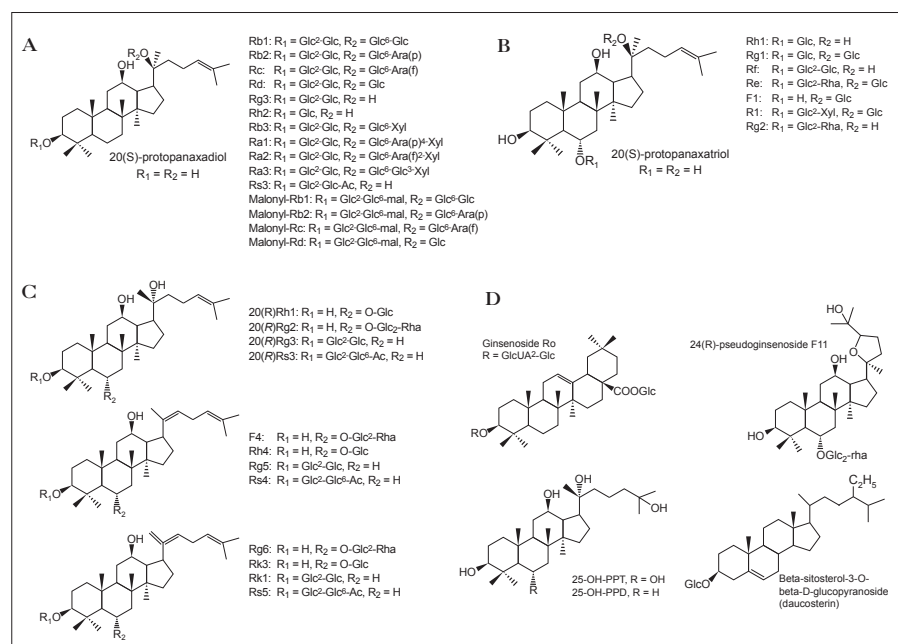


Figure 4. Structure of selected ginsenosides. A. protopanaxadiols (PD). B. protopanaxatriols (PT). C. derivatives of PD and PT. D. new ginsenosides. Glc: β -D-glucose; Rha: α -L-rhamnose; Ara(p): α -L-arabinose(pyranose); Ara(f): α -L-arabinose(furanose); Xyl: β -D-xylose; GlcUA: β -D-glucuronic acid; mal: malonyl; Ac: acetyl.⁽¹²⁾

On a gradual basis since the 1970s, modern scientific theory and technology have enabled scientists to determine the properties of *P. ginseng*. Now it has been reported to have many biological effects such as those to be described below.

General effects of *P. ginseng*

P. ginseng is a general tonic that maintains the body's homeostasis and helps resist adverse factors as well as enhancing physical and sexual functions, general vitality, and having anti-stress and anti-aging effects. Such effects are caused by the action of ginseng components on the hypothalamic-pituitary-adrenal axis and hypothalamic-pituitary-gonadal axis, or more basically through anti-oxidative effects, or enhanced oxygen and cellular glucose uptake.⁽¹⁵⁾

Efficacy of improving cerebral functions

P. ginseng (extract and the saponin component) has been found to increase learning ability and improve memory resulting in improved intellectual ability.⁽¹⁶⁾ *P. ginseng* reduces memory loss and, in exercise integration movements (namely, tendency to easily slip during a rotating bar ride test), counteracts decreased exercise function caused by alcohol administration.⁽¹⁷⁾ In Alzheimer's dementia, ginseng-treated patients showed clinical improvement at 4 weeks and showed continuing effects at 12 weeks. Ginseng treatment can improve cognitive function in Alzheimer's dementia.⁽¹⁸⁾ Ginsenoside Rb1 and Rg1 showed memory-enhancing effects in more than 10 models including aged rats, cerebral ischemia-reperfusion, ovariectomized rats and β -amyloid induced memory impairment. G-Rg1 improved all stages of memory (i.e. registration, consolidation and retrieval of memory).⁽¹⁷⁾

Pharmacologically-active components: G-Rb1, G-Rg1, G-Rg2

Effects on immune system, inflammation and allergy

Inflammation is the response to

infections, antibodies, chemical or physical injuries. However, exaggerated and prolonged inflammation will induce adverse consequences. Interactions of selectin, complement factor C5a, platelet-activating factor, cytokines, interleukin-1, tumor necrosis factor and eicosanoids LTB4 are important factors in affecting the adhesion of leukocytes and platelets to the sites of inflammation. Rb1 inhibits leukotriene release, Rg1 increases the T-helper cell and stimulates immune activity in the aged, polysaccharide and PPT type ginsenosides enhance interferon production, phagocytosis, natural killer (NK) cells, B and T cells.⁽¹⁹⁾ Rb1, Rg1 and Rg3 inhibit cytokine production, inhibit COX-2 gene expression, inhibit histamine release, and stabilize neutrophils and lymphocytes.^(20,21) *P. ginseng* extracts have the ability to revive cellular immune response after it has been decreased by mitomycin. Ether extracts also have the effect of significantly reviving or increasing the activity of cellular immunity or NK cells.⁽¹⁸⁾

Pharmacologically-active components: G-Rh2, G-Rg1, extract.

Anticancer effects

Besides improving cerebral functions and having effects on the immune system, inflammation and allergic reactions, the effect of ginseng on cancer prevention is now under investigation. Saponin and non-saponin ingredients of ginseng have shown an ability to inhibit the growth of a variety of cancer cells.^(22,23)

Saponin Ginsenoside Rp1 suppressed the growth of 21 S and HeLa cells in a dose-dependent manner. It was suggested that ginsenoside Rp1 can be used for anticancer action.⁽¹⁸⁾ Rh2 and Rg3 suppressed breast, prostate, liver and intestinal cancer cells.^(24,25) The ability of G-Rg3 to inhibit metastasis of lung cancer cells was observed in a test in which G-Rg3 was given to a mouse to which tumor cells (colon cancer cells) had been transplanted. Administration of G-Rb2 to the skin of a mouse into which melanoma cells had been transplanted inhibited tumor growth

and the angiogenesis of the tumor related to cancer cell metastasis.⁽²⁶⁾

Pharmacologically-active components: G-R3, G-Rb2, G-Rg3, GRh2, G-Rp1.

Non-saponin An active substance (GFP) that strongly promotes NO production in murine macrophages, that was isolated from the acidic polysaccharide component of red ginseng. It was found to increase the survival rate of male ICR mice into which was transplanted with sarcoma 180, and showed more potent tumoricidal activities than NK cells.⁽²⁰⁾ The post-operative chemotherapy for gastric cancer, the intake of red ginseng extract has the potential to improve anti-cancer immunity through the raising and depressing of interleukin-2 (IL-2) and reducing IL-10 respectively.⁽²⁷⁾

Pharmacologically-active components: polyacetylene compounds (panaxydol, panaxynol, panaxytriol).

P. ginseng is of interest to cancer patients in other countries chiefly for its reputed anti-fatigue properties. An overview of the research of its anticancer effects shows the ginsenosides are the most likely candidates for active compounds. Therefore, additive or synergistic anticancer effects of different bioactive components in *P. ginseng* probably occur.

Effects of ginsenosides on angiogenesis

In atherosclerosis, diabetic retinopathy, psoriasis, rheumatoid arthritis, and with tumors, there is excessive angiogenesis. On the contrary, alopecia, Alzheimer's disease, chronic wound, critical limb ischemia, hypertension, ischemic coronary artery, and ulceration is related to the decrease of angiogenesis. Re⁽²⁸⁾ and Rg1⁽²⁹⁾ enhance angiogenesis. Rb1, Rg3, and Rh2⁽²⁹⁾ inhibit angiogenesis. Rb1, Rb2, Rc and Rg3 inhibit tumor angiogenesis and metastasis. Rg1 inhibits microglia proliferation.⁽³⁰⁾ As pointed out by Fan *et al*, Rg1 leads to angiogenesis, whereas Rb1 exerts an opposing effect.⁽²⁾ Rb1 and Rg1 are major bioactive components in *P. ginseng*. Therefore Rg1 is better for wound healing.

Pharmacologically-active components: G-Rg1, G-Re.

Phytoestrogenic effects

Rb1, Re, Rg1, Rh1 are active components in red *P. ginseng* that help postmenopausal woman with climacteric syndromes, such as fatigue, insomnia and depression.⁽³¹⁾ Re activates eNOS through estrogen activation pathway and promotes vasodilatation. However, Rb1 promotes nitric oxide production in human aortic endothelial cells through androgen receptors.⁽¹⁵⁾

Table 1. Generally Recognized Species of <i>Panax</i> ⁽²⁾	
Species of <i>Panax</i>	
<i>Panax bipinnatifidus</i>	Seem
<i>Panax ginseng</i>	C.A. Meyer
<i>Panax japonicus</i>	C.A. Meyer
<i>Panax notoginseng</i> (Burkill)	F.H. Chen ex C.Y.Wu & K.M. Feng
<i>Panax pseudoginseng</i>	Wallich
<i>Panax quinquefolius</i>	L.
<i>Panax stipuleanatus</i>	H.T. Tsai & K.M. Feng
<i>Panax trifolius</i>	L.
<i>Panax vietnamensis</i>	Ha & Grushv.
<i>Panax wangianus</i>	S.C. Sun
<i>Panax zingiberensis</i>	C.Y.Wu & K.M. Feng

Table 2. <i>Panax ginseng</i> Saponins ⁽²⁾			
Compound Class/Name	Plant Part	Compound Class/Name	Plant Part
Panaxadiol saponins (PPD Type)		Panaxatriol saponins (PPT Type)	
Ginsenoside Ra ¹	Root ^a	Ginsenoside Re	Root
Ginsenoside Ra ²	Root ^a		Fruits
Ginsenoside Ra ³	Root ^a		Root ^a
Ginsenoside Rb ¹	Root		Flower buds
	Root ^a	Ginsenoside Rf	Leaves
	Flower buds		Root
	Leaves		Root ^a
Ginsenoside Rb ²	Root	Ginsenoside glc-Rf	Root
	Root ^a		Root ^a
	Fruits	Ginsenoside Rg ¹	Root
	Flower buds		Root ^a
	Leaves		Fruits
Ginsenoside Rb ³	Root	Ginsenoside Rg ²	Leaves
	Root ^a		Root
Ginsenoside Rc	Root	Ginsenoside Rh ¹	Root
	Root ^a	Ginsenoside F ¹	Leaves
	Fruits	Ginsenoside F ³	Flower buds
	Flower buds		Leaves
	Leaves	Notoginsenoside R1	Root ^a
Ginsenoside Rd	Root	Oleanolic acid saponins (Oleanane type)	
	Root ^a	Ginsenoside R ⁰	Root
	Fruits	Chikusetsusaponin V	Root ^a
	Flower buds	Chikusetsusaponin V	Root ^a
	Leaves		
Ginsenoside Rg ³ 20(R)	Root ^a		
Ginsenoside F2	Leaves		
Ginsenoside Rs ¹	Root ^a		
Ginsenoside Rs ²	Root ^a		
Quinquenoside R ¹	Root		
Malonyl-ginsenoside Rb ¹	Root		
Malonyl-ginsenoside Rb ²	Root		
Malonyl-ginsenoside Rc	Root		
Malonyl-ginsenoside Rd	Root		
Ginsenoside Rh ²	Root ^a		

a. Red ginseng was analyzed

Pharmacologically-active components: G-Rb1, G-Re, G-Rh1.

Efficacy of inhibiting AIDS virus (HIV) growth

AIDS is a chronic disease, and an examination of the anti-HIV activity of red *P. ginseng* components revealed that HIV growth inhibition activity was observed using crude saponin components. There is the possibility that the occurrence of the deleted nef gene (gΔ nef) might be associated with long-term intake of *P. ginseng*.⁽³²⁾

Pharmacologically-active components: crude saponin (no details confirmed)

Other effects

These include a radio-protective potential. A possible mechanism underlying the potential application of *P. ginseng* in clinical radio-protection is related to its anti-oxidative properties. Studies have demonstrated that ginseng root extracts

exhibit both lipid-soluble and water-soluble antioxidant activity ex vivo, and that this antioxidant action occurs both directly through free radical scavenging and indirectly through upregulation of antioxidant enzymes, leading to the prevention of DNA degradation. The other effects may relate to its immunomodulating effects which have been discussed in the above section.⁽³³⁾

DOSAGE RANGES AND DURATION OF ADMINISTRATION

White or red *P. ginseng* standardized to 1.5% ginsenosides, is designated as Rg1. The recommended dose is 1 to 2 g fresh root, or 0.6 to 2 g dried root, or 200 to 600 mg liquid extract daily. Healthy persons using *P. ginseng* for enhancing physical or mental performance or improving resistance to stressors should take these doses in cycles of 15 to 20 days followed by two-week breaks.

For rehabilitation after an illness, the elderly should take 0.5 g bid for three months, or take 0.5 g bid for one month, followed by a two-month break, and repeat cycle if desired.⁽³⁴⁾

ADVERSE EFFECTS

The German Commission E cites no adverse effects with the recommended daily dose. Agitation, addiction, changes in blood pressure, or "Ginseng Abuse Syndrome" are no longer associated with the normal use of ginseng. Adulterants, such as caffeine, are thought to cause these effects; NSAID adulterants may cause ginseng associated Stevens-Johnson syndrome.

The American Herbal Products Association rates ginseng as a class 2d herb. 2d indicates that specific restrictions apply, in the case of ginseng, hypertension is the specific restriction.⁽³⁴⁾

Author's background
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The 60th Anniversary Lecture & Dinner of the Pharmaceutical Society of Hong Kong – From Today Onwards

CHENG, Mary Catherine

The Pharmaceutical Society of Hong Kong (PSHK) was established on August 25, 1949. At that time, there were no more than 30 registered pharmacists in Hong Kong, and today we have over 1800 registered pharmacists in Hong Kong. Members of the Pharmaceutical Society have also grown from its humble beginning of 28 pharmacists to over 300 pharmacists.

To celebrate the 60th Anniversary of PSHK, a lecture and dinner were held on 31st October 2009 at the Hong Kong Jockey Club, Happy Valley Racecourse. Dr. Gloria Tam, the Deputy Director of Health gave a lecture on Public Health in Hong Kong and Professor Vincent Lee of the School of Pharmacy, Chinese University of Hong Kong gave a lecture on Continuing Pharmacy Education - Practice in the Digital World. The lecture was followed by cocktail reception where pharmacists and guests were given the opportunity to mingle and change views with each other.

There were over 200 people who attended the dinner. I was extremely happy to see the familiar faces of pharmacists who have retired, the past presidents and GCs of the Pharmaceutical Society. The dinner began with an entrance dance by all the GCs, followed by them singing the song "Top of the World". This innovative approach immediately created a relaxed and friendly atmosphere for everyone. Mr. Benjamin Kwong, President of PSHK gave the opening speech, Dr. York Chow, Secretary of Food, Health Bureau gave the theme speech and I, as the Vice-President and Chairlady of the 60th Anniversary Organizing Committee of PSHK, gave the welcome speech. As reviewed in their speeches, the theme "From Today Onwards" was

chosen because it was hope that, by joint efforts of all pharmacists and healthcare partners, we would take the pharmacy profession to a higher horizon and move forward in the delivery of good health to our citizens.

After the speeches, dinner began with soft music performed by the Longman Band. The Chinese cuisine served by the Hong Kong Jockey Club was absolutely delicious. The highlight of the dinner was the cake cutting ceremony. The beautifully decorated 6-layered cake represented the 60th Anniversary of PSHK. Together with the President, the Chairlady and Dr. York Chow, the past presidents of PSHK were invited to the stage for toasting. A 15 minutes video highlighting the formation of PSHK and important historical events in the development of the pharmacy profession in Hong Kong was shown. In order to prepare for the video, some of the key pharmacists involved were interviewed to relate the circumstances and events in the past. A full version of the interviews and historical photos will be consolidated in a DVD for distribution to members. After the toasting ceremony, the young helpers distributed to each participant a specially designed 60th Anniversary PSHK watch. The watches were marked with the wordings "PSHK 60th Anniversary" to commemorate the occasion. Everyone was extremely happy with the surprise souvenir. On top of that, there were over 20 lucky draws for the participants. We see many smiling pharmacists going up stage to receive the lucky gifts.

During dinner, award certificates were given to the GCs of PSHK or Pharmacy & Poisons Board Members who have served for 3 years or more during the past 10 years (2000-2009).

They were Mr. Chan Chi Kit, Mrs. Mary Cheng, Mr. Philip Chiu, Mr. Peter Chua, Mr. Ken Hau, Ms. Ritchie Kwok, Mr. Paul Lam, Dr. Grace Lau, Mr. Henry Lau, Mr. John Lau, Mr. Kenneth Lau, Dr. Vivian Lee, Mr. Kenneth Leung, Mr. Peter Leung, Ms. Vivian Ma, Ms. Winnie Ng, Ms. Candy Tai, Dr. Warren Tsang, Mr. Wong Chi Ming, Mr. Rico Yau and Mr. William Yiu. Award certificates were also given to Mr. Michael Leung, Mr. Donald Chong and Dr. Cheung Hon Yeung who have worked zealously as the Managing Editors or Editor-in-Chief of the Hong Kong Pharmaceutical Journal from 2000 to 2009.

It is foreseen that in years to come, there is an urgent need for well-trained healthcare workers to assist pharmacists and other healthcare professionals in the elderly homes. PSHK has recently cooperated with Caritas Bianchi College of Careers (Evening) to organize a certificate course in pharmaceutical care to train healthcare workers. To mark the cooperation, Mr. Benjamin Kwong, President of PSHK signed an agreement with Dr. Reggie Kwan, College President of Caritas Bianchi College of Careers (Evening) on stage.

Another pleasant surprise was the singing performances by Dr. York Chow and Dr. Gabriel Leung. Both were very good singers and their performances delighted the audience tremendously. The dinner ended at around 11 p.m. with the GCs singing the song "Friends" by Allan Tam. It was indeed a successful event and an enjoyable evening for everyone.

Author's background

Mrs. CHENG Mary was the Vice-President and chairlady of the PSHK 60th Anniversary Organizing Committee.



The cake cutting ceremony was held by Dr. York Chow, Mr. Benjamin Kwong and Mrs. Mary Cheng. (From the left)



Mr. Benjamin Kwong, Dr. Gabriel Leung, Ms. Anna Lee, Mr. Shane Solomon, Dr. York Chow, Dr. Gloria Tam, Mrs. Mary Cheng, Dr. Heston Kwong, Mr. Anthony Chan, Ms. Sau-Chu Chiang. (From the left)



Mr. Benjamin Kwong [PSHK] and Dr. Reggie Kwan [Caritas Bianchi College of Careers (Evening)] signed an agreement on organizing certificate course in pharmaceutical care to train healthcare workers.



Mr. Kim Ng, Dr. York Chow, Mr. Benjamin Kwong, Dr. Gabriel Leung, Dr. Heston Kwong, Ms. Anna Lee, Mr. Tong Chan. (From the left)



Our young helpers for the event!



Ms. Ritchie Kwok, Mr. Henry Lau, Mr. John Lau, Dr. Vivian Lee, Dr. Gloria Tam, Dr. Grace Lau, Mr. Paul Lam. (From the left)



Pharmacists from DH showing off the souvenir watches for PSHK 60th Anniversary.



GCs of PSHK waving goodbye to dinner participants at the end of the dinner.



Active Ingredient:
Fulvestrant

Presentation:
Faslodex 250 mg/5 ml solution for injection. Clear, colourless to yellow, viscous liquid.

Pharmacological Properties:
Fulvestrant is an oestrogen receptor antagonist and binds to oestrogen receptors in a competitive manner with an affinity comparable with that of oestradiol. Fulvestrant blocks the trophic actions of oestrogens without itself having any partial agonist (oestrogen-like) activity. The mode of action is associated with down-regulation of oestrogen receptor (ER) protein.

Clinical trials in postmenopausal women with primary breast cancer have shown that fulvestrant significantly down-regulates ER protein in ER positive tumours compared with placebo. There was also a significant decrease in progesterone receptor expression consistent with a lack of intrinsic oestrogen agonist effects.

Indications:
Fulvestrant is indicated for the treatment of postmenopausal women with oestrogen receptor positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant antioestrogen therapy or disease progression on therapy with an antioestrogen.

Dosage and Administration:
Adult females including elderly: The recommended dose is 250 mg at intervals of 1 month.

Patients with renal impairment:
No dose adjustments are recommended for patients with mild to moderate renal

impairment (creatinine clearance \geq 30 ml/min). Safety and efficacy have not been evaluated in patients with severe renal impairment (creatinine clearance $<$ 30 ml/min)

Patients with hepatic impairment:

No dose adjustments are recommended for patients with mild to moderate hepatic impairment. However, as fulvestrant exposure may be increased, Faslodex should be used with caution in these patients. There are no data in patients with severe hepatic impairment.

Administer intramuscularly slowly into the buttock.

Contraindications:
Fulvestrant is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients, pregnancy and in breast-feeding and severe hepatic impairment.

Precautions:
Use Faslodex with caution in patients with mild to moderate, hepatic impairment and with severe renal impairment. Due to the route of administration, use Fulvestrant with caution if treating patients with bleeding diatheses, thrombocytopenia or those taking anticoagulant treatment. Thromboembolic events are commonly observed in women with advanced breast cancer and have been observed in clinical trials. This should be taken into consideration when prescribing Fulvestrant to patients at risk.

There are no long-term data on the effect of fulvestrant on bone. Due to the mode of action of Fulvestrant, there is a potential risk of osteoporosis.

Fulvestrant is contraindicated in pregnancy and has been shown to cross the placenta after single intramuscular doses in rat and rabbit. If pregnancy occurs while taking Fulvestrant

the patient must be informed of the potential hazard to the foetus and potential risk for loss of pregnancy.

Interactions:
A clinical interaction study with midazolam demonstrated that fulvestrant does not inhibit CYP 3A4.

Clinical interaction studies with rifampicin (inducer of CYP 3A4) and ketoconazole (inhibitor of CYP 3A4) showed no clinically relevant change in fulvestrant clearance. Dosage adjustment is therefore not necessary in patients who are co-prescribed fulvestrant and CYP 3A4 inhibitors or inducers.

Side Effects:
Hot flushes, nausea, vomiting, diarrhoea, anorexia, injection site reactions, elevated liver enzymes, Vaginal haemorrhage, Vaginal moniliasis, Leukorrhoea, Urinary tract infections, Venous thromboembolism, headache and backpain.

List of Excipients:
Ethanol 96%
Benzyl alcohol
Benzyl benzoate
Castor oil

Forensic Classification:
P1S1S3



Active ingredient:
Quadrivalent Human Papillomavirus (Types 6, 11, 16, and 18) Recombinant Vaccine

Presentation:
Single-dose pre-filled syringe 0.5ml

Pharmacological Properties:
GARDASIL contains L1 VLPs, which are proteins that resemble wild-type virions. Because the virus-like particles contain no viral DNA, they cannot infect cells or reproduce. In preclinical studies, induction

of anti-papillomavirus antibodies with L1 VLP vaccines resulted in protection against infection. Administration of serum from vaccinated to unvaccinated animals resulted in the transfer of protection against HPV to unvaccinated animals. These data suggest that the efficacy of L1 VLP vaccines is mediated by the development of humoral immune responses.

Indications:
GARDASIL is a vaccine indicated in girls and women 9 through 26 years of age for the prevention of the following diseases caused by Human Papillomavirus (HPV) types included in the vaccine:

- Cervical, vulvar, and vaginal cancer caused by HPV types 16 and 18
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11
- And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18:
- Cervical intraepithelial neoplasia (CIN) grade 2/3 and Cervical adenocarcinoma *in situ* (AIS)
- Cervical intraepithelial neoplasia (CIN) grade 1
- Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- Vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3

Dosage and Administration:
Administer intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh as 3 separate 0.5-mL doses according to the following schedule. Inject the entire contents of the syringe.
First dose: at elected date
Second dose: 2 months after the first dose
Third dose: 6 months after the first dose
Do not inject intravascularly, subcutaneously nor intradermally.

Forensic Classification:
P1S1S3

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