Imagine…the Future of Health

Inaugural Lecture of Distinguished Professorship in Pharmaceutical Sciences
Delivered on Tuesday 24 February, 2004
The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong SAR

Since light travels faster than sound, people appear bright until you hear them speak!

1. Thanks
2. Why China, why HK, why HK Poly U?
3. The achievable
4. The doable
5. The conceivable
6. The Future of Health: the Case for Pleasure
7. The future of this Distinguished Professorship

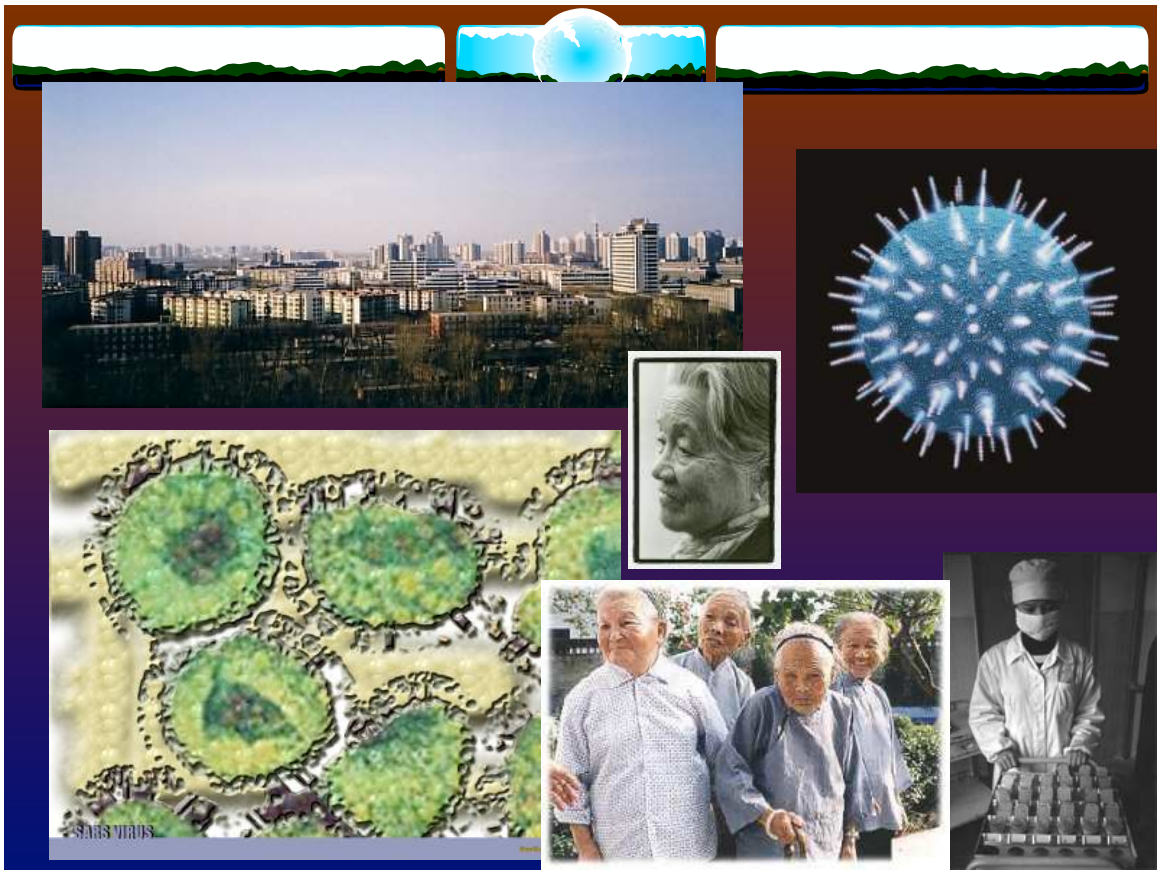
1. **Thanks:**

President Poon Chung-kwong
Professor Albert Chan Sun-chi
Faculty, Colleagues and Friends
Dear Students
Ladies and Gentlemen,

2. **Why China, why Hong Kong, why HK Poly U?**

- Why China? If one does not consider the EU as an economic entity, but as a conglomerate of independent nations, China is now the second economic power in the world. And the US owes China lots of money! The numbers are impressive: not only the 1.3 billion citizens, but also the sheer number of graduates, the impressive equipments manufactured and used, the entrepreneurship sprouting everywhere (I feel at times that each and every scientist wants to start a company!), and the flexibility of the structures that contrast with the rigidity of other places –like Hong Kong. True, Confucianism still has its imprint, and it may sometimes/somewhere be difficult to bypass the prejudices of the elder, but this is changing very fast –and for the better. This is no "Cultural Revolution" but pragmatism at its best. I am impressed, overwhelmed (at times), and enthusiastic. There is also a work ethic that is disappearing fast in other countries: self-esteem is

not the first criterion; the 35-hour week is not a goal; a civilization of leisure does not appear in the books –yet. Teamwork is the rule, and cohesion natural. We sweat together, and we celebrate together.



But China is facing some recent and important challenges. The one-child policy will result in an inverted age-pyramid, with few adults supporting an increasingly graying population. Estimates are >20% of the population being over 65 in a decade or so. These senior citizens will represent a tremendous burden in terms of healthcare. Nothing improves with age (except great red wines). Age-related disease and conditions already plague the sedentary populations of the western world; they will attack the Chinese seniors as cancers, arthritis, auto-immune disorders, Alzheimer's and Parkinson disease, osteoporotic fractures, cardiovascular diseases, and many more. Most are predictable; many are preventable. But time is running.

The other major danger is emerging plagues. HIV, SARS, influenza, Hanta, and others have reached China and are spreading. The Chinese populace has migrated en masse to the cities since the 1960s. Most families are packed in small quarters, with a social proximity and promiscuity that provides ideal conditions for epidemics. The ostrich-type attitude of the regional and local government had been in part responsible for the spread. Some provinces and autonomous regions of China have

been badly hit by unemployment as a result of these migrations; in some areas, close to 50% of young (18-25) males are unemployed, with bleak perspectives for any job. These idling youths search refuge in casual, unprotected sex (with prostitution), and/or intravenous drug use. In every culture, for as long as historical records are available, 10-15% of adults demonstrate homosexual or bisexual orientation; this is, in part, genetically programmed. But the Chinese administration has –until recently- considered such orientation as criminal (while other countries or states treated these persons as insane, and electro-shocked them). The result has been an underground, uncontrolled, at times highly infected homosexual/bisexual community. Short-term official denial always results in major disaster. In 2002, the official number of HIV-positive patients was in the thousands; in November 2003 it was in the millions and still underestimated. The SARS epidemic was another example is mismanagement, misinformation, denial and confusion, until the government decided –quite late- to play it right. The handling of the avian H5N1 epidemic seems (but do we know everything?) to be reasonably handled. These are just epidemics that have broken the veil of silence, of unnecessary deaths, of corruption and nepotism. The central government seems genuinely preoccupied. We have proposed, through the Chinese Academy of Sciences the SENIC project, an early alert network that will help identify, track and control emergency plagues. This SENIC project is the brainchild of Frank Kuo, of SRI, Steve Lewis of Archimedes Capital, myself, and Professor Albert Chan. In a few days, with the Chinese Academy of Sciences, we will review and try to implement it.
The healthcare system of China is not suited for a large, powerful, modern country. The vast mass of poor people does not have any access to even basic healthcare. I have proposed to use the Cuban model. Cuba offers the best healthcare system of the Americas, and it is cheap. It is being actively studied. For the other part of social protection, pension after retirement, I suggested the Chilean model. This too is being evaluated. I have expressed my concerns, my determination, my offers to help, my contacts and connections to the experts in Beijing. I am ready to serve.

- Why Hong Kong? Possibly by chance. I came to Hong Kong, for the first time, in 1969.

Dare I say that it was VERY different? A patient of mine, an orphan at birth, then a very proud Frenchman, had a number of stores in Hong Kong where he was successfully selling ready-to-wear clothes for women. He was doing very well, and was quoted in France-Soir (a French daily) as a "millionaire". He was frustrated by the monopoly of British medications in Hong Kong; he wanted some unique French drugs right here. Therefore we started in 1970 the "French Pharmacy in Hong Kong"; I was the "medical director". My tasks were many: scouting the Dictionnaire Vidal to identify original, purely French medicines; initiate negotiation, and follow-up on supply; train the sales reps in Hong Kong; visit opinion leaders in private practice and hospitals; give occasional lectures to medical or pharmacists societies; and more. This lasted 7 years; I used to come 3, even 4 times each year, and fell in love with Hong Kong. I already loved the food –at least what I thought was the food; I was up for a superb surprise! - but I discovered a whole new universe, with rules I never quite adjusted to; tolerance and contempt for the gweilo; charm, smiles and energy; pride and humility; and, maybe most, things done, done fast, without red tape. It worked. I have seen (almost) all the high-rises being built; Shatin was a small fisherman's place; the bay was a bay, not a channel; and pollution was just a dirty word. Then I connected with the University of Hong Kong; lectured and taught there on allergy/immunology; spent a 1990-1991 sabbatical with the Department of

Pathology; and was recruited in 1998 by vice-chancellor Patrick Y.C. Cheng to join the embryonic School of Traditional Chinese Medicine and bring into it a western approach to research and development; the Department of Pharmacology at HKU offered me a still valid Honorary Professorship.

Things have changed since the 70s, and not (always) for the better. Besides the air pollution, a price paid to wealth, the bureaucratic red tape that surged around 1998 is a sad reminder of the defunct Soviet Union. The endless committee meetings that result in another scheduled meeting are now the hallmark of many academic institutions (apparently not at HK Poly U!). That may be due to fear, cowardice, desire to please the unknown wishes of the Central Government of the PRC, I do not know, but it sterilizes creativity and entrepreneurship. Fortunately these are minor spots on a brilliant environment. I know that Hong Kong has survived many crises; the people are resourceful, and can (should) kick the bureaucracy on time. I trust Hong Kong. I trust Hong Kong even more since it has integrated (or has been integrated to) the Pearl River delta area, and more precisely Shenzhen. The SHIP is amazing. The "Virtual University" complex stunning. That's where science is not only studied; that's where it is "made".

- Why the Hong Kong Polytechnic University? Because President Poon Chung-kwoon, GBS, PhD, DSc. JD, asked me! True. Well, it is a bit more complex. Professor Albert Chan Sun-chi, who I had met at a meeting of the Chinese Academy of Sciences in Shenzhen, communicated with me over a period of a few months, and caressed the idea of getting me back to Hong Kong, to the Hong Kong Polytechnic University.

  After four hard years at the University of Hong Kong, I was not sure. But Albert played the "President card" and I could not say "no"! I am NOT a chemist; I am NOT a biologist. I am a medical doctor, a practitioner with a background in internal medicine, allergy & clinical immunology, public health issues in developing countries, and a late-in-life PhD in Pharmaceutical Sciences. I am also a cook, with a visceral *proprio sensu* interest in pleasurable food, and a fascination with wine. This led to a position in the (largest) Department of Nutrition, in the College of Agricultural and Environmental Sciences of the University of California at Davis.

And here I am, in a Department of Applied Biology and Chemical Technology! In the US, I would say that at times I feel like the skunk invited at a wedding party! This is NOT true: I have been welcomed beyond all my expectations; indeed I feel like a hungry kid in a candy store –where all the candy is up for grab, with a smile. I am thrilled. Challenges are expected, and I long for them. The team is unbelievable: I could not even suspect that so many exciting projects were at hand. I could not dream of such nice, friendly, open faculty, staff and students. Pinch me! It is real. Words cannot express my gratitude, and I just promise to do my best to merit your invitation and your confidence. HK Poly U is also a campus that comprises diverse disciplines I am interested in to achieve my task: applied science, business, communication, construction (and urban planning), engineering, health and social sciences.

The Polytechnic University also knows that public money is drying out and that such an assembly of skilled personalities can/should support the institution through research and consultancy. And it provides unique services to the community, e.g. the Institute for Enterprise (IfE), or the College of Professional and Continuing Education. I tried to get more

information on the Poly U Beijing-HK Medical Clinic, but alas! the beautiful website is in Chinese only!

3. **The achievable:**

A truth passes through three stages. First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as being self-evident.
(Arthur Schopenhauer)

I learned from my masters;
I learned more from my peers;
But the ones who taught me the most were my students.
(Talmud of Ur; circa 4,000 BCE)

All institutions of higher education have one goal: prepare and groom the elite leaders of tomorrow.

We do not want anymore perfect parrots who regurgitate what their parents, teachers or mentors wanted them to learn –i.e. memorize- but smart iconoclastic young mold-breakers who know that science is a process, and that everything you learn today is already tainted with obsolescence. However, one does not start building a house from the roof down; this is a recipe for disaster; we need foundations.

In 1993, at the University of California at Davis, the chancellor noticed that graduate students did most of the teaching provided to the undergraduates. Faculty shunned teaching undergrads. He asked for volunteers, and I decided to team with Jerold A. Last, PhD, a professor of Internal Medicine, but a toxicologist by training. We brainstormed with the department in charge of these Regents' Scholars, and decided on one goal: make them responsible citizens. Easier said than done for a toxicologist and a then-allergist! How to achieve this goal? We decided on the "History of Medicine: From Neanderthal to Molecular Biology"; this was the perfect example, time and time again, of dogmatic –at times criminal-, arrogant incompetence by the establishment. Of course, we expected and anticipated to ruffle a few feathers, but we had a plan: a fun series of shows.

Martin Yan, alumnus of UC Davis and fixture of the Food shows on BBC World, spoke on Chinese Medicine, brought a 35-page syllabus on herbs used BOTH in TCM and cooking, and arranged a surprise lunch at a nearby Chinese restaurant where we tasted food, herbs and medicine. A rabbi-turned-hypnotist demonstrated the Egyptian priest's skills of Moses and a few others by having the whole class plunged into hypnotic trance.

A feminist professor of history reminded us that healers were women, burnt alive as witches because they succeeded where and when the spiked hats of the church-anointed doctors failed. Charles Bond, a lawyer for the California Medical Association, reviewed “from Hammurabi to Hillary Rodham Clinton: physician and the law”.

And Jerry Last did show, to the students’ unknown dismay his 5-year old slides on molecular biology to prove that teaching of science has built-in obsolescence. Our classes were manageable: 24 to 28 bright demanding partners. But most of the teaching was done by/for students themselves: they would form a team of three, conduct the research (bless the Internet!), prepare and present a Powerpoint presentation, and then –only- Jerry and I would, with the class, discuss and comment. I still remember these three girls who presented on abortion; they made all US politicians look tame, bigoted, uninformed, and biased. Our message was perceived as: “Respect your parents, listen to your teachers, read the books and gather information, beware of dogmas, and always, always make up your own mind”. And never, ever, ever trust a politician! We did not know how it would turn, but we made the front page of the quarterly journal of the University of California, by being elected “teachers of the year 1995” by the students. Right now, many of them still communicate, and their parents showered us with thanks for making their son or daughter think by him/herself, away from revealed “truth” or established dogma.

Another experience I want to share with you: in 1952, I was in 12th grade at the Lycée Henri IV –supposed to be the best school in France-, and our physics teacher did not want to talk about quantum physics, “because it was not in the official French national program”….

The message is: team work. I do not teach; I assist; I guide; I support; I orient; I criticize; I console; I comfort. Experience and expertise help, but at the end of the day –or of the year- the student will have to live a successful life (or career) by herself. My students do the research, following some indications, guidelines and list of websites; they prepare a (Powerpoint) presentation they show to all of us: we comment, and I summarize, with a conclusion that will –hopefully- remain valid for some time. We need more than textbooks, classes, databases, or even mentors. We need to know how to succeed in the real world, where sharks roam, unexpected obstacles surge, and fierce brutal competition is the rule. Exposure to and involvement with business(es) is crucial. Forget about the nanny/welfare state that cares for you from cradle to grave! Everyone is on an ejector seat. The goal is to have combative, creative, business-oriented and business-savvy scientists. Fortunately, The Hong Kong Polytechnic University provides the tools, the teaching, the training, the spirit for such achievements, and has already an impressive record in achieving these goals.

4. **The Doable:**

I am always doing things I can't do; that's how I get to do them.

(Pablo Picasso)

This Distinguished Professorship should be devoted to implement productive teamwork with the Chinese community at large: the scientific community, the academic and university-based one, the governmental and provincial leaders, and the business executives. Teamwork with China for the Chinese people –and by extension the world.

The "virtual university" complex located in SHIP (Shenzhen) is a template; the network of institutes of the Chinese Academy of Sciences and its sister academies must be tapped in and linked to Poly U and its sister institutions in Hong Kong. Work is already under way, but most academics and academicians are struggling to expedite their heavy daily load of imposed work; the Distinguished Professor could (and would) devote his/her time to make this network more efficient, more effective, and more productive. Networking is not only "guangxi", but it starts with it. I intend to act as ambassador, negotiator, itinerant pilgrim, preacher and lubricator. I know that I can count on the full support of the Department of Applied Biology and Chemical Technology in this institution, and of its homologue at the City University of Hong Kong. I have also, along the years, established ties with a number of eminent scientists working in different institutes of the Chinese Academy of Sciences, the Chinese Academy of Medical Sciences, and other regional or local institutions in many provinces of China. Regular and recent visits to these institutes confirmed an enthusiastic interest in joining this tentative program. The will and the forces are there; let us harness them. I also contacted and visited R&D centers of major companies located in China, and focusing on the Chinese domestic market. Some are Chinese subsidiaries of multinational (foreign) companies; these feel at times isolated, and do not necessarily know who to approach, who to team with, where to publish, or how to manage the cultural differences. I court them, and try to build up contracts and collaborations. This will –hopefully- be an interesting source of income – both financial and intellectual- for the Hong Kong Polytechnic University, and ultimately benefit the Chinese community at large.

5. **The conceivable:**

Science is built up of facts as a house is of stones, but a collection of facts is no more science than a heap of stones is a house.
Jules-Henri Poincaré

The Legacy of Claude Bernard

In his inaugural lecture, after his election to the Chair of Experimental Medicine of the Collège de France in 1961, my father, Bernard N. Halpern, paid a vibrant homage to Claude Bernard, who inaugurated that very Chair over 100 years earlier. Indeed, the publication in 1865 of the "Introduction à la Médecine Expérimentale" (1) changed the world of philosophy, thinking, science, biology and medicine. Since then medicine has been separated from religion, magic, faith, myths or anecdotal reports. The modern, scientific evaluation of medical diagnosis, devices, techniques or treatment could start. We would look at facts, not faith or belief.

If Claude Bernard had failed as a theater playwright, he became an admirable pharmacist, chemist, physician, rationalist philosopher, prodigious discoverer of physiological functions, inventor of technologies that survive through our days, teacher, and educator. His contributions are too many to list, but for the generations that followed, the approach to medical care was changed irreversibly. I strongly feel that his words must be remembered in order to avoid the slippery slope of irrationality or creed. But Claude Bernard thought clinical medicine, based on observation and comparison, could never be a science; it could at most be physiology's handmaiden. It could help frame hypotheses; it could provide an arena for applying its findings. But it could not in principle *be* a science. Claude Bernard had a particular horror of so-called "observing physicians" who limited themselves to the mere observation of biomedical phenomena. For medicine so conceived:

> ".. Medicine so conceived can lead only to prognosis and to hygienic prescriptions of doubtful utility; it is the negation of active medicine, i.e., of real and scientific therapeutics"(1).

Claude Bernard, it must be said, did not trust statistics at all; whether this was justified in view of the state of the art, or whether he just didn't understand them properly, we couldn't say; he did, however, have some very amusing passages against stupid uses of statistics in biology.

Keeping these principles and the experimental approach in mind, we are nevertheless facing dilemmas these days. The cost for bringing a drug to the US market is currently estimated at $ 802 million, most of these being spent on marketing, promotion, and crass commercial practices. The "big Pharma" firms try to protect the chemistry-based approach to therapeutics, despite the fact –as pointed by Claude Bernard- that medicine will never *be* a science. A reductionist view of the patient is doomed to fail; interactions are the rule; side effects of drugs are inevitable. If we forget to restore *physiology* and concentrate on pathologies we will just increase pain, suffering, failures to heal, and ruin the already damaged reputation of the healthcare providers.

In July of 2002 the risk of hormone replacement therapy (HRT) in increasing breast cancer made the headlines. What happened is that medical practice –*not a science* according to Claude Bernard-, as it often does, got ahead of medical science. We made observations and developed hypotheses –and then forgot to prove them. We start with observational studies, in which researchers look at groups of people to see if we can find any clues about disease. But all this observation –as in pilot studies- can do is find associations: it can't prove cause and effect.

With HRT, we did many observational studies. We found that women who were on HRT had a lower incidence of heart disease, stroke, colon cancer and bone fractures. And we accepted these findings before we did the definitive research, overlooking the fact that these women were also more likely to see a doctor (which is how they were put on HRT in the first place), and probably more likely to exercise and to eat a healthful diet, than women who were not taking the drug. It wasn't clear whether hormones made women healthy or whether healthy women took hormones. To answer this question we needed randomized, controlled research.

The latest study, sponsored by the National Institutes of Health, enrolled 16,608 healthy women from ages 50 to 79 and randomly assigned them to take HRT or a placebo. Much to everyone's surprise, after 5.2 years the study showed that the risk of HRT outweighed the benefits in preventing disease. In fact what the study really –and finally- questions is the idea that we *need* to replace hormones in post-menopausal women for the long term. Menopause is normal. It emerged only with a recent (<200 years) longer life expectancy. Women need high levels of hormones to reproduce, but shift to a lower level to what is now the second half of life. It is puberty in reverse. And, as with puberty, the symptoms are transient, usually lasting between three and four years. In one study following women through menopause, 50% of the participants complained about hot flashes but only 16% felt they were really bothersome.

There is a bigger issue than simply HRT, however. There is a tendency, driven by wishful thinking combined with good marketing and media hype, to jump ahead of the medical evidence. In the 1990's, the bone marrow transplant –high-dose chemotherapy with stem-cell rescue- was proposed and promoted to treat aggressive breast cancers. It was widely used until four randomized, controlled studies showed it was no better than standard therapy, was outrageously expensive, and had far more severe side effects. Arthroscopic surgery for knee osteoarthritis was commonly performed until recently a controlled study showed it had no objective benefit –for the patient. HRT is just one more example of this phenomenon.

These examples show the importance of taking the time to determine the safety and efficacy of a particular therapy before we embrace it. This is particularly true in preventive medicine, since such therapy can create one disease in trying to prevent another that might not occur at all! The foundation of prevention still should be lifestyle changes: quitting smoking, eating a healthy diet, exercising regularly, all while pursuing

happiness. Drugs or other remedies, whether to prevent heart disease, bone fractures or breast cancer (if they exist at all), should be secondary. This is not necessarily an easy lesson, but we need to demand medicine based on solid evidence, not hunches or wishful thinking.

Why Medicines are not Medicine

Until recently metaphors for the doctor-patient relationship evoked intercommunicating vessels between which no liquid passes unless one is set higher than the other. The fluid was, of course the healing influence or *vis curativa*. And the physician had to be the upraised vessel. Only thus would the beneficial contents flow, from all-knowing doctor to appropriately lowered, humble and unquestioning patient. But this peculiar physics is, hopefully, going out of style. Today's ideal reflects the enlightened notion that both doctor and patient are reasonable people whose combined efforts are required to combat disease effectively. And in that harmonious relationship the physician's candor is essential. Physicians must learn, and learning, even in the best organized, most expertly supervised environment, involves mistakes. Alas, some patients will be harmed. Worse yet, the poor, the uninsured, the most disadvantaged populations suffer the most, since it is for these that physicians in training bear the greatest amount of unsupervised responsibility. All this we may find revolting, but in the current system no visible alternative is in sight.

The goal in the clinic, unlike the assembly line, is not the delivery of a fixed product or even a whole catalog of defined products. The goal is health and well being, and these are in no small measure constructs of the perplexing, intricate, idiosyncratic human mind. "From what I've learned looking inside people, I've decided human beings are somewhere between a hurricane and an ice cube: in some respects, permanently mysterious, but in others –with enough science and careful probing- entirely scrutable. It would be as foolish to think we have reached the limits of human knowledge, as it is to think we could ever know everything. The truth is that medical practice may well be more complex than just about any other field of human endeavor "(2).

Diseases come and go, often without apparent cause. Or a causal role is rashly attributed to factors that are purely coincidental. The same demonstrable abnormality shows up in some patients with excruciating symptoms while in other patients it courses unperceived. An epidemic of backache among physicians who formerly withstood endless hours stooping in the operating room may be related to growing dissatisfaction with their profession. We must ponder the knotty philosophical riddles enmeshed in the very texture of disease: what is the meaning of pain; how can it be that intangible, abstract phenomena, like memories and desires, dovetail seamlessly with concrete, organic manifestations; why should bodily reactions, presumably of evolutionary usefulness, suddenly go awry; or how easily the mind-body ties turn to shackles that are disabling. "The core predicament of medicine –the thing that makes being a patient so wrenching, being a doctor so difficult and being a part of society that pays the bills they run so vexing- is uncertainty. Medicine's ground state is uncertainty. And wisdom –for both patients and doctors- is defined by how one copes with it"(2). At a time when a hospital

advertises with the phrase “where miracles happen”; when physicians claim, without blushing, to perform “cardiac resuscitation”, letting people believe that they bring back Lazarus every day, candor deserves unreserved praise. Contrary to what public relations officers seem to think, honesty and frankness do more for the public’s confidence in the medical profession than extravagant boasting or supercilious gasconade.

'Drugs don't work on many people'

On December 6, 2003, a senior executive at Europe's largest drug maker has admitted most prescription medicines don't work for most people; Allen Roses, worldwide vice-president of genetics of GlaxoSmithKline, was quoted in the December 8, 2003 issue of “The Independent” as saying more than 90% of drugs only work in 30-50% of people. He said: "Drugs on the market work, but they don't work in everybody." Dr. Roses, an academic geneticist from Duke University in North Carolina, said new developments should help tailor drugs more specifically. Drugs for Alzheimer's disease work in fewer than one in three patients, whereas those for cancer are only effective in a quarter of patients. Drugs for migraines, for osteoporosis, and arthritis work in about half the patients, Dr. Roses said. Most drugs work in fewer than one in two patients mainly because the recipients carry genes that interfere in some way with the medicine, he said. At present, pharmaceutical companies adopt a "one-drug-fits-all" policy. But Dr. Roses said refinements in genetic technology should make it possible to identify more precisely those people who were likely to benefit from a drug. He said: "By eliminating the people that we predict will be non-responders we'll be able to do smaller, faster and cheaper drug trials. If you can determine who is going to have a response (to a drug) and who is not going to have a response, you can take your next molecule and aim it specifically at the people who haven't had a response with the first one so that you can create a set of drugs that cover the population, and then you are back to selling to everybody." Dr. Roses quoted research published three years ago by Brian Spear, an expert in medical diagnostics, which found that different drugs had vastly different success rates in treating patients. Most drugs had an efficacy rate of 50% or lower. Richard Ley, a spokesman for the Association of the British Pharmaceutical Industry, told BBC News Online Mr. Roses' comments emphasized just how important it was to conduct research into new products. He said: "It's not news to anyone that not all drugs work in all people all the time.”

Dr. Roses has a formidable reputation in the field of "pharmacogenomics" - the application of human genetics to drug development - and his comments can be seen as an attempt to make the industry realize that its future rests on being able to target drugs to a smaller number of patients with specific genes. The idea is to identify "responders" - people who benefit from the drug - with a simple and cheap genetic test that can be used to eliminate those non-responders who might benefit from another drug. This goes against a marketing culture within the industry that has relied on selling as many drugs as possible to the widest number of patients - a culture that has made GSK one of the most profitable pharmaceuticals companies, but which has also meant that most of its drugs are at best useless, and even possibly dangerous, for many patients.

Which brings us back to the Hong Kong Polytechnic University and its program, jointly with the City University, on pharmacogenomics and the development of a “gene chip”. It also makes me –and all of us- consider the modern approach to phytopharmaceuticals, many of which are the tremendous heritage of Traditional Chinese Medicine.

Part Two

6. The future of Health: the case for Pleasure:

Pleasure plays an important role in everyday life, but it is undervalued and under-explored in both science and society. Pleasure activities, enjoyed in moderation, make a positive contribution to and are part of a balanced and well-rounded approach to life. By creating a better understanding of the benefits of pleasure, we will allow people to make informed choices and to enjoy themselves without excess worry or guilt.

We could be healthier and happier if doctors gave up telling us what NOT to do. "Health" has been hijacked by well-meaning but misinformed evangelists. The evangelists preach "healthy" behavior –which includes avoiding fat or sugary foods; cutting out "stimulants" like coffee, tea or tobacco; and taking plenty of exercise. But increasingly evidence suggests that most people's inability to keep to the rules generates GUILT and this in turn may lead to serious illness.
There is ample historic evidence to show that the human pleasures of today were enjoyed by our very distant ancestors –suggesting that mechanisms for experiencing pleasure might be pre-programmed in the human brain.
Of course reasonable concern for our health is fine, but the single-minded pursuit is a symptom of ill health –hypochondria.
These health evangelists do not recognize individuality. They seem to believe that there is a perfect body shape and a perfect way to live. They believe there should be stringent limits for all activities with the ideal of total abstinence. The ideal person would be alcohol-free, caffeine-free, cholesterol-free, salt-free and sugar-free.
.
These health evangelists do not recognize individuality. They seem to believe that there is a perfect body shape and a perfect way to live. They believe there should be stringent limits for all activities with the ideal of total abstinence. The ideal person would be alcohol-free, caffeine-free, cholesterol-free, salt-free and sugar-free.
People's failure to live up to the ideals promoted by healthism leads to powerful feelings of guilt, and this in turn has serious consequences for both mental and physical health. Moreover, a survey has shown that 43 per cent of adults report that they would enjoy things more if they did not feel guilty about them.
Guilt is a stressor releasing the stress hormones including the corticosteroids; sustained steroid release has been shown to have pathological effects including infections, ulcers, heart disease, cancer and brain damage".

The Case for Pleasure

Human pleasures are pre-programmed in the brain: when 370 adult Australians were asked to record the degree of enjoyment they perceived in eight everyday products – coffee, tea, chocolate, cigarettes, beer, wine, potato chips, and sweet biscuits-, men and women largely agreed on the relative enjoyments, except for beer which was MOST enjoyed by the men and LEAST by the women. Different age groups reacted slightly differently, but for each respondent subgroup the overall mean rating for enjoyment across all products was much the same. This suggests the operation of a "pleasure quota" –that is people obtain a constant amount of pleasure or enjoyment from everyday products in different ways.(2)

Pleasure has an important role in the healthy regulation of behavior, both physically and mentally.
Subjects chose pleasant temperatures to achieve temperature regulation and pleasant tastes to achieve body weight regulation. Moreover, the avoidance of unpleasant muscle pain proved to achieve efficient performance in physical tasks: sensory and mental pleasures were the motor for useful performance. The rating of pleasure was the mirror image of performance!
Both the seeking and avoidance of sensory pleasure optimized behaviors that were playing a vital role in life. The process could also be demonstrated with remembered pleasures, some of them life supporting, and showed that strong pleasures were remembered better than modest ones.

Globally, pleasure is aroused by the same mechanisms and follows the same laws in physiological and mental tasks, and it has the effect of allowing an individual to achieve his/her ideal physical and mental performance.

The best things in life are –almost- free. An analysis of a large survey of English people's everyday use of substances like tea and coffee, a smoke, a drink, or some chocolate, indicate that these simple things provided definite pleasures.
Top ranking pleasure for men was food and drink, music, reading, family/children, while women's top ranking pleasures were family/children, nature scenery, entertainment and reading. Sex/love was mentioned frequently, and appeared to be universal and taken for granted. The respondents reported lots of simple everyday pleasures in heartfelt and honest terms and, although there were some examples of self-indulgence or hedonism, there was no evidence that people generally were hell-bent on pleasure seeking. Getting respondents to write about their pleasures and enjoyments –instead of war, famine and disasters, problems, stress, worries and fears- might help them focus on the more positive aspects of life.
Studies of people's enjoyments and pleasure clearly support the message that "a little of what you fancy" does you good, and we should not be made to feel guilty about pleasures. For most people these are the only pleasures they are likely to enjoy in the only life they have.

The Question of Guilt

People's behavior could be controlled by their feelings of guilt or shame, or by bribery. "Guilt" is the feeling one experienced when acting against a personal code, whereas "shame" was the feeling that followed discovery and condemnation by others.
Neither guilt nor shame is the result on innate features of human consciousness, but the product of an educational process allowing both family and State to maintain social control. European society has relied on the imposition of guilt in a child by age three or four, to ensure that it learned the social rules. In some European countries [e.g. Italy], society is moving from a position of control by guilt to control by shame; thus behavior is more and more being dictated by external rather than internal regulation.
Shame and guilt are important behavioral functions, but one might ask whether they make the achievement of happiness an impossible aim.
Shame is not a satisfactory control mode; it was necessary to find an alternative. Offering communal pleasurable reward for acceptable behavior might be effective in reducing anti-social acts.

Preferences could become values, thus converting something that has been good for you to something that is morally correct.
Governments tend to act on questions of morality, whereas they usually do not on questions of preference. In the US, cigarette smoking has been most subjected to moralization, although eating meat, fat and chocolate are rapidly following the same pattern.
Factors encouraging moralization include the Protestant ethic; reported harm to children; association of an activity with an already stigmatized group.

In the US, “food as source of nutrition” has been replaced by “food as source of obesity”. Americans have surrounded themselves with a variety of alternative foods, in the apparent belief that immortality was just around the corner –which is also why enormous (and growing) amounts of antibiotics, vitamins, supplements and nutraceuticals are consumed.
Americans are overloaded with information about what is “bad”. Food is either “good” or “bad”, and the “bad” is not to be touched. Yet salt and fat make food tasty!
The American attitudes to food can be compared unfavorably with the much more pleasure-oriented attitudes in France. The French approach is clearly better for the quality of life, and it might also be better for health. The French woman’s attitude to chocolate cake is to relish it, whereas the American woman thinks about the calorific value!
A combination of the public’s failure to appreciate the true nature of risk; the difference between a risk factor and a disease; and the uneven course of scientific progress have conspired to make eating unpleasant, worrisome and guilt-ridden, particularly for females.

But, in a way, mainstream Western ethical tradition may not be “anti-pleasure” but “anti-license”. Guilt, which has been part of moral and legal language, is now seen by therapists as a nuisance and to be got rid of.
If someone has done something wrong it is only sensible that he/she should feel guilty or acknowledged the guilt. The problem is those who are guilty but do not feel it.
Although feeling guilty might subvert pleasure, there are occasions when morally it should. What is needed is some way of differentiating between good from bad pleasures, so people would know when feeling guilty is appropriate or not.
We do not need a list of scares about diet and health that has characterized Anglo-Saxon cultures. They were promoted by ideologues, meddlers, bureaucrats, politicians and lobby groups for a variety of reasons. But they would not be successful if people were more secure in their food culture. So perhaps what some researchers identify as guilt about food and pleasure should be better characterized as a more general insecurity, showing itself in nervousness, panic and self-reproach.
While feeling guilty about enjoying good food, wine, brandy and cigars might undermine the pleasure they give, that is not the end of the story. There are occasions when people should feel guilty about their pleasures, for example when NOT enjoying them, or NOT providing them for others. If we don’t admit the moral dimension and get it right, the Puritans will have the field left to themselves.

Pleasure and Health

There are “innocent” diseases, and “blameworthy” diseases. The former include athletic injuries, cancer in children, allergies, passive smoke-related illnesses (in which people are victims of the “sinful” behavior of others), and chronic fatigue syndrome. Blameworthy diseases include any transmitted by sexual acts, any related to alcohol use, cigarette smoking or (recently) illicit drug use, and those related to genetics or the natural processes of biology such as obesity, old age, depression, and cancer.
It appears that Americans still promote the idea that “health is good, and if one is good, one will be healthy”. In the US, goodness is equated with health, youth and beauty. With

the rise of *healthism* has come increased emphasis on personal behavior as a cause of illness.
Doctors have promulgated healthy behavior and scolded those whom they considered to have behaved improperly. But what influence did/does this have on the sick?
Physicians have also concurred with laypeople in the categorization of environmental influences. “Good” things include asceticism, vegetables, leanness, exercise, abstinence, optimism, cleanliness, beauty, and youth; while “bad” things include meat, fat, sugar, obesity, smoking, alcohol, drugs, sexual promiscuity, sloth pessimism, dirtiness, ugliness, and old age.
There is evidence that people suffering from so-called “bad diseases” avoid consulting physicians. In one study, 12.7 per cent of women reported delaying or canceling an appointment to see a doctor, because of concern about their weight. It might be that fear of derision was an effective denial of care. We should wonder whether the tendency of physicians to generate guilt in patients might itself cause illness.
The power of the so-called “placebo” effect –psychic influence upon emotional and physical well-being- is well known. But what of the opposite, the “nocebo” effect, which has, as its ultimate expression, the voodoo curse? What is the effect of national pronouncements by scientific and physician bodies, prevalent social beliefs and individual exhortations by doctors on patients who are told that if they act in a certain way they will get sick?
Are we through our emphasis on health actually creating illness? Certainly we are creating anxiety, as evidenced by the public uproar over such things as the rumor of toxic materials in the shiny surfaces of apples, pesticides and dietary carcinogens. Might it be possible that as a profession, physicians are functioning to a degree as Voodoo priests and actually causing diseases in certain individuals? This remains to/must be studied.

There is now substantial evidence that people suffering significant and chronic stress develop an impaired immune response –that is they become vulnerable to illness. The body’s immune response is its natural defense mechanism against infection that gears up white blood cells to attack germ intruders.
Tests on women who had just given birth to babies, and experienced classic stressors, have shown that their immune responses had been boosted by the “pleasure of birth”, as had been suggested by earlier short term acute studies.
One of the strategies for the future therefore would be to look at everyday stressors.
The word “stress” might itself be inappropriate; more suitable would be the term “psychological challenge”.
Since the experience of pleasure can be scientifically shown to help the body’s defenses, it opens up a new approach for maintaining health.

Similar to physical fitness, fitness of the immune system requires training. Increasing evidence suggests that moderate sports can decrease the frequency of infections while excessive exhausting exercise can lead to the opposite, a situation that has been described as a J-curve. Following prolonged exhausting exercise [unpleasant experience!], a transient partial suppression of several immune functions [a.k.a. “AIDS”] can be shown, and this period provides a window for invasion of microbes. Using whole blood cultures a German group found strongly depressed production of γ-IFN (in response to mitogen

or endotoxin) following strenuous exercise. Another study concludes that moderate [emphasis added] exercise influenced the γ-IFN production (PHA-stimulated) that increased significantly 24 h later, whereas thirty minutes after exhaustive exercise the γ-IFN level in the supernatants (SEB-stimulated) was very significantly decreased; the IL-1β and TNF-α production per monocyte was also significantly reduced in the "exhausted" group. Another German group found in 15 athletes, after an exhaustive exercise stress test, that in cell cultures the LPS-induced release of the cytokines TNF-α, IL-1, and IL-6 was suppressed 1 h after exercise. Also, the Con-A- and LPS-induced release of γ-IFN, and the PHA-induced release of IL-2 were suppressed 1 h after exercise; fortunately, 20 h after the exercise, most of the observed changes were back to pre-exercise levels. But what if this type of exercise is repeated daily, or even several times a day as observed in elite athletes? γ-IFN induction may be critically involved, causing the transient immunosuppression following exhaustive exercise stress.

Endurance athletes have been shown to suffer a high incidence of upper respiratory tract infections (URTI); the concentration and flow rate of secretory immunoglobulin A (S-IgA), the major effector of host resistance to URTI, decrease after intense endurance exercises.

When recreational joggers and competitive distance runners ran at the same intensities, S-IgA secretion rate did not change after exercise. But when competitive runners ran intensely on 3 consecutive days, S-IgA decreased 20 to 50% after exercise; this decrease worsened on days 2 and 3 compared with day 1. Finally, elite swimmers were followed over a 6-month season; throughout the season, their S-IgA concentration was significantly lower ($p<.05$) compared with well-trained swimmers [who just enjoyed swimming!]. The Australian Institute of Sport has profiled the immune responses of elite swimmers during training. Serum immunoglobulin and IgG subclass levels were lower in swimmers than controls; those who experienced URTI had lower S-IgA and salivary IgM than the non infected ones. Another Australian study confirmed that low levels –even below the detection limit of the assay- of S-IgA1 and S-IgA2 were associated with recurrent URTI. Measurement of salivary S-IgA levels over a training season may be predictive for elite swimmers at risk of infection. In triathletes, the exercise of a triathlon may significantly decrease the level of IgA-mediated immune protection at the mucosal surface; as these triathletes may during the race be exposed to microorganisms in the swimming water, this deceased immunity may increase the risk of infections. In summary, stress-associated exercise, as practiced by elite athletes, impairs the immune response, both the cell-mediated [γ-IFN], and the mucosal antibody [S-IgA] ones.

But what about psychological stress? A group of the University of Adelaide, Southern Australia examined the effects of anxiety, depression and psychological stress on the secretion rate of S-IgA, in a cross-sectional study of 114 registered nurses; nurses who reported frequent episodes of anxiety had significantly lower rates of S-IgA than did nurses who reported only occasional surges. In Singapore, 124 nurses from surgical operating theaters, medical wards, or outpatient clinics completed a Stress Assessment

Score [SAS] for Asians, and provided salivary samples; surgical nurses had the lowest IgA secretion, and the level correlated inversely with self-reported levels of stress.

What about academic stress? This was studied first in 64 first-year dental school students: perceived stress and S-IgA secretion rate were measured five times –during an initial low-stress period, three high-stress periods coinciding with major examinations, and a final low-stress period. The S-IgA secretion rate was significantly lower in high-stress than low-stress periods for the whole group; but students characterized by a great need to establish and maintain warm personal relationships secreted more S-IgA at each point than did all other subjects, whereas the S-IgA of those with a high inhibited need for power had declining secretion rates through the final low-stress period, and did not recover as all other subjects. The same Princeton University group confirmed that students who reported more adequate before an academic critical examination, and subsequently 2 and 6 weeks later in a no-stress situation. The Dutch researcher studied the aggregation of social support at pre-exam period had consistently higher S-IgA levels than did their peers lacking the support. More important for everyone are daily hassles: a group of the University of Bologna confirmed that there is an inverse correlation between hassles and S-IgA in 24 subjects followed for 4 months! The consequences were dire in a group of 28 dental students: they provided unstimulated whole saliva during 10 minutes *Streptococcus gordonii* (HG 222), a marker of "defense of the oral cavity". The aggregation in the saliva collected before the examination was 13.1%, whereas 2 and 6 weeks later, in a relaxed environment, it was 23.3% ($p<.01$). Furthermore, the decrease in bacterial aggregation was related to the increase in state-anxiety ($p<.05$). Acute psychological stress exerts influence on saliva defenses, and may well be a factor in the often-reported relationship between stress and impaired oral health. And finally, 30 English subjects listed their pleasurable activities and rated them in terms of pleasure and guilt before producing saliva samples for S-IgA. Levels of S-IgA were higher in those subjects with high ratios of pleasure-guilt scores!

Coming back to exercise, I once caressed the idea of using sex as a substitute to gym, and an interesting approach to weight loss. But a recent article in Sports Medicine (3) is rewarding my prescient proposals: "the sexual response is a form of exercise which has strong biological and evolutionary components…there are parallels between the orgasmic response and exercise."

Sex is Good Exercise

Butt DS. The sexual response as exercise. *Sports Med* 1999;9:330-342

"the sexual response is a form of exercise that has strong biological and evolutionary components…there are parallels between the orgasmic response and exercise"

Physiological bases of sexual responses help to explain the well being that often accompanies states of passionate love, addiction and exercise, [e.g. opioids]. Studies suggest that sexual activity is associated with well-being and longevity, yet many health and exercise professionals fail to take account of sexual activity in advancing exercise programs and executing studies; furthermore "investigators need to separate the passionate love stage of relationships, which are biologically based and last 3 to 4 years, from the later stages of long term committed partnerships, in which sexual activity continues as a form of exercise, competence expression and fun". Indeed, chronic activation of endogenous opioid systems augments natural cytotoxicity, and opioids enhance moderate exercise-induced natural immunity. Conversely, large doses of opioids, whether produced endogenously from severe exercise or placed into the body for recreational or medicinal purposes, suppress the immune system; opioids make cells die and induce apoptosis by triggering the expression of Fas [CD95 or APO-1], and then binding to the Fas ligand [FasL].

Endogenous opioid peptides produced by the neuroendocrine system can modulate several immunological functions. Immune system cells also have the ability to synthesize and release such peptides; the same substances released by macrophages that infiltrate inflamed tissue also act in the zone of the affected region.

The influence on γ-IFN induction is just one example. Conversely, a frequent, regular, appreciable pleasurable stimulation is associated with a betterment of the immune response, and should contribute to a reduction of allergic symptoms.

Carl J.Charnetski et al investigated the effects of music and an auditory stimulus on the levels of salivary secretory IgA [sIgA] in groups (N=66) of college students; these were exposed to one of four conditions: a 30-min. tone/click presentation; 30 min. of silence; 30 min. of a Muzak tape a.k.a. "Environmental Music"; and a 30-min. radio broadcast comparable in musical style. Saliva samples collected before and after each 30-min. treatment were assayed for sIgA; analysis indicated significant increases for the Muzak group, but not any of the other groups.

However, the best stress reliever is orgasmic sex. Again, Carl J. Charnetski presented recently results demonstrating that people who have sex once or twice weekly have substantially higher levels of sIgA than do people who have sex less than once a week, or never at all; surprisingly, though, people who perform sex more than twice a week have the lowest sIgA levels of all; Charnetski speculates that the latter may be related to stress. Preliminary studies confirm that regular sexual orgasms, in female subjects, are also associated with an increase in γ-IFN production (Halpern G; unpublished results). Opioids are involved: in 2 studies with 10 women each, vaginal self-stimulation significantly increased the threshold to detect and tolerate painful finger compression, but did not significantly affect the threshold to detect innocuous tactile stimulation. In the first study vaginal stimulation was perceived as producing pleasure; during that condition, the pain tolerance threshold increased by 36,8% and the pain detection threshold by 53%. In the second study, when orgasm was produced, the pain tolerance threshold and pain detection threshold increased by 74.6% and 106.7% respectively, independently of distraction! But orgasm also occurs in response to imagery in the absence of any stimulation. Women who claimed that they could experience orgasm from imagery alone were studied. Orgasm from self-induced imagery [or genital self-stimulation] generated significant increases in pupil diameter, pain detection threshold, and pain tolerance threshold over resting control conditions; the increases were comparable in magnitude regardless of the induction [self-imagery or self-stimulation]. Among the biochemical factors involved in the process of pareunia, the rise in endorphin rate when there is an orgasm is prominent. The new functional imaging techniques, such as positron emission tomography [PET] and single photon emission computed tomography [SPECT], have made it possible to study the neurophysiology of living humans non-invasively, e.g. the regional blood flow with SPECT in 8 healthy right-handed heterosexual males during orgasm; the results showed decrease of cerebral flow during orgasm in all other cortical areas except in right prefrontal cortex, where cerebral blood flow increased significantly ($p<.005$).

Sweet Pleasures of Life

The British are the world's champion chocolate eaters; but why? The average person in the UK consumes 9 kg of chocolate a year, or on average three bars per week –compared to the average in the US of 1.6 kg per year, or $1/6^{th}$ as much. The research has identified a

group who reported eating an average of twelve and half bars a week; one individual ate ten bars a day.

Chocolate beats Prozac®

Bruinsma K, Taren DL. Chocolate: food or drug? *J Am Diet Assoc* 1999;99:1249-1256

Chocolate is the food with the greatest impact on mood.

Besides its hedonic appeal –fat, sugar, texture, aroma-, it is used as self-medication for dietary deficiencies (Mg), or to balance low levels of mood-neurotransmitters (serotonin, dopamine). Chocolate contains appetite regulators, and cannabinoid-like fatty acids.

Arguably, the food with the greatest impact on mood is indeed chocolate; as all palatable foods [vide supra] stimulate endorphin release in the brain, this is the most likely mechanism to account for the elevation of mood. But although hedonic responses to chocolate puddings were based on their perceived sweetness, for those who specifically consider intake of chocolate to be excessive, any pleasure experienced is short lived and accompanied by feelings of guilt. Chocolate is by far the most commonly craved food. Craving, though, is culturally [and possibly gender] dependent: among sweet cravers; chocolate craving was much more frequent for American females (44.6%) than for America males (17.4%), but no such gender difference occurred for Spaniards (28.6 and 22%). Besides the hedonic appeal of chocolate [fat, sugar, texture, and aroma], it may be used by some as a form of self-medication for dietary deficiencies [e.g. magnesium], or to balance low levels of neurotransmitters involved in the regulation of mood, immune response, food intake, and compulsive behaviors [e.g. serotonin and dopamine]. Chocolate contains several biologically active constituents [methylxanthines, biogenic amines, and cannabinoid-like fatty acids], all of which potentially cause abnormal behavior [mostly in females] and psychological sensations that parallel those of other addictive substances.

The association of sweetness with pleasure is apparently universal in humans. The sweet taste is the only one that is innate. In the West however the legitimacy of the pursuit of

pleasure through both sex and sweetness has been questioned in recent decades. It was paradoxical that there seemed much less understanding of the pleasure derived from food than from sex, although until the emergence of HIV/AIDS sexual tolerance was growing.
Foods were often subjected to binary moral judgments, as if the problem was to designate culprit for the eventual death of the eater.
In recent decades several books devoted to the "evils" of sugar have been published, among them "Sugar Blues" by Dufty (1975), which among other things, held sugar responsible for brain malfunction, bubonic plague, heart attacks, criminal behavior, freckles, hair loss, impotence, insect bites, loss of memory, obstinate resentment of discipline, schizophrenia and suicide. Dufty has acknowledged the striking similarity between his views on sugar and 18th Century medical beliefs on the consequences of masturbation, claiming that this was because the ills they attributed to masturbation were actually caused by sugar.

Sweetening the Pain

Mercer ME, Holder MD. Antinociceptive effects of palatable sweet ingesta on human responsitivity to pressure pain. *Physiol Behav* 1997;52:219-225

Palatable sweet ingestion produces a morphine-like analgesia in infants.

Canadian women who consumed a soft drink reported increased pain tolerance. Women who consumed chocolate-chip cookies demonstrated the palatability-induced anti-nociception.

Sweetness has a close association with childhood, and is often seen as having a dark dangerous addictive side. It seems that sweets are a threat to parental authority, and will only be tolerated when administered by the parent for gratification.
One of the constant temptations of medicine is to extend its normative authority on healthy bodies, and day-to-day life and habits. Food has always played an important part in this respect. Contemporary medical stances and discourses on food, nutritional guidelines, nutrition education campaigns, and repeated warnings against poor eating habits based on countless epidemiological surveys, often take on highly moralistic

undertones. Although epidemiology does not prove causality –just association-, some epidemiological findings are quite solid: one of them is that the main risk factor for heart disease, cancer and other diseases of affluent societies, is…**age**.

Hedonia and Anhedonia

Visitors to the US are often struck by the prevalence of obesity, but food abundance is not a new phenomenon. Early settlers rapidly became better fed than their counterparts in the motherland.
Attempts to regulate the national diet started with the food reform movement in the 1830s and 1840s. One of the pioneers was a Protestant preacher, William Sylvester Graham, who launched a crusade against alcohol, on the grounds that it overstimulated the nervous system, and then applied the same strictures to sexual activity and the consumption of meat and spices. Graham was suspicious of "unnatural" foods, particularly the denaturing of wheat for white bread.
Food reform was embraced by social reformers who felt that if the working classes could be taught how to spend less on food, they would have more money for shelter, heating and clothing. Living standards would then rise, and the workers would turn a deaf ear to the radicals fostering anarchy, trade unionism, and other "disruptive principles".
But, continuing to look at the progress of food reform, we must note how charities like the American Heart Association, and the American Cancer Society have subsidized research into the "deleterious effects" of various foods, and disseminated any adverse results. They have been spending millions warning the public about the supposedly terrible consequences of eating foods containing "too much" salt, sugar and animal fats, as well as the perils of being overweight.
It is no wonder that negative nutrition struck a chord with the middle class, and has become the core of national nutrition policy with the same diets for all. A wave of low fat, low calorie, no fat, cholesterol-free and sodium-free products has engulfed supermarkets. The end result has been one of the continuing paradoxes of American abundance. The middle classes swept up by lipophobia took to dieting and exercising in an almost maniacal manner, and many of their daughters were overcome by eating disorders. Yet there is no indication of decline in average weight of Americas over the last 20 to 30 years.
Americans were simultaneously trying to eat more foods that were supposed to cure illness, and less of those deemed to cause it. To make matters worse, they were fed new, and often contradictory, proclamations on what they should and should not eat.
It seems that America is a culture doomed to experience abundance, while simultaneously avoiding enjoying it very much!

The Positive Contribution of Pleasure to Life

In everyday life, some choose to consume caffeine, alcohol and/or nicotine, as strategies for coping with various situations during the day. If people feel drowsy, they reach for a cup of coffee. When they need to think and concentrate, some people have a cigarette.

When they get home after a stressful day at work, then many people like to relax and unwind with a good meal, together with a glass of wine, even a cigarette or a cigar and some chocolate. So, it is clear that the use of so-called social substances is situation dependent.

Recent research has been focusing on the effects of caffeine on behavior and brain activity. The caffeine equivalent of about two cups of coffee decreases reaction time by about 10%. In terms of brain activity, caffeine increases attention to relevant information, while at the same time the rejection of irrelevant information is better. Benefits are seen in both older people and younger people. However, it was found that "evening" types benefit more from caffeine in the morning than "morning" types. Thus, caffeine has positive effects on performance, but with individual d differences.

Now, what about the effects of combinations of food and caffeine on memory, attention and reaction time? Breakfast alone makes people alert, perform better and puts them in a better mood. But if you combine breakfast with a cup of coffee the combination results in even better memory and higher alertness. Even the effects of sweetness (sugar) can boost the effects of caffeine. On the other hand, when performance is impaired by alcohol, a heavy lunch, or night work, then caffeine can reverse the lowered arousal.

The pan-cultural use of pleasure products, which contain alcohol and/or nicotine, indicates that pleasure has a central role in people's lives. Psychometric studies demonstrate the impact of pleasure products on performance in laboratory tests, and tests mimicking everyday tasks. Nicotine, caffeine and chocolate improve cognitive and psychomotor performance over that seen at rested levels, ameliorate the effect of fatigue seen after a prolonged period of work, and counteract impairments in performance seen with doses of alcohol. Not only does the individual benefit, but also society gains, if productivity is increased and accidents are reduced.

While many types of cognitive function are impaired by social doses of alcohol, alcohol may help to aid creativity, especially artists and authors. Although alcohol has some effect on creativity, the expectancy and situational effects result in more creative thoughts. Thus, there is a positive effect on cognition of drinking low-to-moderate amounts of alcohol, besides the well-known relaxant effects.

Wine Brings More than Physical Health

Epidemiological studies from numerous disparate populations reveal that individuals with the habit of daily moderate wine consumption enjoy significant reductions in all-cause and particularly cardiovascular mortality when compared with individuals who abstain or who drink alcohol to excess. Researchers are working to explain this observation in molecular and nutritional terms. Moderate ethanol intake from any type of beverage improves lipoprotein metabolism and lowers cardiovascular mortality risk –in humans and in rats. The first question now is whether wine, particularly red wine with its abundant content of phenolic acids and polyphenols, confers additional health benefits.

Discovering the nutritional properties of wine is a challenging task, which requires that the biological actions and bioavailability of the >200 individual compounds be documented and interpreted within the societal factors that stratify wine consumption, and the myriad effects of alcohol alone. Further challenge arises because the health benefits of wine address the prevention of slowly developing diseases for which validated biomarkers are rare. Thus, although the benefits of the polyphenols from fruits, vegetables, and even green tea are increasingly accepted, consensus on wine is developing more slowly. Scientific research has demonstrated that the molecules present in grapes and in wine alter cellular metabolism and signaling, which is consistent mechanistically with reducing arterial disease. On-going research is addressing specific mechanisms, both of alcohol and of polyphenolic action, and develops biomarkers of their role in disease prevention in individuals.

Life can be lived in a casual way, or plumbed to the depths. We all choose how and where to spend our energy and attention. You may play music, cook seriously, tend a lovely garden. Maybe the things you love aren't vital, but they make life richer. Passion is never wasted effort.

And here's the second question, as a corollary: why wine lovers do learn to taste? We know that the effort we put in understanding and appreciating wine –as opposed to simply enjoying it (or its psychotropic effects) pays big dividends. Really tasting wine adds an extra dimension to the basic daily routines of eating and drinking. It turns obligation into pleasure, a daily necessity into a celebration of life.

Blind tasting is a great parlor game. But the real goal is to understand –and enjoy- a wine, not to unmask it. Through a concentrated application of all the senses, and by comparison of the immediate sense data with memories of other wines tasted, the serious taster can decipher a wine biography to an amazing extent, including the growing season that produced it, the approach of the winemaker who created it, and its relation to other wines of similar type or origin. Every bottle of wine is a message, the physical embodiment of a specific place and time captured and transmitted for the pleasure of the taster. Open a bottle of 1961 red Bordeaux and even a generation later the dusty warmth of that long, hot summer floods the dining room.

Even more, though, wine is a catalyst. The effort to understand it through tasting, and to share that understanding with other tasters, creates a common experience that builds bonds between people. "Great wine has that marvelous quality of immediately establishing communication between those who are drinking it. Tasting it at table should not be a solitary activity and fine wine should not be drunk without comment. There are few pleasures that loosen the tongue as much as sharing wine, glass in hand. In essence it is easy to describe what one senses provided one has made a sufficient effort to notice it. What is clearly perceived can be clearly expressed."(4).

Remember though that tasting is not a test –your subjective response is more important than any "right answers". The bottom line is: Wine tastes good to you is good wine (54), and chances are that this wine will do you good. And more good news: "The world of wine is infinite"(4).

Pleasure and Choice

There are two foci of thoughts regarding the role of pleasure. One is what one might loosely call the "scientific theme" which is focused on the scientific case for the effects of various pleasures, particularly as contributors to enjoyment in everyday life. The second theme, while not at all divorced from this, is focused more on the political, sociological and philosophical aspects of pleasure. The latter stream focuses particularly on the way in which modern society, health promotion, and Government itself, have sought to marginalize and, in some instances, criminalize and prohibit various aspects of pleasure.

Can traditional economic models provide a satisfactory explanation of pleasure choices, particularly the traditional division between "wants" and "needs"? The economics alone have provided a very poor account of the way ordinary people made pleasure decisions, and it needs to broaden the way in which it thought about these decisions by incorporating psychological data.

Investigators looked at governmental attempts to prohibit various forms of pleasure, either through the increasing taxation of it, or the outright criminalization by prohibition, e.g. the United States experience with alcohol. The distinction between high taxation and prohibition turns out, in fact, to be a very small one, and the consequences, which are often not thought about, are quite significant, in terms of wider aspects of society.
For instance, when you deprive people of pleasures to which they are greatly attached, they will be predisposed to resort to all sorts of criminal behavior. Even ordinary citizens can become criminalized if you attempt to overtax out things like cigarettes or alcohol. One case is Canada where in the last 10 years the Government has increased taxes on cigarettes by 400%. The result, not unexpectedly, given the significant price differential between cigarettes in the United States, and Canada, is a very elaborate, criminal network of smuggling cigarettes. Thus, previously quite normal and law-abiding citizens go to significant lengths to deal with the criminal element. There is widespread evasion of the law, and even corruption of the judiciary and the police.

Let us look now at the "New Puritanism". It is made up of a smorgasbord of often contradictory beliefs about the interests of the natural world, the primacy of public policy over private behavior, and the corruption of science.
The New Puritanism has become the ideology of the late 20th/beginning of the 21st centuries, and has replaced more traditional ways of thinking about individuals, their relations to each other, society, and, most particularly, pleasure. All this has occurred with the aid and the connivance of the media. The way in which the media have operated has affected the ways in which both individuals and, more importantly, government seek to think about and control pleasure.

If we look now at the value of pleasure, we should broaden the usual dichotomy between, on the one hand, the interventions of what has been called "The Nanny State" in attempting to look after people, even sometimes against their will, and on the other hand, those who argue for the absolute autonomy and rights of the individual.

This polarization often overlooks a third perspective that arguably is equally valuable, and that is the fact that we are socialized into civilized pleasures. Society has an array of informal controls that develop an individual's self-regulation of pleasure, and so finds self-fulfillment without the heavy hand of state regulation. So when the state attempts to control pleasures, it is not only suppressing individual liberty, but also attacking a long process of evolutionary civilization, which has attached meaning to pleasure in society.

Does health have a moral basis? There is no conclusive evidence that health promotion made a difference to mortality or morbidity. Even if it were the case, there are significant costs of health promotion, in terms of individual autonomy.
Sir Isaiah Berlin developed the distinction between "negative" and "positive" freedom. State attempts to intrude into individual decision-making about pleasure, of whatever form, pose a significant danger to democracy. It is simply a threat to the freedom of individual choice, as an attempt to interfere with the autonomous condition of individuals to make decisions about their own lives. If we allow individuals the right to make decisions about pleasure, we counteract this interference, and strengthen the case for individual liberty.
The pleasure-pain principle dictates much of what we do in life. We are attracted to substances, people and situations that evoke pleasure. When it comes to food and drink, people eat for taste, not for nutrition. ***Nutrition comes as a by-product of eating the foods we like to eat.***

The effect of pleasure can be measured, and for many types of sensory stimulation the ideal level at which pleasure is maximal is called the "bliss point".
The quest for the bliss point features across a multitude of life's activities, and is an extremely powerful motivator. Yet only a minority of scientists seems to be interested in research of this nature, and science has been slow to recognize and investigate the key role of pleasure in life. It is important that we study the science of pleasure. Science must not be manacled by morality.

Medicine has long made use of the body's own healing power. A brand new field is opening: "regenerative medicine" whose advocates aspire to a higher goal than traditional medicine; not just to patch up the body's failing systems, but to make them as good as new. Medical treatments available today, especially for the degenerative diseases of age, generally help patients get along with failing hearts or arthritic joints but do not make whole the underlying damage.
For now, regenerative medicine is merely a concept. Still, there is substance behind the optimistic predictions. In recent years, scientists in the public and private sectors have made several notable advances in understanding how the body repairs itself, particularly in the field of signaling systems. The body's 100 trillion cells govern themselves through an exchange of chemical signals. Cells secrete chemical signals to influence the behavior of other cells, and they receive signals through special receptors embedded in their surfaces. Until recently, only a handful of these signals had been identified, like the interleukins [*vide supra*] produced by the white blood cells and erythropoietin, the blood-stimulating protein that has created a fortune for Amgen, and is used –illegally- by professional athletes.

Now, a set of some 11,000 signaling factors and their receptors –the entire communications system of the human body- has been identified, and possibly captured by the Maryland-based company Human Genome Sciences. Remember that many, probably most, signaling factors and their receptors originate, interact, or end up in the central nervous system, and are influenced by, as well as influencing…pleasure! These do influence lifespan, as well as Quality Of Life [QOL]. We are not talking about the old myth of Tithonus, a Greek youth beloved by the goddess of the dawn, who made the error of asking her for gift of eternal **life** –instead of eternal **youth**. Later, bowed by miseries of age to which death could not put a natural end, Tithonus begged her to withdraw her gift, something that even Greek gods could not do. She did, however, provide the apparent consolation of turning him into a grasshopper. I do not have any current information on the QOL of grasshoppers, but the on-going research in signaling, and, hence, regenerative medicine targeting humans makes more than one jump.

Stressors are inevitable: we cannot avoid them; they are part of living, and a necessary part of it. But the important aspect is to be able to relax and unwind, and counteract these stressors. François Rabelais (1494-1553), one of my favorite mentors, left us with the Rabelaisian view; "by relaxing tension through laughter, one soothes the anxiety that the sexual emotions occasion in certain souls, confusing it with the guilt of sin"[5].
The little pleasures of life –such as a cup of tea or coffee, a glass of wine or beer, a bar of chocolate, or other snacks and sweets- do help in this respect. But the other aspect is that is a bonus that pleasures are an antidote to stressors; pleasures should be enjoyed in their own right.
People have a right to choose their pleasures, even if some are said to be "unhealthy".
People have a right to enjoy their pleasures without guilt –whatever these pleasures are.
People should live a life of moderate hedonism, so that they can live to the full the only life they are ever likely to have!

But we should be vigilant: bigots are everywhere. My late friend Bernard Zacharias, trombonist of the Sidney Bechet & Claude Luter jazz band, created an imaginary principality in the heart of France; its motto was *Stultitia cinget*.
Since I am [mostly] dealing with nutrition, remember that misinterpretation of reliable scientific findings is a major cause of abnormal nutrition behavior. Overreaction to health messages may precipitate such conditions as *anorexia nervosa*, or nutrient toxicity. Adverse food reactions, real or more often imagined, lead to restriction in food selection. Excessive austerity in food –and wine- use negates the pleasure of eating, a useful mechanism in food choice ensuring food diversity – and pleasurable health.
It is not by chance that most peoples toast as *Salute/Salud/Santé*….

7. The future of this Distinguished Professorship:

Facts are the air of scientists. Without them you can never fly.

Linus Pauling

I am a physician. I remain a practicing doctor in medicine. I inherited this vocation from my father who was probably the best physician I ever encountered. He loved his patients; he could spend hours listening to their complaints, imaginary or too often real; he would visit them at home, inquire about their resources, the problems with their children. He would inform them on the latest discoveries of science, and explain in depth all the side effects, cost and dangers of medications. He was as present as possible when they were dying. He was a healer.

I tried to follow on that monumental heritage. He also inspired me with the desire to use evidence-based medicine, and science-based approaches. Including the latest, newest ones, because our patients deserve the best, the most advanced. He introduced the first antihistamine in human medicine, Antergan, in 1942; he discovered a whole new series of indications for the phenothiazines: promethazine (Phénergan) a major antihistamine but also the drug that prevents nausea and vomiting in astronauts and takonauts; chlorpromazine, the first neuroleptic, which family helped empty the "nuthouses" where psychiatric patients were imprisoned. He also discovered the hypoglycemic properties of sulfonylureas. He introduced non-specific (BCG, *Corynebacterium parvum*) and specific immunotherapy in infectious diseases and leukemias. He was a major

player in organ transplantation (heart), and provided sheep anti-lymphocyte serum to Chris Barnard. He was showered with honors, awards, and celebrated; the French advisory committee for the Nobel Prize refused to support him twice, while he was nominated by the Americans and the Swedish Academy (the remnants of the Vichy regime were strong) but he overcame the sadness. Being here, addressing you, I feel like a dwarf trying to climb on his giant shoulders.
But I am and remain a physician. I like places; I love people. I will work to have products, techniques and technologies available to patients. This is my goal here and with the Hong Kong Polytechnic University. Wish me success: you may benefit from these results!

However, I am also reminded of the diversity of fascinating disciplines. In 1530 CE, upon the request of Guillaume Budé, his "master of library", king François the 1st of France named 6 lecturers who had to teach, in all freedom and independence, disciplines that were ignored or banned by the Catholic church-controlled University of Paris. These were Hebrew (F. Vatabie, A. Guidaccerius, P. Paradis), Greek (P. Danès, J. Toussaint) and Mathematics (O. Finé). The Collège de France is not a university, or an institution of higher education that transmits to students knowledge based on programs; it does not prepare to, nor delivers diplomas. Professors must teach ***"knowledge as it is happening"***. Courses and lectures are open to all, without previous registration. The 52 chairs cover a vast array of disciplines: from mathematics to the study of great civilizations; physics, chemistry, biology and medical sciences; philosophy; economy; prehistory, archeology and history; linguistics, and more. Many professors at the Collège de France are Nobel laureates; foreign scientists are welcome, and 2 chairs were recently endowed: a European, and an International (in English).

Since its creation in 1530 until today, 2 specific features have helped develop the creative value of this scientific community:

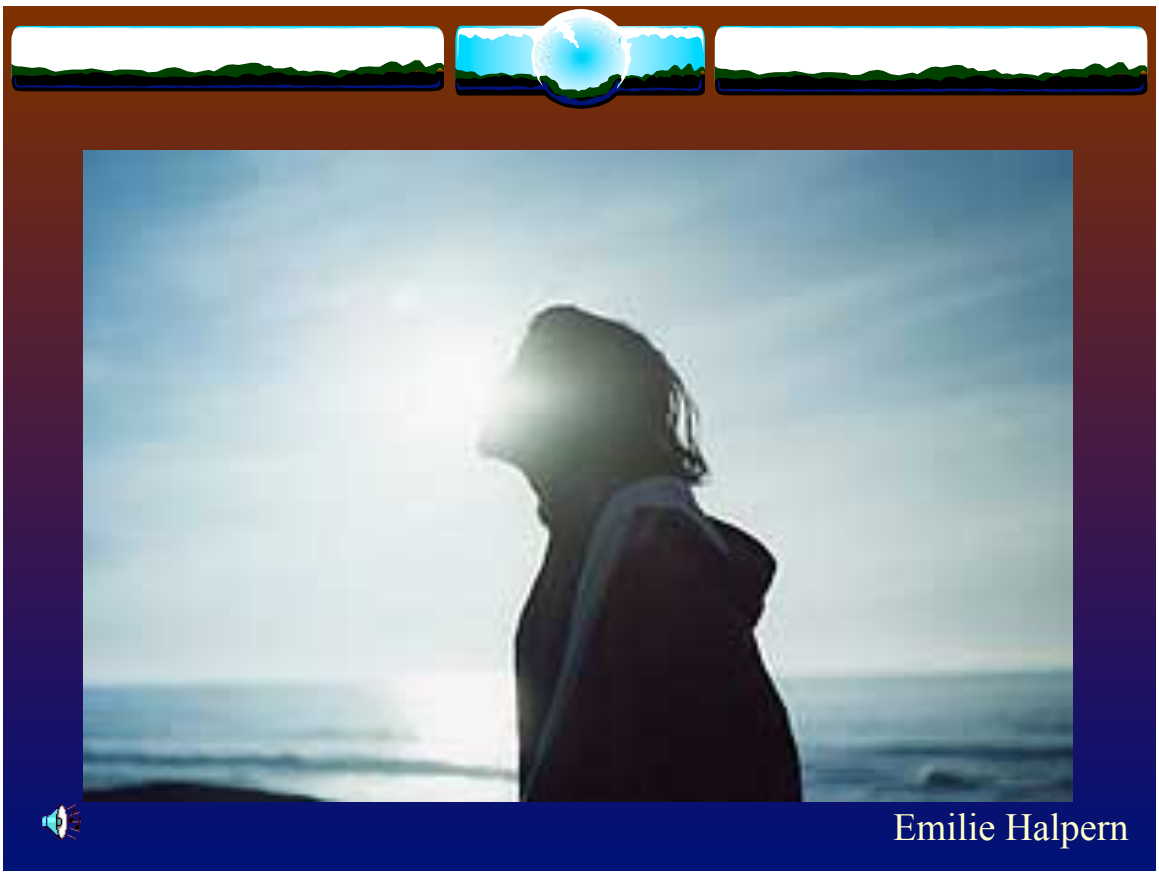
- When a chairperson retires, the chair is reassigned based on the latest developments of science. The "title" of the chair defines the new direction of research (and teaching);
- Free choice of a new chairperson by his/her peers, based on achievements (e.g. very original research and publications) and not on titles, honors or awards.

Science is the ignorance of the expert.
Richard Feynman

Intellectuals solve problems; geniuses prevent them.
Albert Einstein

The Collège de France cannot be and should not be cloned! But this very Distinguished Professorship should be perpetuated based on the Collège's principles. To perpetuate, in principle, Pharmaceutical Sciences is not productive, and I purposely avoided discussing another failing road map of that discipline. Other areas of research exist, and many do have solid foundations and superb achievements at Hong Kong Polytechnic University. This is a unique opportunity to bring together people from all disciplines and initial goals, for the betterment of mankind. I wish the ones who will succeed me, in whichever their field will be, as much dedication and enthusiasm I intend to bring to this Distinguished Professorship.

Scientific knowledge, according to current acceptance, would be like a continent emerging from the vast ocean of ignorance and growing slowly. The ocean image reminds us that we only perceive the surface of our lack of knowledge; we cannot apprehend its vastness and its depth. But the continental metaphor is poorly convincing: on what solid pedestal would the emerging lands of knowledge stand? Our ignorance of the world is abysmal, endless. Another image imposes itself: the iceberg. Science as we see it is just the emerged minuscule part of a vast floating edifice whose major part remains hidden under the surface. This invisible mass is made of our errors: unfinished or corrupted attempts that are separated from the undifferentiated gel of our ignorance. A false knowledge is already knowledge, resulting in a true change from general ignorance. Intellectual crystallizations of knowledge get condensed within the ignored chaos; their confusion lightens; they reach for the surface. When Archimedes formulated his principle, he was also discovering the true mechanism of scientific discovery. But the density of error of emerging knowledge is almost similar to the one of ignorance, since most of its contents are still inadequate. Hence most of it remains immerged –and supports the visible volume. We must recognize the persistence in the core of science of confusions and errors that led to the emergence of what we find acceptable.



But just…

Imagine *(John Lennon)*

Imagine there's no heaven, it's easy if you try,
No hell below us, above us only sky,
Imagine all the people, living for today.
Imagine there's no countries, it isn't hard to do,
Nothing to kill or die for, and no religion too,
Imagine all the people, living life in peace.
You may say I'm a dreamer, but I'm not the only one,
I hope someday you'll join us, and the world will be as one.

Imagine no possessions, I wonder if you can,
No need for greed or hunger, a brotherhood of man,
Imagine all the people, sharing all the world,
You may say I'm a dreamer, but I'm not the only one,

I hope someday you'll join us, and the world will live as one.

REFERENCES

1. Bernard C. Introduction à l'Étude de la Médecine Expérimentale. Paris; Baillière. 1865, 400p.
2. Gawande A. Complications: A surgeon's notes on an imperfect science. New York; Metropolitan Books/Henry Holt & Cy. 2002.
3. Butt DS. The sexual response as exercise. A brief review and theoretical proposal. Sports Med 1990;9:330-343.
4. Peynaud E. The Taste of Wine: The Art & Science of Wine Appreciation, 2nd Ed. (Schuster M, translator). John Wiley & sons, New York; 1996.
5. Barzun J. From Dawn to Decadence: 1500 to the present. HarperCollins, New York, p 133; 2000

All other references are available upon request at: drgeorges@drgeorges.net