HONG KONG MEDICAL FORUM '98

4 - 5 July 1998

Hong Kong Convention & Exhibition Centre

PROGRAMME BOOK

醫學院
Faculty of Medicine

Department of Medicine
The University of Hong Kong
Queen Mary Hospital
Hong Kong

HONG KONG MEDICAL FORUM

The HKMF is an annual event of the Department of Medicine of the University of Hong Kong at Queen Mary Hospital. It is an international weekend postgraduate CME meeting held in July each year.

Advances in today's clinical practice are so swift that it is not easy to keep up with the latest developments. The HKMF thus focuses on topics of current interest and advances in the practice of medicine. We strive to bring together panels of experts to provide critical overviews of the latest topics affecting clinical practice. We aim to bring an up to date programme that will be of interest and value to general practitioners, family and specialist physicians, clinicians, basic and higher trainees, nurses and allied health professionals.

Each year distinguished overseas and local speakers are invited to share with us the latest developments and results in their field of specialty. We aim to provide a forum for participants to discuss issues, and to share their experiences and knowledge with us. Hence promoting and furthering the advancement of knowledge in clinical practice and encouraging clinicians to participate in life long continuing medical education.

This year the HKMF will focus on Endocrinology, Clinical Haematology and Clinical Immunology. There will be a combined medical and surgical symposium on Saturday afternoon on Endocrinology with the Hong Kong Surgical Forum - Summer 1998, organized by the Department of Surgery, HKU. The two Forums will be held concurrently at the Hong Kong Convention & Exhibition Centre. The organizers have plans to continue to hold the two July Forums concurrently in the future.

The Organizing Committee welcomes comments and suggestions from participants so we can better plan your future Forums.

CME ACCREDITATION

The Hong Kong College of Anaesthesiologists

- 1 CME point per hour (under non-anaesthetic activities) for the 2-day programme
- FHKCA should sign the Attendance Record at the Registration Desk

The Hong Kong College of Emergency Medicine

- 3 CME points for the 2-day programme
- FHKCEM should sign the Attendance Record at the Registration Desk

The Hong Kong College of Family Physicians

- 7 credit points in Category 5.2 for the 2-day programme
- FHKCFP should sign the Attendance Record for Accreditation at the Registration Desk

The Hong Kong College of Obstetricians & Gynaecologists

- 5 CME points (under Non O & G category) for the 2-day programme
- FHKCOG should sign the Attendance Record at the Registration Desk

The College of Ophthalmologists of Hong Kong

- 2 credit points for one day, i.e. 4 credit points for the 2-day programme
- FCOphthHK should sign the Attendance Record at the Registration Desk

The Hong Kong College of Otorhinolaryngologist

- 6.5 CME credit points for the 2-day programme
- FHKCORL should sign the Attendance Record at the Registration Desk

The Hong Kong College of Paediatricians

- 2 points in Category A per day i.e., 4 points for the 2-day programme
- FHKCPaed should sign the Attendance Record at the Registration Desk

The Hong Kong College of Pathologists

- 1 point per hour for passive participation, exclusive of breaks
- maximum 7 CME points for the 2-day programme
- FHKCPath should sign the Attendance Record at the Registration Desk

The Hong Kong College of Physicians

- 1 point per hour for passive participation
- maximum 4 points per day, i.e. 8 points for the 2-day programme
- FHKCP should sign the Attendance List at the Registration Desk

The Hong Kong College of Radiologists

- 3.5 CME points for 4th July programme
- 4.25 CME points for 5th July programme
- Totally 7.75 CME points for the 2-day programme
- FHKCR should sign the Attendance Record at the Registration Desk

The College of Surgeons of Hong Kong

- 7.5 CME points for the 2-day programme
- FCSHK should sign the Record of Attendance at the Registration Desk

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4TH JULY 1998, SATURDAY - THEATRE I, 2/F (OLD WING)

TIME	ACTIVITY	SPEAKER / LOCATION
13:00 - 18:00	**Registration**	Theatre Foyer
14:00 - 14:10	**Opening**	S.K. Lam (H.K.) / J. Wong (H.K.)
14:10 - 15:20	**Joint Medical & Surgical Symposium : Endocrinology I** Chairman : K.S.L. Lam (H.K.)	
14:10 - 14:30	*Pathogenesis of Diabetic Nephropathy and Retinopathy*	G.L. King (U.S.A.)
14:30 - 14:50	*Atherosclerosis and Diabetes*	K.C.B. Tan (H.K.)
14:50 - 15:10	*Peripheral Vascular Complications in Diabetes*	S.W.K. Cheng (H.K.)
15:10 - 15:20	Discussion / Question Time	
15:20 - 16:30	**Joint Medical & Surgical Symposium : Endocrinology II** Chairman : W. I. Wei (H.K.)	
15:20 - 15:40	*Pre-operative Localization of Insulinoma*	C.Y. Lo (H.K.)
15:40 - 16:00	*Pathogenesis of Thyroid Cancer*	B.G. Robinson (Aust)
16:00 - 16:20	*Thyroid Cancer: Growth, Invasion, Metastasis and Angiogenesis*	Q.Y. Duh (U.S.A.)
16:20 - 16:30	Discussion / Question Time	
16:30 - 17:00	**Coffee Break**	**Theatre Foyer**
17:00 - 18:10	**Plenary Lectures : Endocrinology** Chairman : R.T.T. Young (H.K.)	
17:00 - 17:30	*Update on the Treatment of Diabetic Complications*	G.L. King (U.S.A.)
17:30 - 18:00	*Medical Management of Thyroid Cancer*	B.G. Robinson (Aust)
18:00 - 18:10	Discussion / Question Time	
18:10	**End**	

PROGRAMME

5TH JULY 1998, SUNDAY - THEATRE I, 2/F (OLD WING)

TIME	ACTIVITY	SPEAKER / LOCATION
10:00 - 16:00	**Registration**	Theatre Foyer
10:30 - 11:45	**Plenary Lectures : Clinical Haematology** Chairman : R.H.S. Liang (H.K.)	
10:30 - 11:00	*Anticoagulant Drugs : What is New*	H.C. Kwaan (U.S.A.)
11:00 - 11:30	*How Studies of Haemopoiesis have Contributed to Diagnosis and Treatment in Haematology*	L.B. To (Aust)
11:30 - 11:45	Discussion / Question Time	
11:45 - 12:45	**Symposium : Clinical Haematology** Chairman : A.K.W. Lie (H.K.)	
11:45 - 12:00	*Homocysteine : A New Look at an Old Player in Cardiovascular Disease*	H.C. Kwaan (U.S.A.)
12:00 - 12:15	*Tissue Engineering in Haematology*	L.B. To (Aust)
12:15 - 12:30	*Venous Thrombo-Embolism and Factor V Abnormalities*	R.H.S. Liang (H.K.)
12:30 - 12:45	Discussion / Question Time	
12:45 - 14:15	**Lunch Break**	
14:15 - 15:00	**Plenary Lecture : Clinical Immunology** Chairman : A.Y.Y. Wu (H.K.)	
14:15 - 14:45	*Adverse Reactions to Foods and Food Additives*	R.A. Simon (U.S.A.)
14:45 - 15:00	Discussion / Question Time	
15:00 - 16:00	**Symposium : Clinical Immunology** Chairman : J.W.M. Lawton (H.K.)	
15:00 - 15:15	*Diagnostic Tests in Clinical Allergy*	E.Y.T. Chan (H.K.)
15:15 - 15:30	*Aspirin Sensitive Respiratory and Cutaneous Reactions*	R.A. Simon (U.S.A.)
15:30 - 15:45	*Update on Urticaria and Angioedema*	A.Y.Y. Wu (H.K.)
15:45 - 16:00	Discussion / Question Time	
16:00	**End**	

ORGANIZING COMMITTEE

Chairman : Prof. Raymond H.S. Liang

Members : Prof. Shiu-kum Lam
Prof. Kar-neng Lai
Prof. Karen S.L. Lam
Prof. Annie W.C. Kung
Prof. Yok-lam Kwong
Dr. Adrian Y.Y. Wu

Co-ordinator : Mrs. Denise Tung

SPEAKERS

Eric Y.T. Chan
Consultant Pathologist
Clinical Immunology Section
Department of Pathology
Queen Mary Hospital
Pok Fu Lam
Hong Kong

George L. King
Professor
Senior Investigator and Section Head
Section on Vascular Cell Biology
Joslin Diabetes Center
Harvard Medical School and
Brigham & Women's Hospital
Boston, Massachusetts
United State of America

Hau C. Kwaan
Professor of Medicine
Division of Hematology & Oncology
Department of Medicine
Northwestern University Medical School
VA Lakeside Medical Center
Chicago, Illinois
United State of America

Raymond H.S. Liang
Professor & Chief
Division of Haematology, Oncology and
Bone Marrow Transplant Unit
Department of Medicine
The University of Hong Kong
Queen Mary Hospital
Pok Fu Lam
Hong Kong

Bruce G. Robinson
Professor of Medicine (Endocrinology)
Department of Molecular Genetics
Kolling Institute of Medical Research
University of Sydney
Royal North Shore Hospital
Sydney, N.S.W.
Australia

Ronald A. Simon
Head
Division of Allergy, Asthma & Immunology
Scripps Clinic & Research Foundation
La Jolla, California
United State of America

Kathryn C.B. Tan
Assosciate Professor
Division of Endocrinology & Metabolism
Department of Medicine
The University of Hong Kong
Queen Mary Hospital
Pok Fu Lam
Hong Kong

Luen-bik To
Head, Division of Haematology
Hanson Centre for Cancer Research
Institute of Medical & Veterinary Science
Royal Adelaide Hospital
Adelaide, South Australia
Australia

Adrian Y.Y. Wu
Assistant Professor
Division of Rheumatology & Immunology
Department of Medicine
The University of Hong Kong
Queen Mary Hospital
Pok Fu Lam
Hong Kong

Pathogenesis of Diabetic Nephropathy and Retinopathy

George L. King

Diabetic retinopathy and nephropathy are the leading causes of blindness and end stage renal failure in U.S. adults. The major risk factor for their developments in diabetes is hyperglycemia. There are common characteristics, which can be applied to diabetic microvascular complications including the chronic duration before their onset, metabolic abnormalities, and genetic modifiers. In addition, the pathologies of the retinopathy and nephropathy are very different from the changes commonly observed in the aging processes indicating that the microvascular diseases of diabetes is not due to an accelerated process of aging. Several theories have been postulated to explain the adverse effects of hyperglycemia including non-enzymatic glycation, increases in polyol pathway, excessive production of oxidants, and activation of diacylgglycerol (DAG)-protein kinase C (PKC) cascades. In addition, abnormalities of cytokine productions such as TGF-β in the renal golmerruli and VEGF in the retina have been strongly implicated. These recent findings have begun to provide molecular basis to the understanding of diabetic microvascular diseases.

Atherosclerosis and Diabetes

Kathryn C.B. Tan

Patients with diabetes mellitus have an increased risk of cardiovascular disease and premature extensive atherosclerosis is one of the major causes of mortality in these patients. Prospective studies have shown that in patients with non-insulin-dependent diabetes mellitus (NIDDM), coronary heart disease events are increased up to fourfold compared with non-diabetics of similar age and sex and once patients with diabetes develop symptoms and signs of cardiovascular disease, their prognosis is generally worse than patients without diabetes. The reasons for accelerated atherosclerosis in diabetic subjects are still not completely understood. NIDDM is known to be associated with several adverse cardiovascular risk factors. These include hypertension, obesity, insulin resistance, albuminuria, and serum lipid and lipoprotein abnormalities characterised by hypertriglyceridaemia, low HDL cholesterol and a preponderance of small dense LDL. The role played by hyperglycaemia has been controversial but recent studies have suggested that poor glycaemic control predicts coronary heart disease mortality and morbidity in patients with NIDDM.

Endothelial dysfunction, which is an early event in atherogenesis and precedes the thickening of the intima and the formation of atherosclerotic plaques, has recently been demonstrated in patients with NIDDM. We have shown that both endothelium-dependent and endothelium-independent vasodilation are defective in non-insulin-dependent diabetic patients without overt vascular disease. Endothelial dysfunction in these patients is related to the increased susceptibility of LDL to oxidation ex vivo. In vitro, oxidised LDL from patients with NIDDM caused a greater degree of endothelial dysfunction in an experimental model using rat aortic rings than oxidised LDL from non-diabetic subjects. Several other mechanisms that have been suggested to cause or contribute to the endothelial dysfunction seen in diabetes mellitus include increased oxidative stress, formation of advanced glycation endproducts, insulin resistance, activation of protein kinase C and expression of certain cytokines.

Abnormalities in endothelial cell function are already present in diabetic patients without symptomatic cardiovascular disease and effective management of conventional cardiovascular risk factors is important in all patients with NIDDM. Lifestyle modification is safe with no side-effects and the benefits of cessation of smoking and treatment of hypertension are proven. However, there remains several unanswered questions in terms of risk factor intervention. The role of glycaemic control in the development of macrovascular complication is not as clear as that of microvascular complication. Ongoing studies will hopefully show what kind of targets with regard to blood glucose control will be necessary to diminish the impact of this risk factor. Only limited information is available on the benefits of treatment of diabetic dyslipidaemia in reducing cardiovascular morbidity and mortality in both primary and secondary prevention and several large clinical trials have recently been initiated to tackle these issues. Until the results from these clinical trials become available, the physician caring for patients with NIDDM still has to make largely empirical decisions.

Molecular Pathogenesis of Thyroid Cancer

Bruce G. Robinson

Thyroid cancer is an important paradigm for the description of the molecular basis of cancer. Germline mutations have been described in familial cancer syndromes in which thyroid tumours occur and mutations have also been described in many sporadic thyroid tumours. The *RET* proto-oncogene is the most frequently altered. *RET* encodes a receptor with tyrosine kinase activity and is constitutively activated by several mutations in multiple endocrine neoplasia type 2, which has medullary thyroid carcinoma (MTC) as its most frequent component. Somatic mutations are also present in up to 66% of sporadic MTC. *RET* is also rearranged in many papillary thyroid cancers (PTC's). There are several forms of RET / PTC, RET / PTC3 predominating in radiation associated PTC's, but RET / PTC1 being the most common overall with frequencies ranging from 3-70%. NTRK1, TSH-receptor, and RAS mutations have also been described in PTC.

Familial thyroid adenomas have been associated with ras mutations and LOH at 11q13. Mutations in PTEN, a novel tyrosine phosphatase have recently been described in follicular adenomas and carcinomas. The most frequently identified mutation in anaplastic thyroid cancer occur in the tumour suppressor p53.

The overall relationship of these and other genetic lesions in the genesis of thyroid tumours will be reviewed and where applicable their clinical relevance will be highlighted.

Update on the Treatment of Diabetic Complications

George L. King

Diabetic vascular complications include microvessels in the retina, renal glomeruli, and peripheral nerves. In addition, excessive cardiovascular diseases are commonly observed in both large arteries and the myocardium. Due to the high prevalence of diabetes in the developed countries and the severity of the vascular and neural complication of diabetes, a great deal of studies has been performed to understand the risk factors involved and possible new treatments. The available evidence indicate that the major causative factor for diabetic microvascular and neuronal diseases is hyperglycemia whereas there are multiple diabetes specific metabolic abnormalities that can accelerate the development of cardiovascular dysfunctions including insulin resistance, hyperlipidemia, and hyperglycemia. Recent clinical studies have clearly documented that beneficial effects of glycemic control, ACE inhibitors and lipid lowering agents in preventing and delaying both microvascular complications and cardiovascular diseases. Newer understanding on the adverse effects of hyperglycemia and insulin resistance on the vascular cells have generated a host of clinical trials to determine the usefulness of antioxidants, aldose reductase inhibitors, inhibitors of non-enzymatic glycation processes, protein kinase C isoform inhibitors and insulin sensitizers. Preliminary results for these agents have been encouraging which have raised hopes that the vascular and neuronal complications which have made diabetes a malignant disease can be prevented.

Medical Management of Thyroid Cancer

Bruce G. Robinson

Recent advances in the molecular pathogenesis of thyroid cancer, the Chernobyl nuclear accident and the advent of recombinant human TSH have all resulted in re-evaluation of the appropriate management of thyroid cancer. Fine needle aspiration biopsy remains the best test for distinguishing benign from malignant thyroid nodules. *RET* gene mutation analysis can be performed to identify at risk individuals in MEN2 families. Generally, initial treatment consists of surgery with strong arguments for total or near total thyroidectomy in differentiated cancer and thyroidectomy plus central lymph node clearance for MTC.

Postoperative I^{131} therapy is administered to high risk differentiated thyroid cancer patients to ablate any residual thyroid tissue and to improve sensitivity of subsequent I^{131} scans and thyroglobulin measurement. I^{131} sans are performed approximately four weeks post cessation of thyroid hormone treatment and are associated with significant morbidity. Recent studies with recombinant human TSH stimulated I^{131} scans suggests it to be comparable in 83% of patients with markedly reduced morbidity.

Recurrent I^{131} avid tissue is treated with repeated I^{131} therapeutic doses while controversy continues regarding treatment of recurrent disease without I^{131} uptake but persistent thyroglobulin production. Palliative external beam radiotherapy and surgery may then be required.

Overall, prognosis is excellent and intensive treatment and follow-up should be reserved for individuals who can be identified by prognostic scoring systems to be at risk of recurrence and disease associated mortality.

What is new in anticoagulants

Hau C. Kwaan

In recent years, the anticoagulant drugs are increasing being used. However, both of the commonly used drugs, heparin and warfarin, have undesirable properties. Both are bound to plasma proteins, limiting their bio-availability, and thus requiring constant laboratory monitoring of their pharmacologic effects. In the case of heparin, there are undesirable complications including heparin-induced thrombocytopenia and osteopenia. With warfarin, there is the serious complication of warfarin necrosis. Thus, there is a great need for the development of newer and more attactive agents. Many of these new agents are developed basing on a better understanding of thrombosis. This is especially true in the case of the role of fibrin bound thrombin in certain clinical situations, such as post-angioplasty and post-cardiac stenting. Some of these new agents are listed in Table 1.

Table 1 OLD AND NEW ANTI-THROMBOTIC AGENTS

Anti-THROMBIN :	Standard (unfract.) heparin Low Molecular Weight heparins (LMWH) Heparan, Dermatan r-Hirudin, Hiralog Argatroban, chloromethyl-ketones (P-PACK) r-Antithrombin III
Anti-FACTOR Xa :	Standard (unfract.) heparin Low Molecular Weight heparins (LMWH) Heparan Antistatin (Mexican Leech) r- TAP (Tick anticoagulant peptide)
Anti-TISSUE FACTO:	r-tissue factor pathway inhibitor
Anti-FACTORS Va, VIIIa & PLASMINOGEN ACTIVATORS :	r-PROTEIN C
De-FIBRINATION :	Ancrod (Malayan pit viper) Reptilase (S. Amer. pit viper)

LOW MOLECULAR WEIGHT HEPARINS (LMWH) : The standard heparin preparation is a heterogenous mixture of complex mucopolysaccharides of different molecular sizes from 3000 to 40,000 daltons. It exerts the anticoagulant action by acting as a cofactor for the physiologic anticoagulant, antithrombin III (ATIII). The ATIII binding region of the heparin molecule lies in a specific pentasaccharide domain of 2300 Da. This pentasaccharide is the smallest of the LMWH, and had been synthesized and available for clinical use. Other LMWH are prepared by fractionation from the parent compound with various methods. They sizes vary from 2000 to 9000 Da and all contain the active pentasaccharide domain. The differences in the properties of LMWH from the parent unfractionated heparin are listed in Table 2.

Table 2 CHARACTERISTICS OF HEPARIN VERSUS LMWH

	HEPARIN	LMWH
Bioavailability	variable	over 90%
Plasma half-life	1-3 hrs (dose dependent)	8-12 hrs
Dose regimen	indiv. variation	fixed dose
Laboratory monitoring	essential	usually not needed
Efficacy / safety	- - - -	better risk / benefit ratio (meta-analysis)
Thrombocytopenia	1-5%	rare
Heparin-induced 0	1-0.5%	rare
Cost analysis	needs hospitalization	home-health / self injection

Danaparoid (Orgaran™, Organon 10172) This is a heparinoid that contains 80% heparan sulfate with activity against Factor Xa , and the remainder being dermatan sulfate, a powerful antithrombin agent. It is less effective as anticoagulant than LMWH but has longer heal-life of about 14 hr, and is thus useful for prophylactic treatment of deep vein thrombosis. It is also an excellent alternative anticoagulant in heparin-inducted thrombocytopenia as it has minimal cross-over immunologic activity with heparin.

Hirudin This is a group of polypeptides extracted from the European medicinal leech, *Hirudo medicinalis*. It binds tightly with thrombin (K_i=0.02pmol/ml) and completely inactivate its proteolytic action. Thus, it has advantage over other anti-thrombin drugs in that it can inactivate thrombin bound to fibrin. It is rapidly cleared from blood, primarily by the kidney, with plasma T½ of about one hour. However, there is no specific antidote (except with anti-hirudin antibody).

In clinical trials, it is an effective anticoagulant for deep vein thrombosis, arterial thrombosis and in reducing rethrombotic rates of coronary angioplasty. It also potentiates the thrombolysis of tPA in the treatment of coronary thrombosis. A synthetic analog of hirudin, hirolog.

Argatroban (Novostan™) It is a synthetic derivative of arginine and acts on thrombin. It has short half-life of 7-30 minutes (T½α 7min.; T½β 30 min). It is a powerful anticoagulant and caution should be exercised when using in patients with abnormal liver function. It should not be used in conjunction with thrombolytic therapy. It is also used as an alternative anticoagulant in heparin-induced thrombocytopenia.

r-Antithrombin III This is used in disseminated intravascular coagulation and in other conditions when the plasma AT-III is depleted. Results of clinical trials showed a highly significant improved mortality rate.

Future Developments of Anticoagulants

1. Drugs will be designed based on a better understanding of thrombogenesis, especially the role of endothelial cells, platelets in addition to the fibrin-thrombin interactions.
2. Future anticoagulants should have improved efficacy and safety features, and should be consumer friendly in terms of administration and cost.
3. Safety features should include the availability of an effective antidote.
4. New anticoagulants should work in conjunction with antiplatelet and thrombolytic agents.

References

Kwaan HC, Samama M: Clinical Thrombosis. Chptr 35 Miscellaneous: Dextran, dermatan sulfate, low molecular weight heparinoids (Org 10172), pentosan polysulfate (SP54), defibrinating agents (Ancrod and Reptilase). Pg527-534, CRC Press, Boca Raton, FL.,1989.

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Lewis BE,Walenga JM , Wallis DE: Anticoagulation with Novastan (Argatroban) in patients with heparin-induced thrombocytopenia and heparin-induced thrombocytonia and thrombosis syndrome. Seminars in Thromb.Hemostas. 23:197-202, 1997.

Eisele B, Lamy M: Clinical experience with antithrombin III concentrates in critically ill patients with sepsis and multiple organ failure. Seminars in Thromb.Hemostas. 24:71-81, 1998.

How Studies of Haemopoiesis have Contributed to Diagnosis and Treatment in Haematology

Luen-bik To

Haemopoiesis, the regulated production of blood cells, is one of the most studied body function because of ready accessibility of haemopoietic cells at various stages of development, establishment of numerous in vitro and in vivo models of proliferation and function, increasing understanding of the genetic, biochemical and cellular events of normal and abnormal haemopoiesis, and valuable interplay between clinical observations and laboratory research.

Studies of haemopoiesis have contributed to increased understanding of the pathophysiology and improved treatment of not just haematological disorders but other disorders. This lecture will illustrate its contribution with two examples: firstly, chromosomal abnormalities and their functional and molecular correlates; secondly, stem cell biology, mobilisation and transplantation.

Chromosomal changes in cancer

The t9;22 translocation (Philadelphia chromosome) is the first tumour specific chromosome abnormality described. The pathophysiological role of the mutant BCR-ABL tyrosine kinase in the proliferative, functional, adhesive and apoptotic defects in chronic myeloid leukaemia is still not clarified. However there are other examples of abnormal apoptosis (bcl2 in nodular lymphoma), DNA repair (non-familial polyposis colon cancer) and tumour suppressor genes (p53) that contribute to carcinogenesis in various ways.

Peripheral blood stem cell mobilisation and transplantation

The field of haemopoietic transplantation has changed from using bone marrow to mobilised blood cells as the cells for rescue because of the avoidance of general anaesthesia, a faster engraftment leading to improved safety and reduced costs and the option of offering multiple high dose therapy. The phenomenon of mobilisation was described in the 1970s but systematic studies only started in the 1980s. The unexpected efficacy of recombinant haemopoietic growth factors, especially granulocyte colony stimulating factor alone or in combination, in mobilising stem cells hastens the change. Currently 80-90% of autologous transplants are performed using mobilised blood cells so is an increasing proportion of allogeneic transplants. The large number of haemopoietic stem cells harvested also allows graft engineeering approaches such as tumour cell purging, normal haemopoietic cell selection and gene therapy.

Homocysteine : A New Look at an Old Player in Cardiovascular Disease

Hau C. Kwaan

The association between a grossly elevated blood level of homocysteine and arterial disease was first observed by McCully in 1969. Findings of endothelial damage caused by homocysteine followed - both in animal studies and in cultured endothelial cells. Additional homocysteine effects are on coagulation and fibrinolytic systems, suggesting the multiple thrombogenic and atherogenic pathways.

Diagnosis	
Clinical suspicion	recurrent thrombosis; early age; thrombosis after trivial provocation; unusual sites
Gene mutation	Cystathionine B-synthase (833TC, 919GA, 1221-2AC) Methylene tetrahydrofolate reductase (677CT)
Blood homocysteine level	Fasting; post methionine load
Coexistence of other inherited abnormalities	Protein C, Protein S, plasminogen, Factor V Leiden
Family history and work-up	

Management	
Homocysteine lowering	folic acid (1 mg/d); colbalamine (200mg/d); pyridoxine (100mg/d); others (betaine,tamoxifen)
Lowering risk factors	lipids, weight control, smoking cessation.

References

Refsum H et al: Homocysteine and cardiovascular disease. Ann.Rev.Med.49:31-64, 1998

D'Angelo A, Selhub J: Homocysteine and thrombotic disease. Blood. 90:1-11, 1996.

Tissue Engineering in Haematology

Luen-bik To

Biological tissue obtained from one individual may exert important physiological function when transplanted into the same or other individuals. Organ transplantation and blood component therapy are prime examples of such applications. Unlike most solid organ transplantations where the organ is used with minimum manipulation, blood component therapy involves various degrees of processing to purify the component and to preserve function on storage while maintaining microbial sterility. However the transplanted tissue is not usually enhanced functionally or modified from its original metabolic / systemic function. Bone and corneal banks and conventional haemopoietic transplant laboratories operate on similar principles. This functional preservation is the hallmark of **first generation tissue engineering**.

A number of new tissue engineering projects are now being developed that are more appropriately called **second generation** applications because they involve ex vivo processes that enhance or modify the metabolic / systemic function of the biological tissues concerned. For instance, skin banks provide skin grown ex vivo in culture. Haemopoietic cell processing that involves selection and ex vivo culture for expansion / functional amplification / immune-reactivity is another example. They require expert knowledge in cell and molecular biology, availability of specific re-agents and devices as well as sound laboratory and manufacturing practices.

Another new direction is to use genetically modified cells for therapeutic purposes, **third generation tissue engineering** applications. These modifications may involve :-

- new genes that correct abnormalities (e.g., a functioning globin gene for thalassemia)
- confer new properties (e.g., a multi-drug resistance gene to protect against the myelotoxicity of cytotoxic drugs)
- even using the cells as a gene carrier and expressor (e.g., Factor IX factor production in stromal cells).
- genes may also be introduced into tumour cells to elicit tumour specific immune response (e.g., CD40 ligand into neuroblastoma cells, GM-CSF gene into melanoma cells).
- production of tumour activated immune competent dendritic cells for immunotherapy

In parallel with the consideration for therapeutic efficacy, **safety issues** are also vital :-

- preventing unwitting use of contaminated tissues with the potential for transmitting infectious diseases such as AIDS and hepatitis; and
- preventing improper handling or processing that might contaminate or damage tissues; and ensuring that clinical safety and effectiveness are demonstrated for tissues that are highly processed, are used for other than their normal purposes, are combined with non-tissue components, or are used for metabolic purposes (i.e., for systemic, therapeutic purposes).

Venous Thrombo-Embolism and Factor V Abnormalities

Raymond H.S. Liang

Human coagulation factor V acts as a cofactor in the conversion of prothrombin to thrombin in the coagulation process. In plasma, it is converted first to its active form (Factor Va) and is then quickly inactivated by activated protein C (APC) for maintenance of haemostasis. Factor Va is first cleaved at Arg 506 and then at Arg 306 and Arg 679. Any defect on one or more of these sites can potentially affect APC inactivation process even though the factor V procoagulation activity may remain normal.

The most common defect among patients with venous thrombo-embolism is related to APC resistance. A molecular defect resulting in APC resistance was identified as a single point mutation (G1691 to A; Arg 506 to Gln) in the factor V gene. This results in the loss of APC cleavage site at Arg 506 and subsequent ineffective peptide bond cleavage processes at Arg 306 and Arg 679. Patients with this genetic defect may have a hypercoagulable state. It is well aware that the heterozygous state for this factor V mutation (Factor V Leiden) is associated with a 5 to 10 fold increase in the risk of thrombosis and a 50 to 100 fold for the homozygous state. Factor V Leiden is found predominantly in Caucasian populations and is extremely rare in Asians.

We have analysed 83 unrelated Hong Kong Chinese for the presence of genetic variants of factor V gene. Forty-three of them had a history of venous thrombo-embolism. Factor V Leiden was not found in any of them. However, a novel mutation of Arg 306 to Gly) has been identified in two thrombotic patients and one non-thrombotic subject. Further functional study is on-going and the clinical significance of this mutation remains to be determined.

Investigators in Cambridge has also identified a new factor V mutation (Arg 306 to Thr) in a patient with venous thrombosis. The mutation is associated with the presence of APC resistance. This confirms the physiological importance of Arg 306 APC cleavage site. It also supports the concept that APC resistance and venous thrombo-embolism can result from a variety of genetic mutations affecting critical cleavage sites of the factor V molecule.

Adverse Reactions to Foods and Food Additives

Ronald A. Simon

The terms food allergy and food hypersensitivity are synonymous and refer to a group of disorders that are mediated by IgE. Food intolerance is used to refer to reactions that are not immunologic in nature and may include idiosyncratic, metabolic, pharmacological, or toxic responses. The prevalence of food allergy is unknown but is more common in children than in adults. Data suggest, despite public perception to the contrary, that food allergy affects only 1-2% of the general adult population. Food allergic reactions usually occur within 2 to 3 hours of eating. Symptoms include nausea, vomiting, cramps and diarrhea. If the food allergen gains access to the systemic circulation, symptoms may include itching, urticaria, angioedema, and even anaphylaxis. Isolated respiratory reactions to foods are distinctly unusual. Eczema is the most common manifestation of food allergy in children (one-third). Foods most commonly associated with eczema include eggs, milk, peanut, soy, fish, and wheat. Anaphylaxis is most commonly associated with shellfish, peanuts, and tree nuts. The oral allergy syndrome (OAS) consists of the development of only oropharyngeal symptoms with the ingestion of food most commonly fruits or vegetables (which cross-react with aeroallergen pollens).

The diagnosis of food allergy involves skin testing with food extracts by the prick puncture technique. False negative reactions are rare; however, false positive reactions may occur up to two-thirds of the time. To confirm a food allergic reaction, double-blind placebo controlled food challenges are considered the gold standard. Strict elimination of the offending allergen is the only proven therapy once the diagnosis of food hypersensitivity has been established. Studies of immunotherapy for food allergy have shown positive results but also yielded many systemic reactions. The status of immunotherapy remains a research technique. Prevention of food allergy is as yet an unrealized goal. Breast feeding for up to 1 year is recommended for the offspring of allergic parents. However, this can only delay the onset of food allergy, not prevents it. Avoidance of peanut is currently recommended for at least 1 year in children of allergic parents. Studies have shown that 80-90% of adverse reactions to foods in infants was no longer observable by 3 years. Although less likely older children and adults may loose their sensitivity if the food can be completely eliminated from the diet for 1 to 2 years. However, patients with peanut, tree nut, fish, shell fish sensitivity rarely loose their reactivity.

There are thousands of additives available to consumers in the food that we eat. What is amazing is not there are adverse reactions to food additives but that there are not more. Tartrazine was originally reported as the first additive to cause problems in patients with asthma and chronic idiopathic urticaria. Our studies have not confirmed these initial observations. Similarly while some studies have reported monosodium glutamate (MSG) provoked asthma our studies again have not confirmed this. Sulfites, used to keep food looking fresh and preventing browning, can produce serious even life-threatening asthmatic reactions in sensitive subjects. Recently anaphylactic reactions to "natural colorings" have been reported; including annato (yellow) and carmine (red).

Diagnostic Tests in Clinical Allergy

Eric Y.T. Chan

A careful and comprehensive allergy history is essential for the identification of causative antigen in an allergic patient. This would help to predict whether avoidance of a specific allergen would improve or abolish symptoms in an individual patient. Further, confirmation of sensitivity to a specific allergen is necessary if immunotherapy is considered.

Skin prick test is the mainstay of allergy diagnosis. Measurement of antigen-specific IgE antibodies in blood (RAST) is of value if skin testing is contraindicated. Other tests, such as basophil histamine release assays are not used routinely in clinical diagnosis as they are often unreliable. In vivo provocation testing, i.e. the direct administration of the allergen to the patient with measurement of target organ response, such as nasal airflow or FEV1 measurement, is an adjunct to skin testing in some patients.

The principal indication for skin testing is a reasonable suspicion that a specific allergen or group of allergens is triggering symptoms in an allergic patient. This can be determined from the clinical history. A positive skin test in a symptomatic person is significant when correlated with clinical history. The procedure carries a very low risk of anaphylaxis and emergency treatment materials should be readily available. Testing can be performed by a trained nurse or technician but only if medical help is immediately available.

Measurement of specific IgE in blood (RAST) is expensive and time-consuming. This has the same indications as skin testing and is needed only when skin testing is difficult to perform, unreliable or contraindicated: for example, in very young children, in patients with severe eczema or dermographism, in those on H1 antihistamine antagonists, in those with exceptionally high levels of sensitization.

Aspirin Sensitive Respiratory and Cutaneous Reactions

Ronald A. Simon

Reactions to aspirin can be divided into respiratory and cutaneous types. Respiratory reactions include rhinosinusitis, and asthma. The disease is not caused by aspirin and persists in the absence of aspirin. The disease is characterized by nasal congestion, polyp formation, anosmia, recurring purulent sinusitis, and asthma. The disease is usually adult in onset and associated with eosinophilia. Aspirin cutaneous disease most often involves exacerbation of chronic idiopathic urticaria. However, what are becoming even more important are urticarial reactions to individual NSAID's. Rarely aspirin has caused anaphylaxis. For the respiratory and chronic urticaria reactions all drugs which inhibit cycloxygenase cross react and therefore illicit reactions. The detection of aspirin / NSAID sensitivity requires performing challenges in order to definitively identify sensitive subjects. In the U.S. oral challenges are required. Inhalation challenges with ASA-lysine are available worldwide. Analgesics with minimal cycloxygenase inhibition such as acetaminophen (paracetemol), and disalicylic acid produce reactions in a minority of patients and only at high dose. Agents which do not inhibit cycloxygenase (i.e. MSG, sulfite, and tartrazine) do not produce reactions in aspirin sensitive subjects. The pathogenesis of aspirin sensitivity is unknown but our studies suggest that the heightened sensitivity and continuous release of leukotrienes explains most of the features of this disease.

Treatment of aspirin sensitivity includes the treating of the underlying respiratory disease with topical (and systemic if necessary) corticosteroids. Antibiotics for episodes of purulent sinusitis and sinus surgery when the above proves insufficient. We have pioneered aspirin desensitization and daily aspirin treatment for these patients, and have shown significant improvement in all clinical parameters measured. Aspirin desensitization is simply an extension of the aspirin challenge procedure. After treatment of the provoking dose reaction that dose is repeated until no further reaction is elicited. This procedure is then followed with increasing doses of aspirin until the patient can tolerate 650 mg. Treatment is begun with 650 mg ASA BID and increased or decreased according to the patients progress. We have found that there is a refractory period following aspirin desensitization that lasts at least 48 hours. Therefore if a patient misses a dose or even a days dosages they may simply restart their ASA treatment as soon as they can. We avoid aspirin treatment in pregnancy. Finally, the use of antileukotriene drugs makes great sense for all these patients. However, they may require greater than usual doses and/or the combination of receptor antagonists and pathway inhibitors.

We have been unable to desensitize the group of patients with aspirin exacerbated chronic idiopathic urticaria and therefore these patients must avoid aspirin and all NSAIDS. Patients with individual NSAID provoked urticaria should avoid the specific NSAID, to which they reacted, but need not avoid any of the other cycloxygenase inhibitors.

Update on Urticaria and Angioedema

Adrian Y.Y. Wu

Urticaria is characterised by the appearance of pruritic, erythematous cutaneous elevations that blanch with pressure. It is a common disease with multiple aetiology. Frequent causes of acute urticaria may include viral infections, food allergies and allergic reactions to drugs or insect stings. However, many physical stimuli such as cold, heat, pressure, friction, ultraviolet radiation and even water can elicit urticaria in some patients. When urticaria becomes chronic, i.e. lasting more than six weeks, it is termed chronic urticaria. The chance of identifying the cause of chronic urticaria in any given patient is less than 20%. It has become recognised recently that a large proportion of chronic urticaria is caused by auto-antibodies against the high affinity IgE receptor.

Angioedema and urticaria have similar pathological alterations, but in angioedema, such alterations occur in the deep dermis and subcutaneous tissue. Angioedema and urticaria in many cases have similar aetiologies. However, there are important entities such as hereditary angioedema and acquired C1 inhibitor deficiency that require separate considerations.

During this talk, the initial evaluation of patients presenting with urticaria and angioedema will be discussed. Recent evidence linking urticaria to autoimmunity will be presented, and tips on how to manage these patients will be given.

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