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Cytokines and Medicine 1: *From fever to phenome*

Prof. Sir Gordon Duff

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Fever is one of the oldest and most frequently recorded physical signs in clinical medicine, but its pathophysiological significance remains unclear. However, over the last 40 years, attempts to understand the mechanism of fever contributed key insights that led to the discovery of several families of intercellular protein messengers and growth factors, now called cytokines. Understanding the cytokines that are produced by blood monocytes and tissue macrophages (monokines) has been especially important in inflammatory and immune diseases. There have already been notable therapeutic successes in chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease and psoriasis. We can expect further significant therapeutic and diagnostic developments in the future.

Cytokines and Medicine 2: *From phenome to genome and back again*

Prof. Sir Gordon Duff

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Modern molecular technologies have allowed an ever-increasing understanding of the role of cytokines and growth factors in a wide range of human diseases. We already have many new cytokine-related medicines that have been highly successful in the clinic. Knowledge of cytokine genes and their epigenetic modifications is contributing to an understanding of inherent susceptibility to infectious and inflammatory diseases and their clinical outcomes, or phenotypes. Looking to the future, these advances promise genomic and phenomic tools for the stratification of patient populations in new medicines development ('stratified' or 'precision' medicine) and for effectively targeted public health strategies in preventive medicine.

Venomous and Poisonous Animals of the Arabian Peninsula

Prof. David A. Warrell

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Snakes: The Arabian peninsula is inhabited by 12 species of medically-important terrestrial venomous snakes, all but three of which occur in Oman, although four (*Atractaspis microlepidota andersonii*, *Naja arabica*, *Bitis arietans* and *Echis pyramidum*) are virtually confined to the Dhofar region in the south of the country. The most frequently encountered snakes are horned vipers (*Cerastes*) and saw-scaled vipers (*Echis*). Viper venoms contain cytotoxic hydrolases responsible for local swelling, bleeding, bruising, lymphangitis, blistering and necrosis; metalloprotease haemorrhagins causing spontaneous systemic bleeding; procoagulant enzymes causing consumption coagulopathy, platelet inhibitors and other anti-haemostatic toxins, and hypotensive oligopeptides causing shock. Microangiopathic haemolysis and shock are two of the possible mechanisms for acute kidney injury (AKI). Ten species of sea-snakes are found in the seas surrounding Arabia but are absent from the Red Sea. Sea-snake venoms contain paralysing neurotoxins and myotoxic phospholipases A_2 that cause generalised rhabdomyolysis complicated by hyperkalaemia and AKI. The venoms of burrowing asps (*Atractaspis*) contain oligopeptide sarafotoxins that are potent endothelin homologues causing coronary vasoconstriction. The venom of the Arabian cobra (*Naja arabica*) has post-synaptic neurotoxic activity causing descending paralysis. First-aid involves reassurance, compression of local veins and lymphatics with a pressure-pad, immobilisation with a splint or sling and rapid transport to medical care. Specific antivenom is indicated if there are evident haemostatic abnormalities, shock, neurotoxicity, myotoxicity, haemolysis or severe rapidly progressive local envenoming. Appropriate specific antivenoms are manufactured by the National Antivenom and Vaccine Production Center (NAVPC) in Riyadh, Saudi Arabia (www.antivenom-center.com) but a variety of antivenoms of uncertain effectiveness are imported from India and elsewhere. The risk of snake-bite is reduced by wearing protective clothing, especially footwear; using lights when walking after dark, and either sleeping off the ground or underneath a well-tucked-in mosquito net. ***Scorpions:*** Throughout Arabia, scorpion-stings are more frequent than snake-bites but fatalities are rare except in children. The most dangerous *genera* are *Androctonus* and *Leiurus* (*Buthidae*) and *Nebo* (*Scorpionidae*). Intense local pain in the stung digit is best treated by digital block with local anaesthetic. For severe systemic envenoming, antivenom is manufactured by the NAVPC. ***Spiders:*** There are a few reports in this region of severe muscle spasms, suggesting the possibility of bites by imported *Latrodectus* (black widow) spiders. ***Hymenoptera (wasps, hornets, bees):***

Sensitised people may be protected from sting anaphylaxis by self-injectable adrenaline or desensitisation. ***Marine stingers:*** Many species of venomous fish (stingrays, catfish, stonefish, lionfish, scorpionfish), jellyfish (*Cnidaria*), sea urchins, bristleworms (*Polychaetes*) and coneshells inhabit the tropical waters of the Gulf and Arabian sea. Enormous swarms of jellyfish occasionally invade the coastline of Oman (e.g. *Crambionella orsini* in 2002). Although no fatal jellyfish stings have been reported here, many painful stings and a few near-fatal systemic envenomings have occurred. Cubozoans (box jellyfish) were implicated in the worst cases, at least one of which had features of Irukandji syndrome (delayed headache, musculoskeletal, chest and abdominal pains, nausea, vomiting, diaphoresis, hypertension, tachycardia and pulmonary oedema) that has been associated with fatalities in Australia. Dangerous *genera* found in Arabian waters include *Tamoya* and *Alatina* (*Carybdea*) but *Chiropsalmus* and *Chironex* have never been recorded. Portuguese men o' war (*Physalia*) are also present. Apart from direct envenoming, sensitised people may suffer anaphylaxis if they are stung on a second occasion. ***Seafood poisoning:*** Algal blooms of *dinoflagellates* (*Alexandrium sp*.) create red tides, creating the risk of shellfish poisoning and threating the fishing industry, wildlife and desalination plants in Oman. High levels of histamine have been found in imported dried anchovies (Arabic, *qasha*), carrying the risk of scombroid fish poisoning. There are many species of potentially tetrodotoxic pufferfish in these waters, but no cases of poisoning have yet been reported.

Malaria and Other Imported Tropical Diseases

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Oman has succeeded or made substantial progress in eliminating many of its endemic tropical infectious diseases such as malaria, lymphatic filariasis and schistosomiasis but others persist at varying levels of incidence or prevalence, such as tuberculosis, typhoid, leishmaniasis, hookworm, brucellosis, trachoma, rabies and Crimean-Congo haemorrhagic fever. Since Oman employs an increasingly large foreign labour force from developing countries, contributing 30% of its population, the country has a growing susceptibility to imported tropical infections such as malaria, a risk compounded by rising international tourism and pilgrimage, together with influxes of immigrants from neighbouring countries, such as from Somalia in 1998. One result of disease globalisation is that medical staff anywhere in the world may be confronted by a patient suffering from an imported disease acquired in an exotic location. An expanded range of differential diagnoses should be considered including the following pathogens, some of which are opportunistic infections in HIV-immuno-suppressed patients. ***Viruses:*** hepatitis, haemorrhagic fevers, encephalomyelitis (arboviruses, lyssaviruses, henipaviruses, etc.); ***Bacteria:*** enteric fevers, melioidosis, tularaemia, leptospirosis, rickettsioses, relapsing fevers, antibiotic-resistant strains (totally drug-resistant *Mycobacterium tuberculosis* (TB), *Acinetobacter barmannii*, carbapenem-resistant *Enterobacteriaceae*, etc.); ***Fungi:*** *Penicillium marneffei*, *Paracoccidioides brasiliensis*, *Cryptococcus gattii*, etc.; ***Protozoa:*** malaria, babesiosis, *visceral leishmaniasis* (kala-azar), trypanosomiasis, amoebiasis, etc.; ***Helminths:*** *Strongyloides*, *Trichinella*, etc. Typical "blind" broad-spectrum antibiotic treatment regimens for patients with assumed community-acquired sepsis such as a broad-spectrum antipseudomonal penicillin or broad-spectrum cephalosporin with an aminoglycoside would fail in all the virus infections, some of the bacteria (carbapenem-resistant *Enterobacteriaceae*, miliary TB, *Rickettsiae*, *Listeria monocytogenes*), and all the fungi, protozoa and helminths. In all cases of suspected imported infection, a detailed travel history is essential, including the precise itinerary, type of accommodation, style of travel, activities, sexual contacts, accidents, unusual events and exposures, infestations with ticks, fleas and other arthropods and bites. The traveller's special vulnerabilities should be explored, such as lack of pre-travel vaccinations (e.g. yellow fever, poliomyelitis, diphtheria, rabies, viral hepatitis A and B) and appropriate chemoprophylaxis (e.g. malaria, *Rickettsiae*, leptospirosis); splenectomy (past surgical or sickle cell anaemia autosplenectomy, e.g. malaria, babesiosis, encapsulated bacteria); pregnancy (e.g. malaria, amoebiasis, listeriosis, hepatitis E virus); drugs (e.g. corticosteroids for TB, amoebiasis, melioidosis, invasive strongyloidiasis, gastric acid secretion inhibitors for gastrointestinal infections), and chronic illnesses (human immunodeficiency virus, human T-lymphotropic virus 1, diabetes mellitus, alcoholic cirrhosis, chronic renal failure, renal stones, sickle cell anaemia). Awareness of current epidemics in the countries where the illness may have been acquired can be provided by websites such as www.promedmail.org/. Severe *falciparum* malaria is one of the commoner imported tropical diseases. Exceptionally, it may prove fatal less than 24 hours after the first symptoms. Malaria must be excluded in every case of acute fever with possible exposure in an endemic area, especially during the previous few months. None of the typical symptoms are specific (fever, chills, pains in head, muscles, back or joints), fatigue, anorexia, prostration, *malaise*, gastrointestinal and respiratory symptoms, postural fainting). Malaria may be misdiagnosed as influenza, travellers' diarrhoea, hepatitis, viral encephalitis or viral haemorrhagic fever. Patients may not volunteer their history of travel to a malarious country and competent parasitological diagnosis may not be generally available. Patients with suspected severe malaria should be admitted to hospital immediately. Their malaria chemoprophylaxis should be stopped to improve chances of microscopic diagnosis. Preferably, thick and thin blood films should be examined daily for at least 72 hours (or rapid antigen detection) or until an alternative diagnosis can confidently be made. If features of severe malaria develop (e.g. declining level of consciousness), a therapeutic trial of intravenous artesunate should be initiated without delay. Other travel companions should also be checked for malaria as they are likely to have shared the same exposure risk as the index case.in the future.

Advances in the Treatment of Bone Diseases

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There have been impressive advances in recent years in understanding the genetic basis of bone disorders, and the regulatory systems that control bone formation and resorption. These advances have not only led to a better understanding of the pathophysiological basis of osteoporosis and other bone diseases, but also to new approaches to therapy. Currently the bisphosphonates (BPs), e.g. alendronate, risedronate and zoledronate, dominate the market as extremely effective agents for the treatment of bone diseases characterised by increased bone resorption, such as Paget's disease, osteolytic bone metastases, myeloma and osteoporosis. The molecular actions of BPs are now well understood and this is leading to a better appreciation of the important but subtle differences among the members of the BP class of drugs. Many BPs are now becoming generic and current issues include how long they should be used and concerns about rare side-effects, such as atypical fractures. Overall the benefits of using these drugs far outweigh any disadvantages, and there is evidence that BPs may have important non-skeletal effects, including anti-cancer effects and extension of the life span. In terms of the

development of drugs to inhibit bone resorption, the discovery of the receptor activator of nuclear kappa beta ligand (RANKL) system has had a profound impact, and the introduction of denosumab, an anti-RANKL fully human antibody, is proving very effective for treating osteoporosis and others disorders of bone resorption. Inhibition of the bone-specific protease cathepsin K is another approach and one such drug, odanacatib, is still in clinical development. Among other approaches, the interest in selective estrogen receptor modulators has declined. There is still intense interest in the development of drugs that stimulate bone formation, but the search for pharmacological stimulants of bone formation to build bone and prevent fractures has proved to be difficult, with only one such agent, parathyroid hormone (PTH), given as pulsatile therapy, having been licensed for this purpose. Developing alternate forms of PTH has not yet been successful, while the attractive concept of using calcilytic drugs, working via the Ca-sensing receptor to stimulate endogenous PTH secretion, has also not yet been successfully accomplished. Much interest is currently focussed on the opportunities that have arisen from the discovery of the genetic basis of the high bone mass syndromes, including sclerosteosis. The targets lie in the bone morphogenetic proteins (BMPs) and the *wnt*/LRP5/6 pathway. Blockade of sclerostin (encoded by the *SOST* gene), an osteocyte-derived protein that blocks BMPs and *wnt* signalling, by using neutralising antibodies, has already been demonstrated to augment bone mass in animals and man.

Bone as an Endocrine Organ

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There have been remarkable recent advances in knowledge about skeletal biology and the changes that take place in disease. These are largely the result of discoveries in genetics and cell biology. Skeletal development is programmed by the sequential activation of specific genetic pathways, that culminate in the production of the adult skeleton which is light but strong. Systemic hormones—including the parathyroid hormone (PTH), vitamin D metabolites, and calcitonin—regulate blood calcium levels and contribute to the overall calcium economy of the body. Many other hormones have effects on skeletal behaviour and its modelling and remodelling activity. In addition to understanding how osteoblasts form bone and osteoclasts resorb bone, the osteocytes are now recognised to have an important role as mechanosensors and endocrine cells. It is becoming clear that bone may itself function as an endocrine organ, not only locally but also sytemically. At a local level, the integration of cellular differentiation and function within the microenvironment of bone is under the influence of a large number of cytokines and growth factors. There are several important recently discovered pathways that are involved in osteoblast regulation and osteoblast/osteoclast interactions; some of these are suitable for pharmacological interventions, including the *wnt*/LRP5 pathway, the ephrin system, PTH-rp and particularly the receptor activator of nuclear kappa beta (RANK) and Ligand/RANK/osteoprotegerin system. At a systemic level, there is evidence that products of bone cells may have distant endocrine effects. Indeed osteocytes have their own repetoire of regulatory molecules, including *FGF23*, which is involved in phosphate metabolism, and sclerostin, which is a powerful negative regulator of bone formation. Furthermore there is evidence that osteocalcin, secreted by osteoblasts, may act as a systemic metabolic regulator by controlling insulin secretion and sensitivity. There are also potential regulatory links between the hypothalamus, gut and adipose tissue involving leptins, serotonin and adipokines. These phenomena link in to the crosstalk between muscle and bone, and into understanding various aspects of ageing. All this new knowledge is offering exciting opportunities for therapeutic interventions.

Acute Medical Problems in Pregnancy

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Medical diseases, either pre-existing or new onset in pregnancy, are now the commonest cause of maternal death in the UK. Successive reports of the confidential enquiries into maternal deaths have demonstrated no significant fall in the number of these maternal deaths due to 'indirect' causes over the last 20 years. Furthermore, the majority of these deaths are associated with substandard care and in one-third of cases, this is classified as major substandard care, where different care might have prevented death of the mother. This substandard care includes failure to diagnose appropriately, investigate and treat women with new onset chest pain, headaches or other medical symptoms. This often arises when well-meaning clinicians prioritise the health of the fetus over that of the mother, withholding essential investigations or drugs, resulting in the demise of both mother and fetus. Cardiac disease (aortic dissection, ischaemic heart disease, cardiomyopathy) is the commonest cause of maternal death in the UK, followed by neurological causes such as epilepsy and subarachnoid haemorrhage. Physicians should be familiar with the interaction between pregnancy and medical disease, with the safety of radiological investigations in pregnancy and with the risk/benefit ratio for the use of different drugs in pregnancy. Physicians looking after pregnant women in their clinics, or in the acute medicine setting, need to have the skills to assess the 'common' symptoms of pregnancy, including breathlessness, headaches, palpitations and epigastric pain. Mostly, these symptoms are benign and a careful history is reassuring but physicians need to be aware of red flag symptoms and signs. The normal ranges of many blood tests are altered by pregnancy and the results must be interpreted with knowledge of normal ranges in pregnancy. Chest X-rays, computed tomography (CT) scans of the head, CT pulmonary angiograms, magnetic resonance imaging and ventilation/perfusion scans are all safe in pregnancy and should never be withheld if clinically indicated. Algorithms for the diagnosis and management of acute medical problems such as acute severe asthma, acute coronary syndrome and headaches are little changed compared to the non-pregnant patient. However, there are important adaptations in the investigation and management of acute venous thromboembolic disease and cardiac arrest in pregnancy.

Renal Disease in Pregnancy

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Kidney disease is relatively common in pregnancy and can be broadly divided into chronic kidney disease (CKD) and acute kidney injury (AKI). The risks for women with CKD include an increased chance of developing pre-eclampsia, a growth-restricted fetus and preterm delivery. The outcome for women with CKD is dependent on the degree of renal impairment, the presence and severity of co-

existing hypertension and proteinuria and, to a lesser extent, the underlying cause of the CKD. Drugs suitable to control hypertension in pregnancy included labetalol, nifedipine and amlodipine, methyldopa and doxasocin. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated in pregnancy. If used to control proteinuria and for renal protection, they may be stopped as soon as pregnancy is confirmed; when used for hypertension they should be changed to a safer alternative prior to pregnancy. Statins should also be stopped prior to pregnancy. Immunosuppressant drugs used for transplantation and in glomerulonephritis that are safe to continue in pregnancy include corticosteroids, azathioprine, tacrolimus and ciclosporin. These drugs are also safe in breastfeeding. Teratogenic drugs that should be stopped prior to pregnancy included cyclophosphamide and mycophenolate mofetil. Intravenous iron and synthetic erythropoietin may be safely administered during pregnancy. The pregnancy outcome for women with renal transplants is usually good but again depends on the pre-pregnancy allograft function. Data from a recent prospective UK study of 105 pregnancies in 101 patients with a median pre-pregnancy creatinine 118 μmol/L showed that pre-eclampsia developed in a quarter, median gestation at delivery was 36 weeks and over 50% of babies were born preterm (<37/40) and a quarter were born small for gestational age (<10th centile). Predictive factors for poor pregnancy outcome were first trimester creatinine >125 μmol/L (P = 0.001), and diastolic BP >90 mmHg in the second or third trimester. Although previously associated with very poor fetal outcomes, women with CKD on dialysis are now usually able to have successful pregnancies, although most deliver preterm babies. AKI in pregnancy is most commonly associated with postpartum haemorrhage and other hypovolaemic states, pre-eclampsia syndromes and sepsis. AKI is also seen in association with use of non-steroidal anti-inflammatory drugs which is common after Caesarean section. The management of women with CKD in pregnancy should involve a multidisciplinary team and should begin with pre-pregnancy counselling to ensure women are informed of the risks and understand any changes necessary in their medication. The timing of delivery involves balancing the risks of early delivery for the baby *versus* the risks of continuing the pregnancy (potentially resulting in irreversible decline in renal function) for the mother.

Hormone Replacement Therapy in 2014

Prof. John A. H. Wass
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There have been many advances and improvements in hormone replacement therapy for all sorts of endocrine deficiencies. In the field of thyroid hormone deficiency, a proportion of patients do not respond to simple thyroxine therapy. Thyroxine needs to be converted to liothyronine and some people have a genetically determined decrease in the enzyme that achieves this. Therefore they may need triiodothyronine replacement therapy if the symptoms of hypothyroidism persist despite thyroxine therapy. A meta-analysis of the use of liothyronine in hypothyroidism does not reveal that this is a problem because of the prevalence of this genetic deficiency. In addition, the treatment of a persistently elevated thyroid-stimulating hormone level in the presence of hypothyroidism and thryoxine therapy has multifarious causes. This therefore needs careful consideration of such aspects as the type of thyroxine preparation being utilised, the presence of coeliac disease and interference with either the absorption or metabolism of thyroxine. There are new ways of treating hypoparathyroidism and parathyroid hormone is becoming available. This is a rare problem most frequently occurring after total thyroidectomy. In the field of adrenal gland problems, long-acting daily-dose steroid preparations are becoming available. Monitoring is done by measuring cortisol levels and urinary steroids. Mineralocorticoid deficiency is treated by fludrocortisone and the adequacy is monitored by measuring renin. In the field of male testosterone deficiency, longer acting preparations of testosterone are now available which may only necessitate therapy every three months. It is important to monitor the haemoglobin for polycythaemia and the prostate-specific antigen for prostate cancer. The latter is not caused but may possibly be exacerbated by testosterone replacement therapy. Growth hormone deficiency is commonly seen in patients with pituitary disease. Double-blind studies suggest that treating such patients with growth hormone, even if they are adult, improves muscle strength, mental function and decreases cardiovascular risk.

Concepts in Obesity

Prof. John A. H. Wass
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Obesity is increasingly prevalent and this is particularly the case in the USA, the UK, Australia and Sri Lanka. A national survey carried out in 2012 in Sri Lanka shows the rates of overweight and obesity are rising to epidemic proportions, especially among women. It is clear that obesity causes an increase in a number of different problems, including diabetes mellitus, hypertension, sleep apnoea and increased rates of cancer. There are also clear problems with obese children who will tend to grow up to be obese adults. Bariatric surgery remains an effective means of combating severe obesity but other treatments also work. Currently, no developed nation has developed an effective strategy to reduce levels of obesity. This would involve the coordination of different government departments, including health, education, agriculture, sport and the treasury. A coordinated approach is necessary but no country on the planet can yet serve as a model for how to tackle the problem.

Acute Rheumatological Emergencies

Dr. Charles Mackworth-Young
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Rheumatological emergencies are not uncommon and appropriate management can radically affect the eventual outcome. The presentation focusses on conditions most commonly seen, including those that often cause the greatest diagnostic difficulty such as septic arthritis, crystal arthritis, giant cell arteritis and cerebral *lupus*. Diagnostic pitfalls and immediate management will be discussed.

Antiphospholipid Syndrome

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It is 30 years since the substantive clinical description of the antiphospholipid syndrome was made. Since then the importance of the condition in many areas of medical practice has been recognised. While it was initially described in the context of connective tissue diseases such as systemic *lupus erythematosus*, it soon became apparent that the syndrome can exist as an independent, primary disorder. It is a frequent cause of venous and arterial thrombosis, and the most common acquired cause of recurrent foetal loss. It explains many cases of early stroke and myocardial infarction, and can account for certain atypical neurological syndromes. The presentation includes a brief history of the condition, a summary of the clinical features and an overview of current management.

Evidence-led Improvement of Patient Outcome and Patient Experience

Dr. Ian Bullock
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The Royal College of Physicians (London) has a highly respected track record of a whole healthcare systems approach and delivering first class evidence-based healthcare products. We offer an international consultancy service providing a range of evidence-based healthcare and quality initiatives tailored to a country's individual requirements. Whether it is setting up international evidence-based guideline development groups or quality initiatives, tailored programmes are shaped in partnership with local healthcare experts to improve both patient outcome and the quality and experience of care. A key aspect of this work is our experience and understanding of the relationships that exist between the evidence, the geographical context and culture where evidence is implemented into practice, as well as understanding the way in which change is facilitated. We are sensitive to cultural needs and aim to bring about evidence translation and utilisation which lead to sustainable healthcare improvements through application of the Promoting Action on Research Implementation in Health Services (PARIHS) framework. The presentation illustrates how, through consultancy support, evidence translation and utilisation should remain high priorities for developing healthcare systems.

Redesigning Service Delivery in Stroke Care to Continuously Improve the Quality of Patient Care

Dr. Ian Bullock
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The Oman Evidence Translation and Utilisation (OETU) project commenced in 2011. In partnership with the Royal College of Physicians (London), the burden of disease areas of national importance to the Omani population were identified with the top five of these prioritised for evidence work. Expert clinicians (stroke, cardiac disease, diabetes, respiratory disease and obesity) from a range of health disciplines, including medicine, nursing and allied health professions, met for a two-day conference focussed on developing knowledge and expertise in evidence-based healthcare, leadership and quality improvement. Of these high-priority areas, experts in stroke care were formed into a quality development group and worked to produce the first Omani National Clinical Guideline—in the management of stroke—launched in December 2013. The OETU project has provided a framework for evidence use, healthcare system improvement, continuous quality improvement and hospital redesign.

The Diagnosis and Management of Cardiac Failure

Dr. Adam Darowski
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The principles of treatment of heart failure are well-established. Diuretics relieve symptoms, angiotensin-converting enzyme inhibitors, beta-blockers and anti-aldosterone diuretics improve survival. Non-pharmacological approaches such as exercise, cardiac resynchronisation and implantable cardioverter-defibrillators also improve survival. Heart failure is a syndrome caused by a wide spectrum of different conditions. There are two broad groups of patients: those whose left ventricular systolic function is impaired (systolic failure), and those in whom it is preserved. Cardiac failure with preserved left ventricular function is the more common form of heart failure, but the variety of methods used to diagnose it lead to confusion in the literature. It has been little studied compared to systolic failure. The presentation will discuss what is known about making the diagnosis of these two conditions and the evidence for their management.

Making Sense of Transient Loss of Consciousness

Dr. Adam Darowski
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Brief episodes of loss of consciousness are rarely witnessed, and only a limited and frequently misleading history is available from the patient. Had Sherlock Holmes been a doctor, this would have been his chosen field. The doctor has to establish whether there really was any loss of consciousness and try to recreate the 'crime scene'. He has to gather evidence of what factors might have led to the event and which of them—there are often several 'suspects'—actually caused it. Frequently, we are left with several possibilities and no 'smoking gun'. The key is to exclude serious causes and work on a balance of probabilities for the others. The likely underlying diagnosis depends to a large extent on the patient's age. Half of our medical students admit to an episode of loss of consciousness. Usually the cause is vasovagal syndrome—a reflex common to all vertebrates—but occasionally sudden death occurs in young people. In older age groups, the focus is on the diagnosis and management of rhythm disorders. Drug-induced paroxysmal hypotension (mostly orthostatic hypotension and vasovagal syndrome) is the most common cause.

Metabolic Surgery in Diabetes: *Cutting to the solution*

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Obesity, which is arguably the single most important public health challenge nowadays, is directly linked to several diseases such as type 2 diabetes mellitus (T2DM), hypertension, ischaemic heart disease, obstructive sleep apnoea, osteoarthritis and various cancers. Public health and legislative approaches are essential to tackling the global epidemic of obesity, together with diet, exercise and medications. However, bariatric surgery remains the most clinically effective and cost-effective intervention for morbid obesity and its global uptake has increased exponentially in the past decade. In Kuwait, more than 6,000 metabolic surgeries are performed each year. Patients with T2DM undergoing bariatric surgical procedures demonstrate substantial and sustained weight loss, reductions in diabetes medications and remission of hyperglycaemia. Surgical intervention in patients with a more recent onset of T2DM appears to result in higher rates of resolution than in patients with a longer duration of the disease. These findings suggest bariatric surgery may represent a potential first-line therapeutic management strategy for T2DM, particularly in those with lesser degrees of obesity or a shorter duration of the disease. Although this has generated substantial interest in the scientific community, minimal level one data is available to guide such an approach. There was what can only be described as a cultural disconnect when bariatric surgery was being promoted for the treatment of T2DM. Diabetologists were interested in the percentage reduction in body weight, HbA_{1C}, lipid profiles and blood pressure, whereas surgeons reported on the reduction in excess body weight and 'cure' rates for T2DM, dyslipidaemia and hypertension. The presentation highlights the current evidence for the success of various types of metabolic surgery and focuses mainly on T2DM from various metabolic and nutritional points of view.

Acute Kidney Injury

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Acute kidney injury (AKI) remains a common complication of many non-renal medical problems. It requires hospital admission and a variety of therapies. With improved renal replacement therapy, it is rare for a patient to die directly as a result of renal failure; however, the mortality of patients requiring acute dialysis therapy remains high. Recent evidence has shown that relatively small changes in renal function are associated with substantial increases in mortality. Moreover, acute renal failure is an independent risk factor for death. This presentation highlights issues related to the diagnosis, new pathophysiological aspects and the non-dialytic management of critically ill AKI patients as well as renal replacement therapy.

Volume Responsiveness

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Volume responsiveness remains an important question in critically ill hypotensive patients. Timely and appropriate use of intravenous fluids can rapidly stabilise a patient's condition and avoid the use of vasoactive drugs. However, excessive fluid resuscitation has been associated with increased complications, increased length of intensive care unit stay and hospital stay and increased mortality. Traditionally, physicians use clinical examination (e.g. jugular venous pressure), central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) to assess volume responsiveness in an unstable patient. Multiple studies have demonstrated that these parameters are unreliable and they have poor sensitivity and specificity. In the past decade, new volume responsiveness methods have been described and studied. Examples of these dynamic methods are pulse pressure variation (PPV), stroke volume variation (SVV) and passive leg raising (PLR). In contrast to static measures (CVP, PCWP), dynamic parameters (PPV, SVV, PLR) rely on the changing physiology of heart-lung interactions to determine whether a patient will benefit from intravenous fluid or an increase in preload.