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Gastrointestinal Endocrinology

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There are two types of endocrine tissue, one gathered in glands – this is classical endocrinology. The other is dispersed endocrine cells spread throughout particular tissues – the diffuse endocrine system. The latter, although less well recognised is the larger and, arguably the more important. Hormones are actually even wider than this – hormones being released from many cells not normally thought as endocrine (paracrine and neurocrine). The gut is controlled by both diffuse endocrine cells and non-endocrine cells producing "hormones". The endocrine cells are mostly in the mucosa and integrate with the submucous neural plexus as well as sensing what has been eaten. From the physicians viewpoint there are two main conditions of interest – gastrointestinal endocrine tumours and dysfunctional regulation of digestion. Endocrine tumours are important because they are eminently treatable. Our understanding of digestive regulation is less well developed but shows the tight integration of the body as several gut hormones have powerful effects on how we think and behave.

Treatment of Obesity

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The treatment of obesity is easy – eat less food. Obesity clinics are frustrating as it is rare for patients to successfully lose weight and they often blame their physician. Obviously low calorie, high fibre foods eaten with restraint and plenty of exercise are the key. Equally obviously it often doesn't work. With chronic conditions we need safe medication (eg hypertension, hypercholesterolaemia, chronic lymphatic leukaemia etc are all handled with chronic medication). Can we treat obesity with a pill? Approaching 130 new obesity treatments have been tested in human trials and only one remains on the market throughout the world – orlistat (Xenical, Alli), an agent which blocks lipase with such significant GI consequences that only 1% of patients are still taking it at the end of a year. Is there no successful approach? Bariatric bypass surgery works well, producing lifelong major weight loss, improving physical activity, halving heart disease and halving cancer and often curing diabetes. The increased release of satiety hormones in mainly responsible and we propose to mimic their increase medically.

Changing Classification of Neurological Diseases

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The naming of disease does not stand still. At first merely providing a description of symptoms or the most obvious physical manifestations, nomenclature later adopted the style of the medical eponym or acronym. Famous figures were remembered through diseases named after them. Many of these designations attracted rival claims for priority in having provided the first account of that disease, but as clinical neurology became more sophisticated and laboratory methods were introduced, the descriptive phenotypes broadened and overlap between apparently different conditions came to be recognised. The beginnings of mechanism-based disease classifications began to emerge. That process has continued with the recognition of a genetic basis for many common disorders, the identification of their environmental triggers, and the characterisation of molecular pathways involved in the pathogenesis of these complex phenotypes. Generic principles such as aberrant protein folding, immune-based disorders and the failure of ion-channel activity have changed the classification of neurological disease. This is not just a matter of naming: the future of neurology may be less colourful in terms of hagiography but it will be more realisticand useful in terms of mechanism-based disease classification and therapeutics.

Neuromyelitis Optica

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The disease that Eugene Devic described in 1894 was largely forgotten as knowledge on the aetiology, pathogenesis and phenotype of more common demyelinating diseases flourished in the 20th century. Although cases were often misdiagnosed, the distinguishing features of neuromyelitis optica have been increasingly recognised and emphasised over the last 10 years. Some patients respond to plasma exchange; antibody and complement deposition are demonstrated in tissue samples; a serum immunoglobulin biomarker for the condition has been described; and aquaporin 4 identified as the target antigen. With improved recognition attention has been drawn to the fact that neuromyelitis optica has a geographical distribution that differs from that of typical multiple sclerosis. This has led to debate on the relationship between these two disorders, the true and the false distinguishing features, and the status of transitional cases. As a result, the phenotype and features of neuromyelitis optica have broadened. Now neuromyelitis optica is a disorder of astrocytes with complex secondary pathological effects, originating from autoimmunity against aquaporin 4, in which lesions usually but not exclusively involve the optic nerves and spinal cord, and with treatments directed at reducing antibody production sometimes altering the otherwise poor natural history.

Non Cirrhotic Portal Hypertension

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Portal hypertension is most commonly associated with cirrhosis of the liver. In this lecture we will briefly review the range of other conditions that can similarly lead to bleeding from oesophageal varices, ascites and even hepatic encephalopathy. Vascular conditions may interfere with the flow of blood into or its exit from the liver. We will discuss occlusion of the portal vein at extra- and intra-hepatic levels, sinusoids and hepatic vein. In addition hepatic problems may induce vascular changes in the pulmonary circulation which have a profound effect on gas exchange and right heart function.

Intrahepatic cholestasis

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Cholestasis may result from purely intrahepatic problems involving hepatocytic function, canalicular secretion, canalicular obstruction and ductular obstruction. Intrahepatic cholestasis may be caused by a variety of factors including inherited genetic mutations, metabolic, endocrine, toxic and pharmacological agents. We will review the symptoms and signs of cholestasis as well as approaches to its treatment.

Oral Diseases: Systemic disease diagnosis from oral signs

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Most diseases (approximately 95%) can be diagnosed by careful consideration of Oral symptoms and signs. These are commonly neglected in the diagnostic hierarchy. The presentation will allow delegates to develop structured methods for examination of the head and neck. It will also give a clinical overview to assist in increasing the diagnostic accuracy within the general medical environment.

Behcets Disease

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Behçet's Syndrome (BS) is an immune related disease which is markedly prevalent in areas surrounding the old silk trading routes in the Middle East, including Oman ,Qatar, and Central Asia. It is a multi-systemic disease characterised by recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions. BS is often associated with other major organ involvement, vasculitis and thrombotic activity. Uveitis is the main cause of blindness while the central nervous system involvement can lead to stroke or death especially in young people. BS is a debilitating chronic disease which severely affects patients' quality of life (Fortune, 2003, Mumcu et al., 2009b). Patients most frequently present with recurrent oral ulceration as the initial sign of the disease. Because of this observation, it is thought that the oral environment may play a very important role in its etiology and pathogenesis. To date the consensus is that the disease is triggered by a profound inflammatory response to an undefined environmental factor in a genetically susceptible host but as yet the etiology remains poorly understood (Lehner, 1999).Diagnosis is based on clinical criteria, dependent on the presence of recurrent oral ulcerations, plus any two of recurrent genital ulcerations, ocular or skin lesions, and a positive pathergy test . Diagnosis is difficult but once diagnosed treatment options lead to good quality of life. The presentation will discuss issues of specific clinical symptoms and signs associated with diagnostic pathways. And current treatment options.Whilst clinical activity is associated with considerable morbidity, specific indicators for onset of disease activity are not known. T cells, neutrophils and inflammatory cytokines and chemokines are all believed to play important roles .recent research associated with disease will be explored.

Individualisation of Cancer Care: Reality or Pipedream?

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Cancer is a complex disease which historically has been largely treated according to the assumed tissue of origin of the tumour. It

has always been known that cancers from a particular site may vary considerably in their histology and treatments sometimes take account of this. Recent research however has demonstrated the considerable molecular heterogeneity of tumours with apparently identical histology. Novel treatments are now being developed to target particular molecular or pathway defects and the necessity of individualisation of care is clear in this cases. What is less clear is how we should progress the stratified medicine agenda in tumours with clearly different molecular make-up but without such obvious molecular targets. We will discuss various aspects of individualisation of cancer care; success stories to date, areas of imminent progress, difficult areas where progress is possible, mechanisms to speed up the discovery phase for molecular therapies and how to create molecular tests which are accessible to non-specialist centres.

The BRCA1 and BRCA2 Genes in Ovarian Cancer: So much more than markers of hereditary risk

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Since the mid-1990s it has been clear that mutations in the BRCA1 and BRCA2 genes predispose female carriers to breast, ovarian and other cancers. Now we know that germline BRCA1/2 mutation carriers who develop ovarian cancer have a different disease course to non BRCA1/2 mutation carriers. They are more likely to: have a serous histology; respond to multiple lines of platinum-based chemotherapy; develop visceral metastases. Despite the propensity for visceral metastases their median survival is approximately twice that of comparable non-BRCA1/2 germline mutation carriers. The recognition of this discrete molecular entity has partly been driven by the development of a new class of anti-cancer agents known as poly (ADP-Ribose) polymerase (PARP) inhibitors. Early phase clinical trials have demonstrated exciting efficacy of these agents. As an extension of this, researchers have sought other ovarian cancer patients who have the 'BRCAness' phenotype without carrying a BRCA1/2 germline mutation (other mechanisms include somatic mutation, epigenetic inactivation or mutation of other pathway members). There is now preliminary evidence that these patients may also benefit from PARP inhibition. The hope is that being able to identify this molecular subtype will allow use of PARP inhibitors and improve the outcome for these ovarian cancer patients.

Lupus: A story of failure and success

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Despite the advances in recognition and treatment of lupus, pitfalls and obstacles persist in the management of this complex disease. Examples of 'failure' at the individual level include the development of strokes or M.I. in under-treated APS (Hughes Syndrome) patients, the treatment- resistance of some cases of severe lupus skin disease, the failure at present to protect against congenital heart block. At a more general level, there remains the problem of under-recognition and under treatment on the one hand, with, perversely, over-treatment and iatrogenic Cushings on the other. It is also apparent that lupus rivals diabetes in its risk of late atherosclerosic disease and that known risk factors such as high cholesterol and positive aPL are inadequately addressed. On the bonus side, the outcome of lupus pregnancy has been drastically improved, and the development of renal failure reduced. New drugs such as Mofetil and Rituximab are already extensively used and, at last, major pharmaceutical firms are keen on developing new agents for lupus Another major 'advance' has been the more conservative approach to steroid and cyclophosphamide treatment, and the wider use of milder agents such as hydroxychloroquine. International co-operation in lupus research is good, and developments in lupus are having an impact on many other diseases.Perhaps the single most important change in lupus has come from the recognition of the importance of APS. Many features such as stroke, migraine, atypical M.S., seizures and M.I., previously ascribed to 'vasculitis' and treated with steroids and cyclophosphamide, are recognised as more likely due to APS and treated more appropriately with anti-thrombotic agents.

Tuesday : A clinician's tale

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In 1983, a detailed clinical description of a new syndrome was published. This pro-thrombotic syndrome was initially called the anticardiolipin syndrome and subsequently the antiphospholipid syndrome (APS) or Hughes Syndrome. Almost uniquely, it results in arterial as well as venous thrombosis and is marked by the presence of circulating antiphospholipid antibodies. Clinical features are protean, ranging from peripheral deep vein thrombosis (DVT) to involvement of internal organs such as the liver, kidneys and adrenals. Likewise arterial thrombosis can result in life-threatening infarction of organs such as the heart. The nervous system is frequently affected, with migraine, memory loss, balance disorders, stroke and atypical multiple sclerosis being prominent. Other features include recurrent miscarriage, thrombocytopenia and livedo reticularis. More recent observations have included ischaemic bone fractures, renal and celiac artery stenosis and a possible tendency to accelerated atherosclerosis. The condition is seen in lupus patients, but, significantly, occurs without associated lupus ('primary' APS) – indeed increasing clinical recognition of Hughes Syndrome suggests that this condition will overtake lupus in prevalence. Treatment at present is by anticoagulation. The mechanisms for thrombosis are being worked out; it has been suggested that in some situations (e.g., in pregnancy loss), an inflammatory component as well as thrombosis may play a part.

Pathogenesis and Management of Osteoporosis

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Osteoporosis is a common disease characterised by reduced bone mineral density (BMD), and an increased risk of fragility fractures. It has been estimated that about 30% of women and 12% of men will suffer fractures related to the presence of osteoporosis at some point in life. Genetic factors play an important role in regulating susceptibility to osteoporosis and account for up to 80% of the variance in peak bone mass. However, many other factors such as diet, exercise, sex hormone deficiency, co-existing diseases and drug treatment such as corticosteroid therapy interact to modulate the risk of developing osteoporosis. Although low bone density is a major risk factor for the development of fractures, the majority of fractures occur in patients who do not have osteoporosis, as defined on the basis of low BMD, illustrating the importance of falls as a risk factor for the occurrence of fractures. The most useful tool for assessing patients at risk of osteoporosis is dual energy x-ray absorptiometry (DXA) and individuals with a BMD T-score of -2.5 or less at the spine or hip on DXA examination are considered to have osteoporosis. Measurements of BMD are important not only for diagnosis but also in targeting therapies since most of the pharmacological treatments for osteoporosis have undergone clinical trials in patients with osteoporosis as defined by DXA. Optimal management of osteoporosis requires a multidisciplinary approach. Lifestyle modifications such as increasing dietary calcium and vitamin D intake; taking regular exercise, stopping smoking and limiting alcohol intake to within recommended levels are beneficial in osteoporotic patients and those at risk of the disease. Drug treatments for osteoporosis can be divided into two broad groups depending on whether they inhibit osteoclast activity (antiresorptive drugs) or stimulate bone formation (anabolic drugs). The most widely used drugs in the treatment of osteoporosis are bisphosphonates which are antiresorptive. These agents typically reduced the risk of vertebral fractures by about 50% and non vertebral fractures by 25-30%. The most widely used anabolic drug is the 1-34 fragment of parathyroid hormone (Teriparatide) which stimulates new bone formation. This agent reduces the risk of vertebral factures by about 65% and non vertebral fractures by 50%. It is particularly effective in corticosteroid induced osteoporosis and seems to be superior to the bisphosphonate alendronic acid in this situation. Although the treatments currently available are effective, none are completely effective in preventing fractures emphasising the importance of combining drug treatment for osteoporosis with falls prevention to reduce the risk of fractures.

Vitamin D Metabolism, Osteomalacia and Rickets

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Osteomalacia is a bone disease characterised by reduced mineralisation of bone, which in most cases is due to vitamin D deficiency. When osteomalacia occurs in the growing skeleton it is known as rickets. Muslim women and elderly housebound individuals are at increased risk of osteomalacia, since vitamin D is mostly derived from exposure to sunlight. Osteomalacia and rickets occur because of deficiency of the active metabolite of vitamin D (1,25(OH)2D). The most common cause is deficiency of the precursor cholecalciferol which is synthesised in the skin from 7-dehydrocholesterol under the influence of UV light or obtained from the diet. Cholecalciferol is converted in the liver to 25(OH)D and then in the kidney to (1,25(OH)2D) which is biologically active. When vitamin deficiency occurs, intestinal calcium absorption is reduced, stimulating production of parathyroid hormone which stimulates bone resorption and promotes renal phosphate wasting resulting in defective mineralisation of bone. Osteomalacia and rickets may also occur in patients with renal failure, as the result of drug treatment (bisphosphonates, fluoride, aluminium); inherited defects in vitamin D metabolism (vitamin D resistant rickets); inherited defects in phosphate metabolism (hypophosphataemic rickets) and acquired defects in phosphate metabolism (tumour induced osteomalacia). Major advances have been made in understanding the pathophysiology of hypophosphataemic rickets over recent years leading to identification of the PHEX, DMP1, MEPE and FGF23 genes as key regulators of mineralisation and phosphate homeostasis. Osteomalacia and rickets due to vitamin D deficiency can be treated with vitamin D supplements whereas active vitamin D metabolites and/or phosphate supplements are required for hypophosphataemic rickets.