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Vascular Disorders Involving the Liver

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In the Budd Chiari syndrome hepatic venous outflow typically presents with ascites, sometimes accompanied by pain over the liver. Interventional radiology produces excellent results from treatment by hepatic vein angioplasty and transjugular intrahepatic portosystemic shunt (TIPS). Haematological investigations have a high yield revealing a prothrombotic condition such as Factor V Leidenn (circa 25%) and myeloproliferative disease. Hepatic veno-occlusive disease is typically due to an inflammatory and fibrotic reaction which occludes the hepatic sinusoids. Historically, it was associated with a variety of toxic injuries (e.g. bush tea disease), but now almost exclusively in the context of bone marrow transplantation. Typically portal vein thrombosis presented with bleeding varices, but increasingly it is recognized as a cause of cholestatic jaundice with choledocholithiasis from portal biliopathy. The hepatopulmonary syndrome is characterized by dilatation of pulmonary capillaries to such an extent that oxygen is unable to diffuse adequately to prevent hypoxemia. The diagnosis of portopulmonary hypertension requires a demonstration of increased pulmonary vascular resistance. Congential and hereditary vascular anomalies include persistent patency of the ductus venosus. Liver involvement by hereditary haemorrhagic telangiectasia may produce symptoms from high output cardiac failure, portal hypertension or biliary disease. Both benign and malignant primary vascular lesions also occur.

An Update on NASH (Non-Alcoholic Steatohepatitis)

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Fatty Liver is most commonly associated with obesity, Type II diabetes mellitus and hyperlipidemia. It is known that free fatty acids (FFA) are mobilized far more readily from visceral than subcutaneous adipocytes, and visceral fat also drains directly to the liver via the portal blood supply. Insulin resistance is a key feature in its causation, even in the non-diabetic and non-obese. Lipid peroxidation due to oxidatie stress may arise from induced and highly active polymorphic forms of CYP 2E1, peroxisomal β-oxidation of FFA or coexistent liver disease such as iron overload or viral hepatitis C infection. Splanchnic adipocytes have long been known to be several-fold more resistant to insulin than their peripheral counterparts. One of the new understandings to emerge is that these splanchnic fat storage cells constitute a major endocrine influence on the liver and that imbalance of their hormonal products, "adipokines" (adipocyte cytokines) influences hepatic fat deposition, insulin resistance and pro-

gression to NASH. The role of insulin resistance in promotion of NASH provided the rationale for treatment with metformin, rosiglitazone and pioglitazone. Stomach stapling (laparoscopic adjustable gastric binding) has been shown to be beneficial since weight loss was sustained and accompanied by complete resolution of the histological changes of NASH in a majority of patients.

Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

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Six healthy young male volunteers at a contract research organization were enrolled in the first phase 1 clinical trial of TGN1412, a novel supragonist anti-CD28 monoclonal antibody that directly stimulates T cells. Within 90 minutes after receiving a single intravenous dose of the drug, all six volunteers had a systemic inflammatory response characterized by a rapid induction of proinflammatory cytokines and accompanied by headache, myalgias, nausea, diarrhea, erythema, vasodilatation and hypotension. Within 12 to 16 hours after infusion, they became critically ill, with pulmonary infiltrates and lung injury, renal failure and disseminated intravascular coagulation. Sever and unexpected depletion of lymphocytes and monocytes occurred within 24 hours after infusion. All six patients were transferred to the care of the authors at an intensive care unit at a public hospital, where they received intensive cardiopulmonary support (including dialysis), high-dose methylprednisolone, and an anti-leukin-2 receptor antagonist antibody. Prolonged cardiovascular shock and acute respiratory distress syndrome developed in two patients, who required intensive organ support for 8 and 16 days. Despite evidence of the multiple cytokine-release syndrome, all patients survived. Documentation of the clinical course occurring over the 30 days after infusion offers insight into the systemic inflammatory response syndrome in the absence of contaminating pathogens, endotoxin, or underlying disease.

Infections in the Immumocompromised

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The number of people who are immunocompromised continues to rise, as more patients undergo invasive support with indwelling lines and tubes, radiotherapy, chemotherapy and immunotherapy, and with increased survival of those with malignancies and other inherently immunosuppressive conditions. This creates challenges in the diagnosis, treatment and prevention of a variety of infections, and offers fascinating insights into the pathophysiology and significance of different forms of immunosuppression. For example, CMV (cytomegalovirus) infection in patients with solid organ transplants typically causes pneumonitis and transplant rejection, while in those with advanced HIV the predominant syndromes are in the eye, central nervous system and gastrointestinal tract.Diagnostic techniques need critical revaluation in different groups of patients and settings, using as much rigour as that applied to multicentre therapeutic trials. Tests may be overly sensitive e.g. molecular diagnostics, or perform less well in immunocompromised groups e.g. tests based on host antibody response. Examples include the measurement of CMV viraemia levels in HIV, the new gamma-interferon release assays for past exposure to tuberculosis, and galactomannin assays for invasive aspergillosis. Supportive therapies such as the use of cell growth factors and the true benefit of protective isolation of patients with neutropenia need further evaluation. In the HIV setting, endpoints for starting primary and/or secondary prophylaxis have been determined (or discarded as unnecessary) for many opportunistic infections, but endpoints for stopping such prophylaxis are more difficult to define, especially in the presence of immune reconstitution syndromes. In some cases, e.g. oropharyngeal candidiasis in HIV, preemptive therapy is preferable to prophylaxis, and more such comparisons are needed for other opportunistic infections and hosts. The care of immunosuppressed patients requires coordinated multidisciplinary teams, which should critically evaluate the clinical approaches most appropriate for their own geographical setting.

Fever in returned travellers

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Febrile illnesses account for about 40% of acute hospital admissions for tropical illness in British referral units. A sensible working diagnosis can usually be formulated on the basis of a good history and examination and initial simple investigations. History should include details of exactly where the patient has been, what conditions they were living in, and the exact dates of arrival and departure. The quality of pre-travel advice and vaccinations, adherence to chemoprophylaxis against malaria, avoidance of insect bites and general behaviour abroad (including sexual history) are also important. Other localizing features of the illness should be sought, particularly rashes, chest signs, hepato-splenomegaly, lymphadenopathy etc. Maintain a high index of suspicion for underlying HIV especially in expatriates or immigrants from Africa but increasingly sex tourists from Thailand, India etc. (NB. oral candida, past or present herpes zoster are 2 common physical signs missed by general physicians). The most important illness to consider and to exclude is malaria (approximately 40% of cases), and the majority of the remainder will have cosmopolitan viral infections or imported infections such as arboviruses (dengue fever), enteric fever or viral hepatitis. Rarer causes will usually be evident from the history and examination, which presupposes a good knowledge of geographical medicine. The possibility of a viral haemorrhagic fever should always be considered. Late presentations of imported infection, including tuberculosis and vivax malaria, should always be borne in mind and recent immigrants or those going from the UK to visit family abroad are a particularly high risk group for such infections. Initial investigations should include adequate malaria films (supplemented by quick antigen detection tests in many labs) and blood count, repeated as necessary, blood, urine and faecal cultures, serum biochemistry, chest x-ray and other imaging e.g. liver ultrasound as indicated, and storing serum for virus serology. For patients in whom malaria is still suspected despite negative films, the combination of thrombocytopenia and hyperbilirubinaemia is supportive but not diagnostic of malaria. Eosinophilia suggests worm or fluke (e.g. schistosomiasis) infections, serology for which may be negative during early invasive stages.

Autoimmune potassium channelopathies

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Ion channels are fundamental to the function of every cell in the nervous system. Pioneering work on acetylcholine receptor antibodies in myasthenia gravis and calcium channel antibodies in the Lambert-Eaton myasthenic syndrome established, the concept of the channelopathy and laid down the principles for the study of both autoantibodies and ion channels in the pathogenesis of peripheral neurological disorders. The large extracellular domains shared by many types of ion channel, including potassium channels, seem to be favoured targets for humoral and cellular immune attack in the central as well as the peripheral nervous system. Autoimmunity - especially the autoantibody-mediated pathways - is now recognized as the crucial pathogenetic process in a diverse range of acquired conditions caused by channel dysfunction including peripheral nerve hyperexcitability, paraneopiastic and autonomic syndromes, and some forms of limbic encephalitis, epilepsy, and narcolepsy, as well as in diseases of neuromuscular transmission. Further advances in the characterization of ion channels and autoimmune mechanisms combined with improvements in the clinical understanding of the phenotypes of hereditary as well as acquired channelopathies have the potential to transform the diagnosis of these disorders, shed light on the pathogenesis of many common neurological diseases and open the gates for novel treatments based on modulation of channel and immune function.

The neurology, oncology and immunology of paraneoplastic syndromes

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Paraneoplastic neurological syndromes (PNS) occur in 1 - 2% of people with cancer. They are usually caused by autoimmune responses triggered by and directed against a tumour that cross-react with proteins expressed by neural tissue. Any part of the nervous system can be affected and patients often develop severe and permanent disability. Diagnosis can be difficult as two-thirds of patients develop their neurological problems up to 5 years before the tumour manifests. However, the discovery that many PNS are associated with serum autoantibodies against neural antigens expressed by the tumour-onconeural antibodies - has greatly improved our ability to identify neurological disorders as paraneoplastic. In addition, the finding of a particular onconeural antibody can help focus the search for an underlying tumour thus allowing earlier identification and treatment of the cancer. The first antibodies to be isolated, and their associations with clinical syndromes and tumours defined, were Hu, Yo, and Ri - the classic onconeural antibodies. Others characterized over the past 10 years, including CV2, Ma, amphiphysin and Tr, are proving to be equally useful tumour markers and have been crucial to the identification of novel pathogenic mechanisms for several PNS such as stiff person syndromes and some types of encephalitis.

The role of chronic inflammation in cancer

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Chronic inflammation has long been known to increase the risk of cancer in the affected tissues. This complication is particularly notable in the gastrointestinal tract. Helicobacter pylori (H. pylori -associated gastric cancer represents a classic example of this paradigm, and the unravelling of this model will enhance our understanding of many other cancers of unknown aetiology. Gastric cancer occurs in a milieu characterized by severe inflammation, hypochlorhydria and atrophy, all of which precede malignant transformation by decades. H. pylori infection is now recognized as the initiating factor for this cascade of pathophysiological abnormalities that culminates in cancer. There is ample epidemiological evidence to support this link, but increasingly the basic molecular pathways of this association are being uncovered. Inflammatory cells produce a wide range of mediators including pro-inflammatory cytokines, chemokines, reactive oxygen species, growth factors and eicosanoids. COX-2 may be a linchpin in orchestrating many of the mutagenic effects of these products and this is supported by the studies showing the chemo-preventative benefits of COX inhibitors. Cytokine gene polymorphisms undoubtedly contribute to individual risk of malignancy, but their importance lies in their contribution to the understanding of inflammation-mediated carcinogenesis. The fact that chronic inflammation impacts on crucial cellular processes, such as proliferation, adhesion, apoptosis, angiogenesis and transformation, highlights its pivotal role in the pathogenesis of gastrointestinal malignancy.

Helicobacter pylori: current concepts and management

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Helicobacter pylori infection affects half the world's population and is responsible for significant gastroduodenal diseases including peptic ulcers and gastric cancer. The European Helicobacter Study Group (EHSG) convened the third Maastricht Consensus conference in 2005, to update guidelines on the management of Helicobacter pylori. The guidelines cover indications for therapy, management strategies and potential for gastric cancer prevention. The eradication of H. pylori infection is recommended in patients with (i) gastro-duodenal pathologies such as peptic ulcer disease and low-grade gastric mucosa-associated lymphoid tissue lymphoma (MALT lymphoma), (ii) atrophic gastritis, (iii) first-degree relatives of gastric cancer patients, (iv) unexplained iron deficiency anaemia (v) chronic idiopathic thrombocytopenic purpura. Recurrent abdominal pain in children is an indication for a test and treat strategy if other causes are excluded. The eradication of H. pylori infection (i) does not cause gastro-oesophageal reflux disease (GORD) or exacerbate GORD, and (ii) may prevent peptic ulcer in patients who are naive non-steroidal anti inflammatory drugs (NSAIDs) users. H. pylori eradication is less effective than proton pump inhibitor treatment in preventing ulcer recurrence in long term NSAID users. In primary care a 'Test and

Treat' strategy using a non-invasive test is recommended in adult patients with persistent dyspepsia under the age of 45. The non-invasive tests that should be used for the diagnosis of H. pylori infection are the urea breath test, stool antigen tests and serological kits with a high accuracy. Triple therapy using a PPI (??) with amoxiciliin and clarithromycin or metronidazole given twice daily remains the recommended first choice therapy. Bismuth containing quadruple therapy, if available, is also a first choice treatment option. Rescue therapy should be based on antimicrobial susceptibility. Eradication of H. pylori infection has the potential to reduce the risk of gastric cancer development.

Therapeutic strategies in haematologic malignancies

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In the 1960s all haematologic malignancies were regarded as incurable and treatment was directed only at palliation. The suggestion that any form of leukemia might be curable was regarded as highly unlikely and indeed heretical. It became clear, however, in the 1970s that children with acute lymphoblastic leukemia (ALL) who achieved remission and then continued maintenance therapy might not relapse; this benefit was enhanced when neuroprophylaxis was added to the systemic regimen and a cure became a reality. In the 1980s, it began to be gradually accepted that younger patents with acute myeloid leukemia (AML) who received intensive chemotherapy or post-remission therapy followed by allogeneic stem cell transplantation (SCT) might similarly survive without relapse for many years. The more recent introduction of all-trans retinoic acid (ATRA) in conjunction with anthracyclines seems to be a way to cure AML-M3 (acute promyelocytic leukemia) without the need for SCT. While progress was made in treating and sometimes curing the acute leukemias, the chronic leukemias continued until recently to be regarded as incurable. For chronic myeloid leukemia (CML), however, the introduction of allogeneic SCT in chronic phase did indeed result in cures in eligible patients; in the last 7 years the possibility that selected patients may cured by administration of the tyrosine kinase inhibitor imatinib has become a reality. By contrast, relatively few patients with chronic lymphocytic (CLL) leukemia have been treated by SCT, but there is a real possibility that some of these may be cured. Monitoring of minimal residual disease (MRD) after chemotherapy or allogeneic SCT has become extremely important for assessing benefit, predicting clinical relapse and adjusting therapy when appropriate. The principal techniques are immunophenotyping and monitoring expression of leukemia-specific or leukemia-associated genes. For the present, CML and AML lend themselves most obviously to molecular monitoring, but it is likely that within a few years all haematologic malignancies will be followed routinely either by immunophenotypic or molecular studies for MRD. Lung cancer remains the biggest killing cancer in the world for men and is rapidly becoming the biggest killer for women. 80% of lung cancer are caused by smoking and smoking trends in young women are increasing. There are no good prognostic symptoms to detect the disease early and presentation is almost always too advanced for surgery, only 10% of patients with non-small cell lung cancer (NSCLC) go to resection.. Considerable efforts are being made to improve staging with the use of PET scanning and mediastinal assessment using transbronchial and transoesophagel ultrasound guided cytology and biopsy sampling. Advances in treatment have been poor in small cell lung cancer with very little new emerging in the last 15 years. In NSCLC, there is emerging a clear role for adjuvant chemotherapy following successful surgery. There is no role for neo-adjuvant chemotherapy or peri-operative radiotherapy. Chemotherapy in advanced NSCLC offers some advantages both in terms of median survival and quality of life. Targetted therapy is another potential treatment in some patients relapsing after initial chemotherapy. Screening for lung cancer is currently being assessed by CT and endobronchial surveillance in randomised controlled trials. These subjects will be discussed and summarised.

The Treatment of Obstructive Sleep Apnoea (OSA)

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Sleepy people are dangerous. In doctors, there is a 50% higher serious error rate to patients and a fivefold serious diagnostic error rate as well as a 2.3 hazard ratio of the risk of car crashing. 1-2% of Western middle aged men have OSA. OSA and snoring is the commenest outpatient respiratory referral to most UK hospitals, but around 90% remain undiagnosed. The main causes are obesity in 70%, retrognathia and oropharyngeal abnormalities in a small numbers. The condition is familial. Its association with road accidents is increased three to sixfold. OSA is. associated with increased systolic blood pressure, arterial wall stiffness and imparied glucose tolerance in diabetes. The condition is underprovided for, particularly in the UK, with 1.4 sleep laboratories per million of the population. Treatment with CPAP is extremely effective for severe OSA, but compliance is poor for mild or moderate severity individuals. Mandibular advancement splints are extremely effective provided the individual is motivated to wear the splint. Although common and dangerous, OSA has not yet achieved the level of importance in funding for treatment and multidisciplinary care in the UK.