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Horizons in Medicine is a series produced annually by the Royal College of Physicians. Volume 19 is based on their Advanced Medicine Conference held in 2007 and offers updates on a wide range of topics in clinical medicine. This 'review of reviews' covers developments described in a selection of chapters. The chapters summarised include: Contemporary management of acute myocardial infarction; Imported infectious disease emergencies; New therapies in the management of type 2 diabetes; Stress and adrenal insufficiency; Making sense of a 'funny thyroid function test'; Myeloproliferative disorders: management and molecular pathogenesis; Drug allergies; Osteoporosis; Rheumatoid arthritis; Understanding migraine from bench to bedside.

Introduction

Horizons in Medicine is a series produced annually by the Royal College of Physicians.¹ Volume 19 is based on their Advanced Medicine Conference held in 2007 and certainly constitutes a tour de force of major advances in clinical medicine. It provides essential updated information pertaining to a wide range of different medical specialties and interests, and in the process touches on a mix of cutting edge scientific and clinical developments. The topics covered in each of the diverse chapters should be of some interest to the relevant specialists, but are even more likely to excite doctors and others not working in that particular field. Moreover, changes in medical understanding and practice occur very rapidly, and there is an increasing overlap between disciplines. Thus, whether in advanced or less developed countries, the contents could well provide eye-openers for medical students, trainee physicians, general practitioners and consultants, whatever their specialty. In a book of just under 400 pages, the expert contributors cannot cover all advances in their respective fields comprehensively, however, areas as diverse as radiology and imaging, respiratory medicine, renal disease, rheumatology, and neurology get relatively generous airings. Finally, readers of this 'review of reviews' of practical and theoretical aspects of general medicine, should appreciate that in an article of this size it was only feasible to cover a selection of the chapters. No doubt these reflect the biases of this particular reviewer. Moreover, the topics referred to in each of the items captioned below correspond to chapters and are only summaries that are not referenced. Interested persons can consult *Horizons in Medicine 19* directly for appropriate details, including references.

Contemporary management of acute myocardial infarction

This chapter concentrates on acute ST elevation myocardial infarction (STEMI), a topic with practical implications for many doctors and a large proportion of the general public. Based on the widely accepted premise that early establishment of an 'open artery' improves short- and long-term outcomes and symptoms, the author sets out the pros and cons of thrombolysis versus percutaneous coronary intervention (PCI) including stenting. Key observations include that: (i) fibrinolysis within 12 hours of symptoms reduces the 35-day mortality from about 13 to 8-9%; (ii) the earlier the treatment the better the outcome, irrespective of age, gender, prior hypertension or diabetes; and (iii) intervening after 12 hours confers uncertain benefit. It is noted that the fibrin-specific agents, such as tissue-type plasminogen activator achieve patent vessels in about 70% of patients compared to about 35% following streptokinase administration, with a small corresponding benefit in terms of mortality (6.3 vs 7.3%), but a slight excess in strokes. Thus, fibrin-specific agents are increasingly favoured for thrombolytic reperfusion of STEMI. Several studies indicate inferior long-term benefits with the former, particularly if good flow rates are not achieved. For this reason, adjunctive anti-platelet agents (aspirin or clopidogrel) are suggested as one option to augment vessel patency and may well become standard practice. A further limitation of thrombolysis was late re-occlusion (ensuing within 3 months) in up to 30% of patients, especially in poorly perfused vessels. Recognition that early reperfusion (within 70 minutes of pain onset) is critical, has led to pre-hospital thrombolysis being

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全科醫療

Royal College of Physicians出版的*Horizons in Medicine*系列，每年都會按臨床醫學不同的領域發展更新資料。第19版正是根據2007年舉行的Advanced Medicine Conference而出版。本文綜述此書部分的課題，包括：急性心肌梗塞的現代診治觀念、外地傳入的急診傳染病、II型糖尿病的最新診治方法、壓力與腎上腺功能不全、了解「有趣的甲狀腺功能測試」、骨髓增生性疾病：診治與分子機制、藥物敏感、骨質疏鬆、風濕性關節炎，以及頭痛：從實驗室到臨床研究。

administered by paramedics. Several studies reported that this strategy conferred significantly improved pain resolution and superior outcomes. One trial revealed an improved trend for all cause mortality (9.7 vs 11.1%), and significantly improved cardiac mortality (8.3 vs 9.8%), and a meta-analysis of six trials also showed consistent benefits. Compared to PCI, the key advantages of thrombolysis were that it is, safe, easily administered and likely to be available in the facilities that patients are likely to use.

Several studies indicated that PCI (balloon angioplasty and stenting) on presentation (within 3 hours of onset) conferred a highly significant absolute benefit compared to 'optimal' thrombolysis, both in terms of short-term mortality and reinfarction, and less-frequent late re-occlusions. These studies had several critical shortcomings, however, including small patient numbers (wide confidence intervals) and comparisons only with hospital thrombolysis controls. Moreover, the logistics of providing highly trained intervention teams round-the-clock and within easy reach of the majority of patients is daunting. Options to overcome these challenges include: thrombolysis facilitated by PCI; more intervention centres; patients being transferred from or bypassing non-intervention centres. The latter strategies have been criticised as being expensive, largely untested or of no benefit, and liable to pose major logistic problems.

Thus early thrombolysis still appears to be the most feasible option for most patients, and, if it fails, early rescue PCI is a reasonable compromise. Even if thrombolysis is successful, pre-discharge follow-up PCI (if indicated) appears a sensible course of action.

Imported infectious disease emergencies

This is a useful and informative topic, not only for specialists in infectious disease, emergency medicine, and intensive care physicians, but also for other doctors and the public. The subject matter is particularly germane in this era of globalised business,

educational travel, non-governmental organisation activities, and exotic tourist destinations.

Key points are made through the use of case histories. Crucial information to glean from a travel history and some useful web addresses are also provided. The discussion of rabies lacks immediacy, however, there being no mention of risk conferred by licks from feral dogs, and post-exposure prophylaxis (a practical option) is given no greater importance than pre-exposure prophylaxis.

Update on HIV

HIV infection used to be relentlessly progressive and fatal in most cases. Yet within the last 25 years, and largely due to unparalleled global commitments, it can now be regarded as a chronic, stable condition (if appropriately treated). Several challenges remain, however. Principally due to an explosion in heterosexual transmission, about 30% of those afflicted are unaware of their condition, forming a large reservoir of occult infectors. This results in late diagnosis when the disease is less amenable to effective treatment. In many parts of the world, co-infection with rapidly progressive tuberculosis (TB) is becoming the leading cause of death and also, possibly, of AIDS-defining illnesses. HIV testing is therefore being routinely recommended in patients aged 15 to 64 years with newly diagnosed TB. Such TB is frequently atypical (extrapulmonary or disseminated). Sometimes (particularly in Africa), it is resistant to first- and many second-line anti-TB drugs and is therefore referred to as extensively drug-resistant TB (XDR-TB). Transmission of XDR-TB to the general population obviously poses a major problem, requiring new global initiatives.

Highly active anti-retroviral therapy (HAART) consists of treatment with various combinations of nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors. Each of these drugs has its own propensity to a variety of adverse reactions (eg lipodystrophy, heart disease). Moreover, as treatment regimens become safer, earlier initiation of HAART is increasingly recommended; the threshold for starting therapy has shifted from CD4 lymphocyte counts of <200 towards <350 mm³. Newer and, hopefully, safer and more effective classes of anti-HIV drugs (fusion inhibitors, integrase inhibitors, and others) are under development. The advantages of earlier treatment (preserved immunity, decreased risk of transmission, prolonged disease-free survival, fewer adverse events, reduced mortality) are believed to outweigh the disadvantages (various drug toxicities, development of drug resistance, exhaustion of options). Strategies for HIV prevention that appear to work are: education (abstinence, condoms); preventing peripartum mother-to-child infection using anti-retroviral drug combinations for both parties, elective caesarian

delivery, avoiding breastfeeding; male circumcision; and post-exposure prophylaxis (eg after needlestick injuries and perhaps after risky sexual exposure). Finally, a trend towards HIV testing being offered more readily is highlighted, along with the possibility of removing the current requirements for counselling and written informed consent.

Highly pathogenic avian influenza H5N1 in humans

This still rare form of influenza is covered in the context of influenza in general. The author rightly points out that preparing for a pandemic due to the virus becoming capable of transmission from human to human is fraught with uncertainty. The premise on which current recommendations are based and the potential waste of resources and effort are questioned, especially as the next influenza pandemic could just as easily entail entirely different virus serotypes.

New therapies in the management of type 2 diabetes

This discussion concentrates on newer glucose-lowering strategies and drugs developed in 2006 and 2007. As background, cannabinoids injected into the hypothalamus of animals stimulate feeding and weight gain, whilst knock-out or blockade of the corresponding receptors has converse effects. Several clinical trials have reported using rimonabant (a cannabinoid receptor blocker) in patients with type 2 diabetes. These confirmed that treated patients lose weight, and have lower levels of fasting glucose and HbA_{1c} (by 0.7%). This treatment also improved features of the metabolic syndrome, including dyslipidaemia and abdominal adiposity, but many patients developed nausea and/or mood disturbance (depression and anxiety), effects predictable from the opposing effects of cannabis on mood. These symptoms contributed to high discontinuation rates with this therapy. Another approach involves enhancement of so-called 'incretin' activity. This refers to the observation that the insulin level increments seen in response to a meal far exceed those produced by intravenous infusion of equivalent amounts of glucose. Thus, feeding appears to stimulate insulin secretion additional to that induced by increased circulating glucose concentrations alone, for which gut derived peptides (including GLP-1) appear responsible. Patients with type 2 diabetes produce less GLP-1, which normally helps to reduce postprandial glucose levels via increased insulin secretion and decreased glucagon release. This peptide is rapidly degraded by endothelial receptors, and must be given parenterally (not by mouth). Exenatide, a currently marketed GLP-1 mimetic (derived from lizards) is much more potent than the human variety, and much more resistant to degradation by the corresponding human enzyme

DPP-4. Evidently, daily exenatide injections and use of the DPP-4 inhibitors sitagliptin and vildagliptin are currently being investigated in humans as aids to the treatment of type 2 diabetes. Both options are reported to be relatively safe, in the short term at least. How these new forms of drug treatment (cannabinoid receptor blockers, GLP-1 mimetics, and DPP-4 inhibitors) will fit into overall drug treatment for type 2 diabetes remains to be seen.

Management of adrenal insufficiency in severe stress and surgery

Stress and adrenal insufficiency is discussed with respect to the role of glucocorticoids, not only in the presence of primary or secondary adrenal insufficiency but also in subjects not known to have defective adrenal function (but possibly exhibiting relative deficiency). The relevant stress could be physical (due to surgery or trauma), or emotional (social). Moreover, the acute adrenal insufficiency could manifest as a 'shut down' akin to hypovolaemic shock, or as a vasodilated hyperdynamic state resembling 'septic' shock, depending on preserved mineralocorticoid secretion and attempted prior fluid resuscitation. Notably, for critical illnesses in patients not previously known to have adrenal deficiency, some evidence favours the use of low-dose supplementary steroids, even though basing decisions to intervene on the results of short Synacthin tests, is debatable. The aptly named 'CORTICUS' trial,² that was published after Volume 19 of *Horizons in Medicine*, showed no benefits from steroids and therefore sheds further light on these issues.

Making sense of 'funny thyroid function tests'

This is a must-read for every general physician. Total thyroxine (T4) and total triiodothyronine (T3) levels can be misleadingly high in euthyroid patients, due to elevated levels of thyroid binding globulin, prealbumin and albumin (in pregnancy, after oestrogen intake, and in hepatic disorders). Thus, modern clinical laboratories should be able to measure free thyroxine (FT4) and free tri-iodothyronine (FT3) levels, in addition to offering a highly sensitive assay for thyroid stimulating hormone (TSH). The author points out that claims that patients have genuine hypothyroidism (warranting treatment), despite all three of the latter test results being within normal limits, are untenable. Exceptionally, T4 replacement therapy for hypothyroidism restores TSH to normal but with low-normal FT4 and FT3 levels; ideally such patients (having a reset feedback axis) need TSH levels to be high-normal. Divergent (funny) test results referred to include: (i) low TSH with normal FT4 and/or FT3 levels; (ii) vice versa; (iii) high TSH but normal FT4 and/or FT3 levels; or (iv) vice versa.

Numerous possible causes for each set of

these possibilities (including pituitary disorder, drug effects, and non-thyroid disease) are itemised and discussed.

The modern management of chronic myeloid leukaemia

This myeloproliferative disorder caused by a consistent chromosomal translocation (the Philadelphia chromosome), results in dysregulated tyrosine kinase activity and a characteristic leukaemic proliferation. Hitherto, the treatment of choice for all eligible patients has been allogenic stem-cell transplantation (the only curative treatment), so long as suitable matched donor cells were available. For all others, α -interferon-based treatment and simple cytoreduction were used. Now, however, the tyrosine kinase inhibitor (TKI) imatinib has become the preferred treatment over all other previously available alternatives. A pivotal phase III study showed markedly superior rates of complete haematological remission and cytogenetic response (95 and 94% vs 55 and 8%) and progression-free survival at 18 months (97 vs 92%) compared to older forms of treatment. Nevertheless, in a small minority of patients, imatinib therapy continues to pose problems, including failure to respond, loss of responsiveness, resistance (related to mutations and other factors), and disease acceleration and blast crisis. Options to overcome these problems include dose escalation, use of alternative newer TKIs, and reversion to older forms of chemotherapy.

Myeloproliferative disorders: management and molecular pathogenesis

This deals with polycythaemia vera (PV) and essential thrombocytosis (ET). In PV, according to the efficacy and safety of low-dose aspirin in polycythaemia vera (ECLAP) study, aspirin significantly reduced the risk of the combined primary endpoint (fatal and non-fatal stroke or myocardial infarction, pulmonary embolism, major venous thrombosis, or death from cardiovascular disease). Further analysis indicated that all PV groups showed benefit, independent of disease duration, cytoreduction therapy, and blood counts at trial entry. The fact that this trial did not entail a factorial design (aspirin versus placebo, and cytoreduction versus phlebotomy) is not made clear by the reviewer. Moreover, patients for whom aspirin was clearly indicated were excluded per protocol (n=742); yet out of the remainder that were randomised (n=518), why would up to 5% who had experienced a prior arterial thrombosis not have had an indication for aspirin? Regarding ET, a Medical Research Council trial of more than 800 patients (aged >60 years) with a prior thrombosis or platelet count $>1000 \times 10^9 / L$ showed clear benefits for those randomised to hydroxyurea plus aspirin rather

than anagrelide plus aspirin. In the former group the benefits extended to reduced rates of arterial thrombosis, major haemorrhage, myelofibrotic transformation (diagnosed by trephine biopsy), and treatment withdrawal; only venous thromboembolism was more common. Whether hydroxyurea protects against myelofibrotic transformation or anagrelide increases the risk remains unclear on the basis of this trial.

The discovery of a single acquired point mutation in the *JAK2* gene of haemopoietic stem cells in nearly all patients with PV and about half those with ET has important implications, since this genetic change appears to dysregulate tyrosine kinase activity and erythrocytosis. Moreover, *JAK2* mutation negative ET patients do not become positive for the mutation over time, indicating that there are two distinct forms of ET, one of which overlaps with PV. This finding raises the possibility of new approaches to the diagnosis, classification and treatment of these diseases.

Drug allergies

These are evidently the most important cause of type B adverse drug reactions (idiosyncratic, not predictable from pharmacological properties, and having no obvious relation to dosage), and are mainly immunological. Non-immunologic (ie chemical) type B reactions (eg dapsone-induced neuropathy, azathioprine-induced marrow suppression) are also noted, but only occur in very few susceptible individuals. Drug hypersensitivity linked to underlying immune mechanisms depends on drug-protein combinations (haptens) being recognised as 'non-self' by receptors on T-cells, and have been classified into four types.

Type I

Type I (immediate or late) hypersensitivity reactions involve immunoglobulin (Ig) E antibodies bound to mast cells and basophils. Corresponding antigens reaching and combining with relevant antibodies release histamine, other vasoactive mediators, and eosinophil and neutrophil chemotactic factors. Characteristic type I reactions are: asthma, urticaria (weals lasting only a few hours), angioedema, and anaphylaxis. These reactions occur within 15 minutes, or 6 to 24 hours after exposure to the relevant drug, so long as drug exposure continues for more than 7 days or there has been prior exposure. Such IgE mediated type I reactions are often due to antibiotics (especially penicillins), or anaesthetic agents, including muscle relaxants. There are identical reactions (eg to non-steroidal anti-inflammatory drugs [NSAIDs], opiates, and muscle relaxants) termed 'pseudoallergic' (or anaphylactoid), because no immune mechanisms

have been demonstrated and they seem to occur without a 7-day latent period. About 1 in 10 000 courses of penicillin are noted to result in reactions resembling anaphylaxis, about half of which may be pseudoallergic.

Type II

Type II reactions entail antigenic determinants on cell surfaces, which are targeted by circulating IgG or IgM; after binding these immunoglobulins activate the complement cascade, leading to cytotoxicity. Such toxicity includes: (i) drug-dependent pemphigus that regresses after discontinuation of treatment (eg due to penicillamine and captopril); and (ii) drug-triggered (true) pemphigus (eg due to penicillins, cephalosporins, and piroxicam) that then follows its normal natural history, even after drug withdrawal.

Type III

Type III reactions are caused by circulating immune complexes (antigen-IgE/IgM) depositing in vessel walls. About 8 to 10 days after drug exposure these give rise to a variably persistent vasculitis in skin and elsewhere (via complement cascade activation). A wide range of agents (antibiotics, NSAIDs, cytotoxics) may be responsible.

Type IV

Type IV (delayed, T-cell mediated) hypersensitivity takes around 48 hours to evolve and may be systemic, or topical (manifesting as indurated contact dermatitis or eczema). The latter reactions are commonly due to topical antibiotics, antiseptics, local anaesthetics and even corticosteroids. Among others, systemic reactions include: maculopapular eruptions, toxic erythemas, and the increasingly serious reactions termed erythema multiforme (EM), toxic epidermal necrolysis (TEN), and Stevens-Johnson syndrome (SJS). These rashes are often due to anticonvulsants, allopurinol, NSAIDs and antibiotics; the maculopapular eruptions can be diverse, and include urticarial weals that last several days. In contrast, urticaria due to type I reactions only lasts up to 12 hours. Characteristically, EM, TEN and SJS manifest 'target' lesions (that blister), particularly around muco-cutaneous junctions. The reactions seem to involve CD4 and CD8 T-lymphocyte mediated apoptosis, are associated with systemic features (fever, tachycardia, lymphadenopathy, renal and liver dysfunction, haematological abnormalities) and have a high mortality (30% or more). Regarding management, apart from withdrawal of the offending drug, corticosteroids and immunosuppressive agents are advocated. The role of early intravenous Ig remains controversial. If causality is not established, a meticulous chronology of the drug history can help. A variety of in-vitro and in-vivo tests are available

but are not consistently useful, and some are not applicable during or soon after an acute reaction.

Osteoporosis

Osteoporosis and its consequential fractures (mainly hip, wrist and vertebral) are increasingly important direct and indirect causes of morbidity, mortality and health care costs. In both developed and developing countries, osteoporosis is largely due to an increasingly aged population and sedentary lifestyles. Hypogonadism, malabsorption, endocrine disorders, immobility, chronic renal or liver failure, and treatment with certain drugs (glucocorticoids, aromatase inhibitors) predispose to this condition (defined by bone densitometry). Other major factors associated with corresponding fractures, some of which are preventable, include: old age, previous fragility fractures (especially hip), smoking, alcohol abuse, rheumatoid arthritis, low body mass index, and falls. Several pharmacological interventions have now been approved for osteoporosis prevention, though the optimal length of treatment is unclear and compliance is often unsatisfactory. Bisphosphonates (eg alendronate) are the first-line drugs, taken orally (and rarely intravenously). Precautions listed to avoid upper gastro-intestinal (oesophageal) symptoms include: taking them while standing or sitting up, with a full glass of water, and in the morning. In the very elderly, strontium ranelate is another first-line agent taken orally once a day. It increases spine and hip bone mineral density (by yet-to-be defined mechanisms); diarrhoea, nausea, headache and venous thromboembolism are infrequently associated adverse effects. Raloxifene (a selective oestrogen receptor modulator) taken orally once a day, is a second-line option; leg oedema and cramps, hot flushes and venous thromboembolism are its adverse effects, whereas the risk of breast cancer appears reduced. Parathormone (also a second-line agent) is very costly and usually reserved for patients intolerant of alternatives, or those with severe vertebral osteoporosis. Due to its perceived unfavourable risk-benefit balance, hormone replacement therapy is also deemed a second-line treatment, often restricted to the treatment of younger post-menopausal women at high risk of fracture, especially those with vasomotor symptoms. Calcium and vitamin D are not regarded as evidence-based treatments able to counter osteoporosis.

New biologics for rheumatoid arthritis

Rheumatoid arthritis is an important cause of disability and premature death (from cardiovascular causes, malignancy and infections), and its management has undergone a paradigm shift. Based on randomised clinical trials in thousands of patients, early diagnosis

and early intervention with disease-modifying anti-rheumatic drugs (DMARDs) usually involving methotrexate, have proved highly efficacious and become the norm. If necessary, biologically targeted agents are added to these regimens, and may arrest/minimise clinical and radiological disease progression. That the highly specific marker anti-cyclic citrullinated peptide antibody has a possible role in the pathogenesis of rheumatoid arthritis is discussed, though there is no mention of testing for it to augment early diagnosis of the disease. Biologically targeted constituents in DMARD regimens include tumour necrosis factor (TNF) blockers (infliximab, etanercept, adalimumab) given as courses of injections over several weeks. These appear to confer dramatic benefits in some patients, but may also manifest important toxicities (local reactions, long-term risk of TB, and possibly increased risk of malignancy and heart failure) that should be vigilantly anticipated. Rituximab (a monoclonal B-lymphocyte depleting antibody) infusions are also being used as a component of DMARD therapy. The latter combinations counteract antibody-mediated cytotoxicity, and often relieve symptoms, even in patients for whom anti-TNF treatments have failed. Apart from hypersensitivity reactions, other forms of clinical toxicity have not been reported to date.

Understanding migraine from bench to bedside

This is taken from the Croonian Lecture given by Peter Goadsby, and draws attention to aspects of this

common condition that many doctors are not aware of. Whilst migraine is commonly familial (hereditary), about 50% of such patients have the variety known as familial hemiplegic migraine that is linked to specific ion channel gene mutations on chromosome 19. These mutations may be related to the aura process that in animal models at least, reduces the threshold for 'cortical spreading depression'. Only in the latter families, attacks can be triggered by minor trauma, can result in coma, and can have associated cerebellar ataxia. Exactly how the migraine aura fits into the pathogenesis of the headache remains unclear. Most individuals with classical migraine headache have no aura, whereas others often have aura without headache. Aura suppression by ketamine does not abort the headache, and 'aura' can ensue during or after the headache, as well as with other headache types.

Based on animal and human studies, it is proposed that small myelinated and non-myelinated fibres of the trigeminal ganglion and upper cervical routes that innervate cerebral, pial, and dural vessels have a role in pain perception from these structures. Pain-producing substance, calcitonin, and plasma protein extravasation may also be involved. Whatever actually transpires during a migraine attack, episodic, central nervous sensory sensitisation seems to be a key feature, such that ordinarily non-noxious stimuli (sound, light, even odours, and sometimes head movements) become uncomfortable and associated with throbbing pain in the head. Merely being touched ipsilaterally and/or contralaterally can produce pain (allodynia).

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