Molecules, management and medical outcomes: an international review

The first major joint conference between the Royal College of Physicians of London and the American College of Physicians was held at the Royal College of Physicians on 7–8 June 1993. The large enthusiastic audience from the UK and the USA demonstrated the cordiality which exists between the two colleges. The objective of the conference was to further an exchange of ideas about the influence of science and technology upon current and future medical practice. Four major areas were chosen for review: diabetes, viral hepatitis, cerebrovascular disease and asthma. Presentations within each area were devoted first to scientific principles, secondly to aspects of clinical management, and finally to issues of clinical outcome.

Diabetes

Non-insulin dependent diabetes mellitus: genes versus environment

C N Hales (Professor of Clinical Biochemistry, Addenbrooke's Hospital, Cambridge) indicated the complexity of insulin deficiency and resistance in non-insulin dependent diabetes mellitus (NIDDM). Chronic hyperglycaemia reduces the insulin response to glucose in NIDDM and it is improved by normalisation of glucose. The high insulin concentrations originally noted in NIDDM have been due partly to high levels of proinsulin cross-reacting in the radioimmunoassay. In impaired glucose tolerance (IGT) currently used assays do not show high fasting insulin levels, but during a glucose tolerance test levels are subnormal at 30 minutes and high at two hours because of delayed secretion. Thirty per cent of subjects with IGT become overtly diabetic over ten years. Insulin deficiency might itself lead to insulin resistance by such mechanisms as alternative non-glucose fuels competing with glucose for oxidation, increased antagonistic hormones and decreased glucose transporters by downregulation, decreased synthesis and enzyme adaptation.

Genetic factors are evident in the development of NIDDM, which has a concordance rate of 60–100% in identical twins and occurs in 40% of adult Pima Indians. Genetic factors may influence the insulin response to glucose and the capacity of pancreatic beta cells to hypertrophy in response to insulin resistance. The thrifty genotype theory seemed to explain survival in adversity, with the development of obesity and NIDDM at times of plenty. However, Eskimos related to North American Indians have a low incidence of NIDDM, and a Finnish study showed a concordance rate amongst monozygotic twins of only 34%, suggesting that environmental factors may also play a major role in the development of NIDDM.

Factors operating in early life may be a strong determinant of subsequent risks to health; there is, for example, a link between coronary heart disease and low birth weight. In men with IGT aged 59–70 years there is also an inverse relationship between the two-hour blood glucose level after a 75-g glucose load and weight at birth or at one year. This has raised a thrifty phenotype, rather than genotype, hypothesis, suggesting that maternal malnutrition, together with other maternal and placental abnormalities, could lead to fetal malnutrition, particularly of amino acids which, in the fetus, are a powerful stimulus to insulin secretion which acts as a major growth factor. The decreased islet cell mass and function might thus result in decreased fetal growth. Beta cell mass grows until one year of age, so infant malnutrition might cause reduced adult beta cell function which is revealed later in life by obesity. A similar relationship prevails between syndrome X (the metabolic syndrome) and birth weight. The best buy for long-term health is to be large at one year, then stay thin; the worst is to be small at one year, and then get fat.

Rational clinical management

Dr J R Gavin (Howard Hughes Medical Institute, Bethesda, and President-Elect of the American Diabetes Association) said that no treatment strategy will work unless underpinned by education, monitoring and empowerment using a patient-centred model. This leads to greater personal awareness and self caring, less dependence and less expense. The implications of NIDDM should not be underestimated. Compared to the normal population, there is an increased incidence of stroke (2–6 times), blindness (25 times), renal failure (17 times), myocardial infarction (2–4 times), and peripheral amputation (5 times). Mortality from ischaemic heart disease and myocardial infarction is also increased in IGT. Therapy should be planned early to prevent micro- and macro-vascular complications, but in the USA about 50% of cases of NIDDM may be undiagnosed. Screening may be opportune for those at risk, for example with a strong family history and if there is central obesity.

When possible, NIDDM should be managed by lifestyle changes. In the diet, the emphasis is on reduction of saturated fats and sugar, increased fibre, and frequent small meals which reduce glycaemic excursions. Exercise increases fitness, decreases blood

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glucose and lipids, helps with weight loss and reduces hostility scores. To be successful, exercise needs to be prescribed in specific detail, ideally taken three times weekly and of appropriate type, duration, frequency and intensity. Treatable risk factors for macrovascular disease include hypertension, obesity and smoking. Hyperlipidaemia should be treated more aggressively than in the non-diabetic, but the exact roles of HMGCoA reductase inhibitors and antiplatelet drugs, such as low-dose aspirin, need to be clarified in NIDDM.

IGT should be treated by diet, weight loss and exercise, with attention to other risk factors such as hypertension and smoking.

When drug treatment is needed in NIDDM to control hyperglycaemia it should include sulphonylureas, with the doses adjusted according to blood testing and later stopped if possible. Metformin is not available in the USA. Primary sulphonylurea failure occurs in 10–15% of cases per year and secondary failure in 3–10%. The causes include non-compliance with diet and disease progression. Secondary sulphonylurea failure may be temporarily reversed by continuous subcutaneous insulin infusion, but it worsens again after several weeks. This suggests a possible role for intermittent insulin treatment in such cases. Insulin is usually given regardless of symptoms or body mass index, if fasting blood glucose on sulphonylureas exceeds 11 mmol/l. These patients need a mixture of short and intermediate insulins to simulate the normal pattern of insulin release including the rapid first phase. Combined use of sulphonylureas and insulin confers only modest benefit and there is a cost disadvantage.

Quality improvement through the monitoring of diabetes care

Dr P D Home (Freeman Hospital, Newcastle upon Tyne) described how quality of health care could be assessed by measuring resources and facilities, by audit of process and by determining biomedical outcomes. Outcomes are of particular relevance to patients, but may be difficult to assess meaningfully and depend on factors operating over a decade or more, including degrees of self care. Adverse outcomes tend to occur late and erratically in the course of the disease. Their incidence may be low; for example, none of the 150 patients with NIDDM in a large UK general practice needed to have an amputation.

The Diabcare group has developed datasets and computer technology to study and compare quality improvement at different centres. The database includes background information, details of catastrophic end-points, acute emergencies, diabetes-related symptoms, pregnancy outcomes, quality of life, health status, smoking, hospitalisation rates and sick days. Markers of adverse outcome include early complications, background retinopathy, glycated haemoglobin, raised cholesterol and triglycerides. Process measures include diabetes-related drug treatments and access to education and teaching. A feasibility study has data on over 3,000 patients in 25 centres. A 12-month audit study of routine diabetic care by the Royal College of Physicians and the British Diabetic Association should also be compatible with the Diabcare database.

As information on current practice becomes available, it can be used in a continuous development spiral where assessment is followed by change and reassessment. Quality targets might include progressive improvement in biochemical parameters (eg glycated haemoglobin or microalbumin excretion), a reduction in adverse outcomes (eg retinopathy, foot ulcers and limb amputation), the development of protocols and of changes in educational programmes. Specific quality of life assessments need to be developed for diabetes.

Viral hepatitis

Molecular biology of the hepatitis virus

H C Thomas (Professor of Medicine, St Mary's Hospital, London) described how liver damage after hepatitis B virus (HBV) infection coincides with the immune reaction, and that this response rather than the virus itself is the cause of the hepatitis. Elimination of infected cells depends upon both humoral and cellular immune responses. Viral proteins synthesised in the rough endoplasmic reticulum of the liver cells are partially degraded by proteases and then secreted by peptide transporter proteins into the endoplasmic reticulum where they associate with major histocompatibility complex Class 1 glycoproteins to be transported to the cell membrane. Recognition by cytotoxic T cells of the 11–27 amino acid sequence in the nucleocapsid antigen in HLA-A2 individuals then results in lysis of infected cells. Interestingly, in contrast to other viral-host systems, the humoral response to the core proteins in HBV infection may sometimes inhibit the killing of hepatocytes by cytotoxic T cells.

Spontaneous genetic variations occur in HBV which may have clinical significance. Envelope variants with single amino acid substitutions which impair binding of neutralising antibodies may allow viral infection or chronic hepatitis in subjects with vaccine-induced immunity. Stop-codon mutations in the precore region may result in fulminant hepatitis, severe chronic hepatitis or cirrhosis, despite positivity for surface antigen and envelope antibody.

Over 50% of patients infected with hepatitis C virus (HCV) will progress to chronic hepatitis and about 20% to cirrhosis and liver failure. Little is known about the immune control of this infection, but rapid mutations in envelope proteins E1 and E2 have implications for vaccine development.

Transplantation in acute and chronic hepatitis

Dr R Williams (Director, Institute of Liver Studies, King's College Hospital, London) reviewed the selection criteria used by different centres for liver transplantation for fulminant hepatic failure (FHF). These include age, cause of hepatic failure, the presence of coagulation disorders, encephalopathy or time from onset of jaundice to encephalopathy, biopsy data and liver volume. At his centre, 10% of patients with FHF have hepatitis A virus (HAV) or HBV infection and up to 30% are classified as non-A non-B (NANB). The aetiology in this group is in doubt, but cryptogenic HBV is a contender. HCV does not seem to be a cause of FHF in the UK and USA but cases are reported from Japan. Hepatitis E, an enterically transmitted virus, may lead to FHF, particularly in pregnant women in whom mortality may be up to 60%. Hepatitis F, shown on electron microscopy to be a togavirus-like particle, is found in a number of cases of FHF. However, a considerable number of cases of NANB FHF cannot be accounted for by any of these viruses.

Survival after liver transplantation for FHF is about 50% at one year, with sepsis accounting for over one third of failures. Post-transplant regimes using FK506 and prednisolone seem more effective than combinations of cyclosporin A, prednisolone and azathioprine. HAV may recur in the graft and cause a clinical hepatitis, but this is usually milder than the original disease. Recurrence of HBV is unusual, in contrast to transplantation for chronic HBV, and is also rare for NANB FHF, but it is seen in cases where toga-like particles have been identified in the original liver.

The indications for liver transplantation for chronic viral hepatitis are similar to those for end-stage liver disease from other causes. They include Child's Grade C cirrhosis with poor quality of life, intractable ascites or encephalopathy, uncontrolled variceal bleeding, and hepatocellular carcinoma less than 4 cm but not multifocal. Active replication in chronic HBV, indicated by HBeAg and HBV-DNA, is a relative contraindication to transplantation because of the high rate of recurrence leading to graft loss. Replication is unaffected by FK506 and cyclosporin, but it may be aggravated by prednisolone, which should be reduced and phased out as soon as possible after transplantation. Prophylactic immunoglobulin given during surgery and after transplantation prevents post-transplant hepatitis. HBeAg-positive cases can therefore be transplanted but hyperimmune immunoglobulin probably needs to be given lifelong. Co-infection with deltavirus reduces the frequency and severity of recurrent disease, and deltavirus may recur without HBV reactivation. Interferon and retransplantation are of little benefit if there is recurrent severe HBV hepatitis after transplantation. Fibrosing cholestatic hepatitis, a distinct histological pattern seen in grafts after recurrence of HBV, may result in rapid graft loss in 3–6 weeks. Analysis of the core region in these cases shows a mutation with a number of amino acid substitutions, but not the precore stop-codon described in chronic carriers with aggressive HBV and FHF. In transplantation for hepatocellular carcinoma associated with HBV infection, 75% of grafts fail by two years, over half being related to recurrent HBV.

Transplantation for HCV is nearly always followed by recurrence of HCV in the graft. Although the clinical picture is mild in over half the cases, it may progress to cirrhosis in 2–3 years. It is the second commonest cause of graft failure in a series in the USA. Experience with interferon is limited. It may decrease serum transaminase levels but the histology remains unchanged. Ribavirin, an oral antiviral which sometimes causes haemolysis, may normalise transaminase levels and lead to histological improvement.

In the UK, more than 500 transplants are performed annually, the cost per transplant is £35,000–50,000 and there is a waiting list of about 80 patients. In the USA, 3,000 liver transplants are performed annually in 60 centres, each at a cost of $90,000–140,000. Transplants for alcoholic liver disease and small hepatocellular carcinoma are in increasing demand but, without sufficient donors, the waiting list is lengthening. Because the chimpanzee liver is resistant to HBV, transplantation into humans has been tried in a small number of cases but without prolonged survival.

Results of therapy for chronic viral hepatitis

Professor W C Maddrey (Vice-President for Clinical Affairs, Southwestern Medical Center, Dallas) explained how, in the immune response to HBV infection, primed lymphocytes lock on to infected hepatocytes which express two cell surface markers. One is either core or 'e' antigen produced by replicating virus, the other is an HLA Class 1 protein produced by hepatocytes after stimulation by intracellular interferon. If the HLA Class 1 marker is inadequately expressed, as in chronic HBV infection, the hepatocyte is effectively shielded from immunological attack. Interferon therapy for chronic HBV infection is given on the assumption that it will stimulate production of the HLA Class 1 protein and allow infected cells to be recognised by primed lymphocytes. Recombinant interferon alpha-2b is usually given for 16 weeks at a daily dose of five million units. In one trial, there was loss of replicating virus in 36% of patients, with return of transaminase levels to normal and less inflammatory activity on liver biopsy. Factors predictive of a good response included female sex, Caucasian origin, heterosexuality, human immunodeficiency virus negativity, disease acquired in adult life and absence of delta infection. A good response to interferon was also predicted by low initial levels of HBV-DNA (below 100 pg/ml), indicating a partial immune response before treatment. Treatment-induced loss of HBeAg and HBV-DNA tends to be long-lasting with few relapses.

HCV is currently the most important hepatitis virus in the USA, Western Europe and Japan, whereas HBV is numerically more important in the rest of the world. Second-generation enzyme-linked immunoadsorbent assay (ELISA) testing shows that there is one main type in the USA, one in Japan and a variety of others elsewhere. About one-third of cases arise from blood transfusion or drug abuse; in the remainder the mode of transmission of the virus is unknown. After acute infection chronic hepatitis C develops in 50–70% by an unknown mechanism, often causing few or no symptoms but progressing slowly to cirrhosis in 10–20%. In the USA, it is the most important cause of cirrhosis after alcohol, and the commonest cause of hepatocellular carcinoma. Treatment for chronic HCV infection should be considered if serum transaminase levels are increased 2–3 fold, if there is histological evidence of active cirrhosis, bridging or multilobular necrosis or chronic active hepatitis. Interferon is the only effective treatment; 40–50% respond with a return of transaminase levels to normal, but many of them relapse after treatment is stopped. Interferon alpha-2b is given three times weekly for 24 weeks at a dose of three million units. In a multicentre study, there was a complete or partial response in 46% compared with only 8% in the control group. Most responses occurred within the first 12 weeks of therapy, with a fall in transaminase levels to normal and a reduction in inflammation on liver biopsy.

Interferon is a first step towards treatment of chronic HBV and HCV infections. Ribavarin, thymosin and other recently recognised agents which promote or block the actions of several cytokines are in the early phases of trials.

Cerebrovascular disease

New aspects of the biology and mechanisms of stroke

Professor J W Norris (Stroke Research Unit, University of Toronto) indicated that the incidence, severity and mortality of stroke have steadily declined, partly because of better management of hypertension and other vascular risk factors. Major advances in stroke treatment may become possible with the advent of detailed imaging techniques. Rapid changes in brain perfusion and metabolism can be studied using positron emission tomography and magnetic resonance spectroscopy (MRS). Combining magnetic resonance imaging and MRS allows differentiation of acute and chronic metabolic changes in cerebral infarction. Magnetic resonance angiography is still being developed but it can already detect in fine detail extracranial vascular stenoses and occlusions. It has demonstrated a surprising frequency of extracranial arterial lesions responsible for stroke, such as acute dissection, vasospasm and fibromuscular dysplasia. Single-photon emission computed tomography is a more practical way of viewing focal cerebral perfusion and produces a colour-coded perfusion map superimposed on computed tomographic (CT) imaging. It can detect reactive hyperaemia after cerebral embolism and the focal oligaemia of transient ischaemic attacks (TIAs) where CT imaging otherwise appears normal.

Transcranial Doppler (TCD) of the intracerebral circulation is now overtaking carotid duplex (extracranial Doppler plus B-mode 'real-time') imaging as a clinical tool. It can monitor vasospasm after subarachnoid haemorrhage, assess intracranial pressure after head injury, evaluate the extent of intracranial artery occlusion after stroke, and locate possible sources of silent emboli. Two-dimensional transthoracic echocardiography and transoesophageal echocardiography have also thrown light on proximal causes of stroke.

Taken together, these techniques suggest that carotid artery stenosis (CAS), which is considered to be the commonest cause of ischaemic stroke, may account for fewer cases than previously thought. Asymptomatic atrial fibrillation is a potent cause of cerebral embolism. It is possible that the majority of cryptogenic strokes have cardio-embolic stroke which can be revealed only by cardiac imaging and detailed monitoring of cardiac rhythm. Coagulation disorders, such as protein C and protein S deficiency, may be associated with stroke in the young. There is a twofold increase in intermittent right-to-left shunting through a patent foramen ovale in stroke patients under 45 years. Serial studies with TCD confirm acute occlusion of intracerebral arteries in most cases of ischaemic stroke, with varying degrees of collateral flow and recanalisation afterwards. Thrombolysis is a logical approach to such cases, but cytoprotection is also highly relevant.

Calcium ion release into damaged brain cells is highly toxic. Preventing this release, perhaps with drugs which close these calcium gates, might reduce focal cerebral damage.

In the discussion of this paper it was remarked that a theoretical window of opportunity for treatment of only 5–6 hours would put pressure on ambulance services. A European study of nimodipine in stroke was abandoned because of problems with acute hypotension and bradycardia. Two-thirds of patients with stroke also have ischaemic heart disease which is the commonest cause of death in stroke patients. Although haemodilution increases cerebral blood flow, it does not improve outcome. Professor Norris felt that all patients with atrial fibrillation (who have a risk of stroke 4–6 times higher than age-matched controls) should be anticoagulated with warfarin, or given aspirin if warfarin is contraindicated.

What can be done for the patient?

Professor J F Toole (Department of Neurology, Bowman Gray School of Medicine, North Carolina) said that stroke was the third leading cause of death and

disability in the USA. Carotid artery bruits and CAS are important markers of atherosclerosis, especially in coronary and peripheral vessels. Severity of CAS correlates with risk of cerebral infarction, but CAS can progress to occlusion without causing symptoms and some lesions even regress. The annual stroke rate amongst asymptomatic patients with cervical bruits is 1–1.5% without treatment but jumps to 3–5% when CAS is 70% or greater. The incidence of stroke unheralded by TIAs in patients with asymptomatic CAS is 1.7% within the first year and about 5% if the stenosis is greater than 75%.

The window of opportunity for restoring circulation may be as little as 90 minutes so there must be continuing emphasis on stroke prevention. Systolic hypertension and smoking are the most important risk factors; diabetes, hyperlipidaemia and obesity are all amenable to treatment with diet, and drugs if needed. The effect of aspirin in primary stroke prevention is unclear, but it may reduce emboli without slowing the progress of complicated plaques and thus increase unheralded infarction. Whilst endarterectomy for 70% CAS is helpful in patients with TIAS, 20% of whom will have evidence of infarction on CT scanning, it is of unproven value in asymptomatic patients. These issues should be resolved by the trials in progress.

In discussion of this paper, ticlopidine, a new antithrombotic drug, was suggested as an alternative if aspirin is contraindicated or ineffective, but it may cause aplastic anaemia.

How successful are we in stroke management?

C P Warlow (Professor of Medical Neurology, University of Edinburgh), in assessing the benefit of treatments in acute ischaemic stroke, indicated that a Dextran 40 trial showed some value but was too small to give certainty. An overview of all trials, including the use of fibrinolysis, heparin, calcium antagonists, steroids and haemodilution, suggested no benefit. Although several studies of the value of stroke units suggested that they conferred no benefit, a meta-analysis revealed a better outcome, with reduction in death rate, dependency and disability.

It may be difficult to agree upon reproducible measures of clinical outcome in patients who do not die of a stroke but they need to be sensitive, reliable and cheap. The Matthew stroke scale may be misleading; disability scores such as the Bartel activities of daily living do not give a picture either of sensory loss or of cognitive function. A simple system for assessing patients over a period of time describes the outcome as 'poor' if help is needed from another person to perform everyday activities, 'indifferent' if recovery is incomplete, and 'good' if it is complete.

Several treatments for acute ischaemic stroke are undergoing controlled trials but they need to be large to demonstrate a 15% reduction in mortality at two weeks. Aspirin may theoretically be of benefit but carries the risk of a small increase in haemorrhagic stroke. Heparin may also improve outcome but, although it reduces deep venous thrombosis after stroke, it is still not proven to reduce pulmonary emboli in this context, and it too may increase the risk of haemorrhagic stroke. The potential window of opportunity for thrombolysis still needs to be defined. Experience with cardiovascular disease suggests that it may be as long as 12–24 hours. The international stroke trial now in progress aims to look at the value of aspirin and heparin in acute stroke in 20,000 patients. A simple classification of stroke is used and data are collected centrally in Oxford at two weeks, at discharge or death, and again at six months.

In discussion it was suggested, first, that meta-analysis should be used to generate hypotheses rather than to prove a therapy and, secondly, that treatments for stroke might reduce the death rate and increase the numbers of severely disabled without restoring the less disabled to normal. It was also stated that there are several on-going Italian trials of aspirin and thrombolysis which have yet to be reported.

Asthma

Molecular biology of lung receptors

P J Barnes (Professor of Thoracic Medicine, Royal Brompton National Heart and Lung Institute, London) explained that several receptors relevant to lung disease have been cloned, thus allowing a better understanding of their function and regulation. They include beta-adrenergic, muscarinic, neuropeptide and inflammatory mediator receptors, and also cytokine, growth factor and steroid receptors.

The three subtypes of beta receptors have all been cloned. Their polypeptide chains, which cross the cell membrane seven times, are coupled to G proteins. The receptor binding site is a cleft inside the cell membrane which undergoes conformational change on binding. $Beta_2$ receptors predominate in the human lung and airways and are traditionally believed to relax smooth muscle via G_s protein and an increase in cyclic AMP. They also seem to act through direct coupling via G_s protein to a large conductance, calcium-activated potassium channel which is more important at low concentrations of beta agonists.

Desensitisation of beta receptors takes place by several mechanisms. Short-term exposure to beta agonists leads to phosphorylation of the receptor and G_s protein via several kinases. Long-term exposure results in reduced receptor synthesis and downregulation. Prolonged infusion of beta agonists lowers the amount of the cyclic AMP response element binding factor (CREB) which controls gene expression. Smooth muscle is less susceptible to downregulation than other cells in the airways because it may have a high rate of basal transcription. There is some

evidence that beta receptors in airway smooth muscle may be uncoupled in fatal asthma.

Glucocorticoids bind to an intracellular glucocorticoid receptor (GR), and the activated GR then translocates to the nucleus where it binds to glucocorticoid response elements (GRE) which regulate gene transcription. Steroids are the most effective therapy for asthma and act on numerous genes for enzymes, receptors, cytokines and regulatory proteins. They prevent the downregulation of beta receptors by beta agonists. High-dose inhaled beta agonists, on the other hand, may impair the anti-inflammatory effects of steroids in asthma by activating CREB which directly binds to activated GR. In such cases of severe asthma, when the high-dose beta agonists are gradually reduced, lung function improves on continuing steroid. Some patients with asthma are resistant to the anti-inflammatory effects of steroids, apparently because of a defect in binding of GR to GRE and reduced binding of GR to activator protein-1 (AP-1).

Cytokine surface receptors usually have only one transmembrane spanning segment. Cytokines produce their effect by regulating gene transcription, for example by activating the transcription factors AP-1 and NF_KB in human lung and inflammatory cells. AP-1 is a heterodimer of the proto-oncogene products *jun* and *fos,* activating some genes such as those for tumour necrosis factor (TNF), and repressing others. The transcription of cytokines, including interleukin (IL) -1, -3, -4, -5 and -8, TNF alpha and granulocyte macrophage-colony stimulating factor (GM-CSF), is inhibited by steroids which can also increase the rate of cytokine degradation. The activated GR may also interact directly with AP-1.

The mechanism of action of theophylline is still not clear; its effects are probably not due to phosphodiesterase inhibition.

Clinical implications for considering asthma as an inflammatory disease

S T Holgate (Medical Research Council Professor of Immunopharmacology, Southampton General Hospital) discussed genetic aspects which lead to atopy and in some cases to the development of asthma. Abnormal immune reactions may develop *in utero* and 20% of children of atopic mothers are already sensitised to house-dust mite at birth. In the first few months of life dendritic and other cells in the airways act as antigen-presenting cells; the level of allergen exposure in the first year is a major determinant of asthma by the age of 11 years in susceptible individuals. Important allergens are derived from house-dust mite, cat dander and fungi. Penetration of airway walls is enhanced by factors such as viral infections which provoke 80% of all asthma episodes lasting more than two days, rhinoviruses being most commonly involved. The response to house-dust mite allergen is rapid, with mucosal oedema occurring within 15 minutes as a result of mast cell degranulation. The late reaction lasts 4–24 hours or even 2–3 days, during which intense inflammation occurs with free fluid and submucosal haemorrhage.

T lymphocytes become activated in asthma and secrete cytokines such as IL-3, -4 and -5 and GM-CSF. This causes the expression of intercellular, vascular cell, and endothelial leukocyte adhesion molecules which recruit mast cells and eosinophils. These cells then mediate the inflammatory response and tissue damage in asthma, even when it is mild.

The old concept that freedom from symptoms implies freedom from disease is clearly untrue and the use of bronchodilators as the main treatment for asthma is unsatisfactory. Asthma is a disorder of the immune system associated with persistent inflammation, so all cases need anti-inflammatory treatment. This might include inhaled steroids which reduce mast cell and eosinophil numbers, sodium cromoglycate which reduces cytokine release from mast cells and neuropeptide release from nerve fibres, and nedocromil which reduces eosinophils in the airways.

Outcome of asthma management

Dr B Littenberg (Department of Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire) outlined stages of disease management amenable to assessment: plausibility, feasibility and clinical effects such as cure rates and mortality. Patient outcomes such as satisfaction, functional status and long-term mortality, and social outcomes such as resources allocation are not always sufficiently assessed. These aspects should all be examined in the evaluation of asthma therapies, including drugs, education, respiratory training and diagnostic tests. Dr Littenberg also described emergency room studies of methylprednisolone, beta agonists and aminophylline in acute asthma. Methylprednisolone, 125mg intravenously on presentation, reduced expected hospital admission rates by over 50%.

Correction: 'Hepatic lipocytes, TIMP-1 and liver fibrosis' (May/June, pages 200-28). The first sentence of the Abstract should read: 'In progressive liver fibrosis, the *rate* of extracellular collagen exceeds its rate of degradation'.