THERAPEUTICS SYMPOSIUM

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INTRODUCTION

The 41st St Andrew's Day Symposium on therapeutics was held 6–7 December 2001 and covered a wide range of current topics ranging from new drug development to surveillance systems for adverse drug reactions. The symposium was conducted over six sessions, and included the Al Hammadi Lecture, the Sir James Cameron Bequest Lecture, the Sydney Watson Smith Lecture and an interactive debate on the subject of postcode prescribing.

SESSION 1: DISEASES OF AGEING

CAN WE IMPROVE WHAT YOU SEE?

Prevalence of visual impairment and blindness increases with advancing age, from five per cent in those aged 74–9 years to 30% in those aged 90 and over. These figures may underestimate the true extent of the problem by as much as ten per cent, and over the past 15 years a 40% increase has occurred in the number of elderly patients registered with partial blindness. Reasons for this dramatic increase may include an increased level of patient awareness of new treatments and detection by screening programmes. Visual impairment risk is strongly correlated with gender and age; for example, there is a 17% year-on-year increase in risk. Visual loss is defined as 6/18 vision, and blindness as 6/60 vision; by contrast, 6/12 vision is used to determine fitness to drive. The commonest causes of visual loss in the elderly are age-related macular degeneration (AMD) and cataract, together accounting for over 70% of cases. Other causes include glaucoma and diabetic eye disease (Figure 1).

Age-related macular degeneration is a significant problem, and in 1990–1 it accounted for as many as 4·9% of all cases of blindness in those aged 65 years or over. The aetiology of AMD remains unclear and may be genetically determined in many cases. Smoking is certainly a major risk factor. The prevalence of AMD is increasing, consistent with trends towards an increasingly elderly population. Age-related macular degeneration is associated with characteristic defects in Bruch's membrane separating the choroid and retina. This allows overgrowth of choroidal blood vessels, which impregnate the retina and result in a number of abnormalities, including macular pigmentation, drusen and retinal atrophy.

Targeted argon laser treatment is one of the methods in current use for dealing with AMD. This acts by sclerosing newly proliferated vessels; it is, however, potentially destructive and its use is thus confined to peripheral macular lesions, avoiding areas close to the fovea where the risks of causing significant visual loss are greatest. Other novel treatment approaches have been applied to AMD, including surgical removal of the sub-macular part of Bruch's membrane, with translocation of healthy membrane from an adjacent retinal site, and photodynamic therapy with lower intensity laser, with such treatment being preceded by intravenous administration of photosensitising drugs.[1] About five to ten per cent of patients treated in the latter manner respond well; however, it is costly at around £800 per treatment, and multiple sessions are required. Therefore, at present, it is not routinely available to NHS patients. Its cost-effectiveness and potential role are currently being

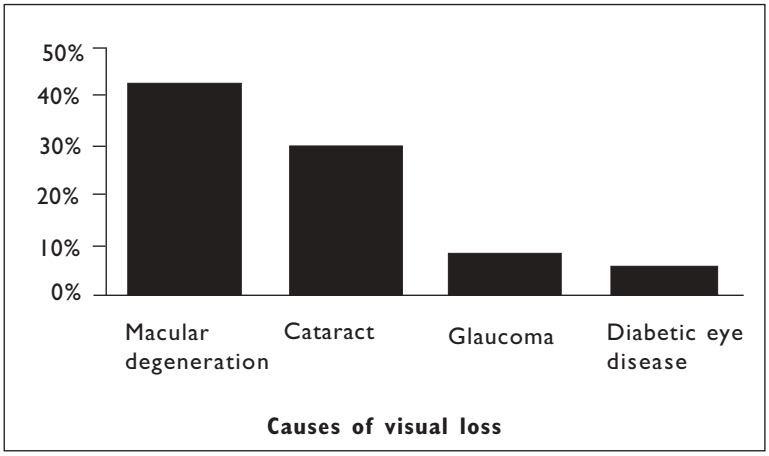

FIGURE 1
Common causes of visual loss in elderly patients.

considered by the National Institute for Clinical Excellence (NICE).

A further recent therapeutic approach has been to administer intra-ocular triamcinolone: this corticosteroid can be injected directly into the vitreous humor to cause pressure on, and flatten, the retina and macula. In addition, possibly because of its anti-inflammatory properties, it reduces macular oedema. However, clinical trials of triamcinolone have been disappointing and have generally failed to show any reduction in visual loss.

The role of multivitamin treatment in AMD has been examined in a recent National Institute for Health study, where the effects of a combined antioxidant preparation containing vitamins C and E and zinc were compared to placebo.[2] Interestingly, those patients with severe AMD or AMD-induced loss of vision in one eye experienced significant benefits over a six year follow-up period, with slower decline in visual acuity (defined by loss of three or more lines of Snellen chart vision).

Statins have been used in large trials to examine their role in prevention of cardiovascular disease, and subgroup analyses have also suggested that treatment may benefit patients with AMD. This is difficult to interpret given the comparatively small patient numbers involved, and because there is no obvious link between cardiovascular disease and AMD that could suggest a common aetiology. Clinical studies are presently underway to assess the effects of statin treatment in AMD.

Cataracts have been assigned to various descriptive categories, but essentially all result in glare and loss of vision. The optimal treatment is intra-ocular lens implantation, where the standard implant lens is refracted for distance; however, middle vision lenses and lenses that allow accommodation are also now available.[3] The latter work by changing shape in response to ciliary muscle action; however, while they can allow casual reading, most patients still prefer glasses for prolonged reading. Resources are probably insufficient to treat all cataract patients, and this has resulted in delayed access to ophthalmology services and inconsistent waiting times across the UK. Several nationwide initiatives are now in place that may address this and lead to improved service delivery and utilisation.

Glaucoma can present with insidious visual field loss and, at present, the optimal treatment is with eye drops to reduce intra-ocular pressure. Despite adequate pressure control, the loss of ocular neurons continues with progression of visual loss. Some advocate surgery to very effectively lower intra-ocular pressure, but because of a lack of supporting clinical evidence of effectiveness, it remains a less favoured option than eye drops. Various neuroprotective agents have now been proposed and are subject to ongoing clinical studies. Several issues need to be assessed, such as the need for early patient identification and assessment of the complications of long-term drug administration.

PROTECTING OLD BONES

Osteoporosis is defined by the World Health Organisation (WHO) as a 'disease characterised by low bone mass and micro-architectural destruction of bone tissue, leading to enhanced bone fragility and increased fracture risk'.[4] It is highly prevalent, and more than 80% of females have a bone mass density (BMD) less than two standard deviations below the population mean. It presents most commonly with fractures at the wrist (including Colles fractures), spinal column and hip, and the incidence increases exponentially with advancing age in both sexes, except for wrist fractures, which show a more gradual increase in males; this latter may be due to a greater likelihood of females to outstretch their arms and hands during falling. Treatment of fractures due to osteoporosis costs approximately £1,400 million annually in the UK.

Bone constantly undergoes repair and regeneration processes, and osteoporosis is thought to arise from an imbalance between the rate of bone formation and bone resorption. The major determinants of osteoporosis in later life are early peak BMD and the rate of inexorable bone loss that occurs beyond this into later life. The strongest risk factor for fracture is advanced age. Peak BMD is determined by a number of factors including genetic constitution, body weight, diet, exercise and sex hormone exposure. Currently, osteoporosis is diagnosed by bone densiometry X-ray scanning of those at high risk because of an identifiable risk factor (Table 1). Sensitivity and positive predictive power of this method are each approximately 36%, and specificity 90%; therefore, densiometry is not a good diagnostic tool in general, unselected populations. Quantitative ultrasonography of bone has been shown to predict future fracture risk almost as well as bone densiometry scanning. However, it is unclear whether the two tests identify the

TABLE 1

Identifiable risk factors for osteoporosis; note that advancing age and female sex are the most important, non-modifiable risk factors for osteoporotic fracture.

Risk factors for osteoporosis
• Early menopause
• Corticosteroid use
• Coexisting disease
• Family history
• Radiological osteopenia
• Smoking
• Low body weight
• Height loss

same patients, and this has important implications for treatment allocation on the basis of the technique. It is predominantly a research tool at the present time, until data supporting its more widespread clinical application become available.

Within the context of a finite treatment resource, greatest absolute benefits of osteoporosis treatment are gained in those at highest risk, predominantly those with osteoporosis who have had a previous fracture. For example, 30 patients with osteoporosis and previous fracture would require to be treated in order to prevent one new fracture over a ten year period, contrasting with 150 patients who have osteoporosis alone, or 270 patients with osteopenia (decreased bone density not amounting to osteoporosis). Treatment consists of adopting a number of lifestyle changes, including stopping smoking, taking regular exercise and ensuring adequate calcium intake.

Many of these steps have been shown to improve BMD, although objective evidence of reduced fracture risk is lacking. Drug treatments include hormone replacement therapy (HRT), calcium and vitamin D supplementation, bisphosphonates, calcitonin, roloxifene and intermittent parathyroid hormone (PTH) supplementation. Hormone replacement therapy, calcium and vitamin D supplementation, bisphosphonates, calcitonin and roloxifene are 'anti-resorptive' drugs, in that they impede bone breakdown. Bisphosphonates are phosphate analogues incorporated by active bone and taken up by osteoclasts, which are responsible for bone resorption. Bisphosphonates are toxic to osteoclasts and limit the extent of bone resorption, and serve as an excellent example of specifically targeted drug therapy. Exposure to excess PTH, as in secondary hyperparathyroidism, is often associated with osteomalacia and bone loss; paradoxically, intermittent PTH administration is very effective at enhancing the rate of new bone formation, hence reducing overall bone loss.

Clinical studies have demonstrated the effectiveness of all the above agents in enhancing BMD and reducing the rate of vertebral fracture. However, only HRT, intermittent PTH treatment and bisphosphonates have been shown to reduce the rate of non-vertebral fractures, suggesting that they may be preferred overall.

It was noted that the overall use of osteoporosis prophylaxis in patients receiving corticosteroids in a university teaching hospital was only 5·6%, which emphasises the under-utilisation of osteoporosis prophylaxis among high-risk patients.[5] In future, effective existing treatments should be targeted better and administered through an integrated service that also involves orthopaedic and A & E specialties. Novel therapeutic agents include the further development of anabolic agents that may restore bone density in the setting of established bone loss.

DEMENTIA

The presence of dementia is established using the mini mental state examination (MMSE) assessment, where diagnosis is critically dependent on the cutoff score used. The MMSE is a 30 point scale which forms a core component of the NICE recommendations for the management of dementia.[6] The prevalence of moderate to severe dementia is reportedly 4·6% among over 65 year olds, representing about 40,000 patients in Scotland (Table 2).

Diagnosis has to be pursued further, particularly to distinguish between Alzheimer's disease and 'vascular dementia'. This is aided by several diagnostic tests which are currently largely confined to research centres. Volumetric analysis of CT or MRI scanning has not been proven to be clinically useful. Dynamic and functional tests have also been used; for example, technetium-99m-labelled hexamethylpropyleneamine oxime (Tc-HMPAO) SPECT scanning gives a measure of blood distribution in the brain and is sensitive to both structural and functional influences. In multi-infarct or vascular dementia, a patchy uptake pattern is identified on the scan, whereas in Alzheimer's disease focal bi-temporal perfusion defects are present, and frontal lobe dementia is associated with localised perfusion loss. Other novel functional investigations include cholinergic receptor density mapping.

In general, however, there is poor correlation between clinical assessment and SPECT diagnosis in approximately 50% of cases. About two-thirds of cases of clinically suspected Alzheimer's disease are confirmed by SPECT scanning, while three-quarters of suspected vascular

TABLE 2
The prevalence of dementia of varying severity, assessed by the MMSE score and Cambridge Index.

	Score (MMSE/30)	Functional ability	Prevalence (%)
Normal	>25		
Minimal	22–25	Variable ability	23·5
Mild	18–21	Most require at least minimal assistance	4·7
Moderate	12–17	Unable to cope at home	
Severe	<12	Requiring long stay care	4·6

dementia cases are confirmed by scanning. The clinician is most likely to detect vascular dementia where a clear case of step-wise disease progression has occured, and where there are established atherosclerotic risk factors.

Studies over a six year period of untreated patients with dementia showed that about one-third of them deteriorated, while 10–20% improved, which has important implications for interpreting the active arm of placebo-controlled trials. The recent evaluation of anticholinesterase inhibitor treatments for dementia has been difficult, because the long-term consequences of treatment have been extrapolated from trials of 6–12 months' duration.[7] Donepezil, rivastigmine and galantamine have been evaluated in mild to moderate dementia, and they delay the progression of dementia in most patients, postponing the onset of severe impairment without affecting the eventual outcome. Typically, MMSE improvements of 1–2 points over placebo are seen during a six month treatment period. In Scotland, approximately 5,000 new cases of dementia are diagnosed each year; life expectancy varies between three to nine years from onset, and during this time annual treatment costs are currently around £1,200 per patient. The major potential for cost savings is delay in requirement for nursing home care, although the actual impact of this in practice remains to be seen. Treatment requires specialist centres for investigations and monitoring (e.g. 'memory clinics'), and these are likely to be associated with a further economic burden. At present, drugs are used in the context of complex care pathways involving multidisciplinary team input. Further research is required to compare the effectiveness of individual drugs and to establish whether their effects are cumulative over a prolonged period. Furthermore, it remains to be seen whether they have a role in the treatment of severe dementia, and whether they are equally efficacious in the treatment of Alzheimer's disease and vascular, or other forms of, dementia.

SESSION 2: DISEASES OF EXCESS

WHAT'S NEW IN TYPE 1 DIABETES?

Insulin first became commercially available in 1922 as Iletin®. However, 'insulin marked the end of one era in diabetes management, not the end of diabetes', to quote Elliot Joslin several years later. Type 1 diabetes is a field that exemplifies the explosion in therapeutic developments over the past 50 years, and advances over this period are typified by improvements in insulin delivery methods.

In order to more closely mimic pancreatic physiology, implantable pumps have been devised, for example the Medtronic Minimed pump, which allows continuous intraperitoneal insulin administration. Use of these devices is currently less than one per cent among Type 1 diabetic patients in the UK, whereas their use is increasing exponentially elsewhere; for example, they are used in 30% of patients in Germany. This delivery device has not yet been assessed in randomised controlled trials against regular subcutaneous injections. One observational study suggested that these pumps may allow better glucose control, because HbA_{1c} was 7·5% after one year compared to 8·3% on conventional therapy, and 50% fewer episodes of hypoglycaemia were observed.[8]

A further recent advance has been the development of short-acting insulin analogues, insulin lispro and insulin aspart,[9] which attain rapid onset and offset of action compared to conventional 'short acting' insulin and avoid the need to wait for 30 minutes before eating. Insulin glargine, on the other hand, may represent an important advance over current long acting insulins, acting as a basal insulin analogue.[10] It is highly soluble at pH 4, but precipitates at pH 7·4, and this physiochemical change is responsible for altering the subcutaneous kinetics to give a peakless profile and a much longer half life.

Inhaled insulin was first explored in 1925 and found to have 10–30% systemic absorption. In view of this, large doses would be required to achieve adequate systemic levels, and possible mitogenic pulmonary effects have been a cause for concern. A recent study has shown that the inhaled route permits a very similar kinetic profile to subcutaneously administered insulin and appeared to be well tolerated with no adverse effects on pulmonary function.[11] The effects on HbA_{1c} and occurrence of hypoglycaemia were similar, and inhalation insulin therapy is subject to ongoing investigation.

Another interesting prospect for the future management of Type1 diabetes is islet cell transplantation. In a study of seven patients, transplantation of 11,547 islet equivalents (high cellular load) was associated with 100% survival at one year.[12] Subjects demonstrated a consistent decrease in plasma glucose concentrations during the 12 month follow-up period. The benefits of this procedure are that patients may avoid the need for future insulin administration and avoid the occurrence of hypoglycaemia because transplanted islet cells are glucose-sensitive like innate cells. However, there are potential short- and long-term side-effects associated with this procedure. The risks and benefits of islet cell transplantation and a subsequent period of immunosuppression can only be compared effectively by randomised controlled trials in a number of patients over a longer follow-up period.

WHAT'S NEW IN TYPE 2 DIABETES?

In 1998, 100 million patients were reported to have Type 2 diabetes worldwide, and this is estimated to double by 2020. It is now recognised that Type 2 diabetes is a disease characterised by increased cardiovascular risk, including a 2·5-fold increased risk of acute myocardial

infarction. About 40% of patients will have hypertension, and ultimately 80% of patients will die from cardiovascular disease. The Framingham Study showed a continuum of risk associated with insulin resistance, manifesting as elevated serum glucose, and this held true for both diabetic and non-diabetic individuals (Figure 2). Microvascular disease risk is associated with fasting glucose concentrations, more specifically post-prandial glucose concentrations, and the UKPDS study showed a strong association between microvascular disease risk and HbA_{1c}. Macrovascular disease, and myocardial infarction in particular, is less closely linked to glucose control, although insulin resistance is a major risk factor. Sulphonylureas give a 25% reduction in microvascular complications, and a non-significant 16% reduction in macrovascular complications, and the UKPDS study suggested that metformin may be a more effective treatment, causing a 36% reduction in all cause mortality and a 39% reduction in myocardial infarction. The SIGN (Scottish Intercollegiate Guidelines Network) guidelines for management of diabetes indicate a target HbA_{1c} of 7·5%,[13] which poses a considerable challenge, because data collected from the Diabetes Audit and Research in Tayside Scotland (DARTS) registry indicates that the majority of patients in Scotland currently exceed this. New anti-hyperglycaemic treatments may help us to achieve these targets, including thiazolidinediones, which act on the peroxisome proliferator activated receptor-γ (PPAR-γ) pathway and increase insulin receptor sensitivity. This class of drugs, which includes rosiglitazone and pioglitazone, cause a modest reduction of HbA_{1c} concentration, typically one to two per cent when given in combination with metformin or sulphonylurea.[14] At present, they are not licensed for use as monotherapy or for use in combination with insulin alone. They appear to be best suited for use in combination with either a sulphonylurea or metformin in patients who are intolerant of a combination of the latter. They also agonise the PPAR-α moiety, the pharmacodynamic target of fibrate therapy, and the effects on lipid profile appear to be favourable. The cost of adding thiazolidinedione treatment in Type 2 diabetes is less than that of adding insulin. However, their impact on macrovascular outcomes has yet to be established, making cost-effectiveness comparisons difficult. The potential cardiovascular benefits associated with reversing, or partially reversing, the insulin resistance syndrome require further study.

TACKLING THE OBESITY EPIDEMIC – DO DRUGS HAVE A ROLE?

The word obesity is derived from the Latin preposition *ob*, meaning 'on account of', and the verb *esito*, 'to keep eating'. It is generally perceived that drugs are less important in obesity than in other medical conditions, perhaps because it is viewed as a self-inflicted, and possibly self-limiting, condition. Obesity is defined by the WHO as a body mass index (BMI) >30 kg/m^2 (Table 3), and in the UK average BMI is increasing in both males and females.

Obesity is a polygenic disorder, where environmental factors account for around 75% of predisposition and genetic factors for the remainder; more than 240 candidate genes have been implicated in the pathogenesis of obesity. It is a major risk factor for cardiovascular disease, and predisposes to increased morbidity across several organ systems. Beyond the top 20th BMI percentile patients are likely to suffer excess tiredness, breathlessness and back pain by the age of 40 and increased risks of osteoarthritis and ischaemic heart disease by the age of 60. In terms of financial costs, obesity is a major drain on health care resources; for example, hypertension due to obesity costs an estimated £1,816 million annually in the UK. By contrast, provision of anti-obesity treatment to all patients with BMI >30 kg/m^2 would cost an estimated £19 million annually.

Many anti-obesity agents have been found to be ineffective, or have been withdrawn due to safety concerns. The fact that a wide variety of different drugs can promote weight gain, for example anti-epileptic and anti-diabetic agents, emphasises the complex aetiology of obesity and

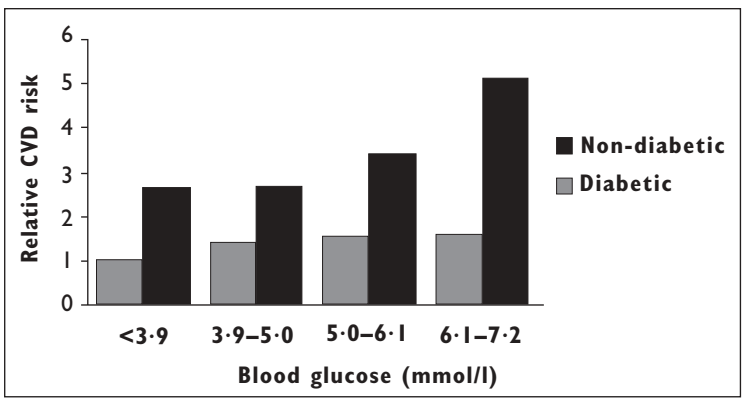

FIGURE 2

Cardiovascular mortality, relative to a non-diabetic with glucose <3·9 mmol/l, rises with increasing fasting blood glucose concentration, in diabetics and non-diabetics.

TABLE 3
Obesity, as defined by the WHO in 1995, is where BMI exceeds 30 kg/m².

BMI (kg/m²)	Definition of weight status
>30	Obese
25–30	Overweight
18·5–25	Normal
<18·5	Underweight

underlines the importance of multiple potential mechanisms for novel anti-obesity drugs. In any weight loss programme there will be an early weight loss phase over weeks or months, and a subsequent weight maintenance phase over years, or the span of a patient's life. Body weight, or BMI, provide short-term markers of successful intervention; however, the secondary goal of reducing complications may be more difficult to assess. Typically, maintained weight loss of 5–10 kg is associated with >20% reduction in overall mortality rate.[15]

Two of the most promising therapeutic adjuncts in obesity management are sibutramine and orlistat, both of which have striking differences in their modes of action. Sibutramine, originally developed as an antidepressant agent, inhibits the central neuronal re-uptake of noradrenaline and serotonin. It increases satiety and reduces appetite to the order of about 300 kcal/day, which would amount to 27,900 kcal over three months – approximately 4 kg of weight loss. Side-effects include tachycardia, palpitations and hypertension, and it is contraindicated in patients with a history of established cardiovascular disease or uncontrolled hypertension. Heart rate and blood pressure require close monitoring, particularly during the first few weeks after commencing treatment, and patients must have demonstrated >2 kg weight loss over four weeks before treatment is commenced. The maximal treatment period is one year, and it should be discontinued if weight loss stabilises at less than five per cent of initial body weight, or there is a regain of 3 kg or more after commencing treatment.

Orlistat, a pancreatic lipase inhibitor, prevents breakdown of triglycerides to free fatty acids and reduces absorption of dietary fat by approximately 30%. Some of the weight loss in patients taking orlistat may result from subjects consciously reducing their fat intake to avoid steatorrhoea. Depending on dietary fat content, orlistat may reduce calorific absorption by up to 840 kcal/day, and studies have shown that it can reduce body weight by 7·9%, compared to 4·5% for placebo. Patients must demonstrate >2·5 kg weight loss over four weeks before treatment, and it should be used in conjunction with a mildly hypocaloric diet. It is licensed for up to two years of use and, on stopping treatment, there may be reversal of weight loss.

Existing drug therapy can offer up to 10–12% weight loss in responders, for the duration of treatment, up to two years. At present, these agents are licensed for weight loss rather than cardiovascular disease management, although treatment has favourable effects on major cardiovascular risk factors. Both sibutramine and orlistat are adjunctive treatments, and both stop working when discontinued. The Royal College of Physicians of London and SIGN have both produced ethical guidelines on the optimal management of obesity which address the role of drug therapy.[16, 17]

While the role of the secondary care specialist is very important, it is recognised that obesity is predominantly a primary care problem. Devolving responsibility for these patients to specialist physicians only may be dangerous because of the risks of inadvertently enhancing the profile of private clinics which may not adhere to high standards of practice in some circumstances.

SESSION 3: TREATMENT FAILURES

INTELLIGENT MONITORING OF COMPLIANCE (The Al Hammadi Lecture)

For centuries, the main focus of clinical study has been observation-based intervention, spanning from an era when medicine and surgery were integrated specialties. The foundation of medicinal chemistry caused a revolution in our approach to disease management from the time of the discovery of aspirin, which was the first purposeful medicinal product. The use of pharmaceutical preparations is now a leading aspect of intervention in modern health care. The level of the drug's action is proportional to the dosage of response and inversely related to the time interval between doses. Nonetheless, a basic premise remains, namely that 'the drugs won't work in patients who don't take them'. They may work partially in patients who omit many doses. However, so-called 'drug holidays' can be hazardous for several reasons (Table 4).

The medicinal power of drugs has increased substantially, with their direct impact widening the gap between use and non-use; drug response is also increasingly subjected to diagnostic interpretation in stepped-care management systems.[18] Thus, compliance has become an increasingly important issue in both interpreting clinical trial data and monitoring treatment effectiveness in practice. Compliance is defined as the extent to which the actual dosing history conforms to the prescribed drug regimen and depends on both the expected treatment outcome and human behaviour. For example, conception rates reported for the use of the combined oral contraceptive pill are 0·1% for 'perfect' use and 5·0% in typical use, while rates for implanted progesterone are 0·05% and 0·05% respectively. Thus, even when 'perfect' compliance is reported, effectiveness can be substantially improved

TABLE 4
Adverse consequences of 'drug holidays', where drugs are omitted frequently, or infrequently, from an intended regimen.

Complications of 'drug holidays'	
Ineffective (partial or no response)	
Rebound effects	e.g. beta blockers, alpha blockers
Recurrent first dose effects	e.g. Vasodilators
Emergence of drug resistance	e.g. Anti-retrovirals, anti-tuberculous drugs

by using a method of drug delivery that is not patient-dependent. 'Drug holidays' have been linked to emergence of drug-resistant HIV, indicating that poor compliance is important, even in diseases usually perceived by patients as very serious.

Development of electronic monitoring devices in the 1980s revealed gross over-estimates of compliance by non-electronic methods which included histories, patient diaries, returned tablet counts and measurement of drug levels.[19] One of the first reports of such an electronic monitoring device was a study of pilocarpine eyedrops which showed that compliance was as low as 25%. Compliance appears to be mostly a patient attribute and is largely independent of drug, nature of illness, prognosis or symptoms. In most cases 'the rule of sixes' can be applied to compliance in unselected medical patients (Figure 3). It is important in cases of treatment failure that non-responders are distinguished from non-compliers; this is especially important where treatment is likely to be escalated. In hypertensive patients Brunner and Burnier found that 53% of patients with drug-refractory hypertension were clinically unrecognised non-compliers.[20] All had been escalated to triple therapy and some had troublesome hypotension when they started complying with their prescribed drug regimen. Electronic monitoring removes uncertainty about compliance by showing when dose omissions occur and whether steps taken to improve compliance are working. So-called measurement guided medication management (MGMM) can achieve satisfactory compliance in around three-quarters of previously poor- or non-compliers.

'Pharmionics' may be a useful term to describe a new specialty arising from the need to understand patterns of prescription drug usage, and the clinical consequence thereof. Pharmionics should be based on reliable measurements of exposure-dependent drug effects, targeted interventions to achieve adequate exposure and validation that intervention is effective. This has major implications for the design and interpretation of clinical trials, where compliance is rarely assessed adequately,

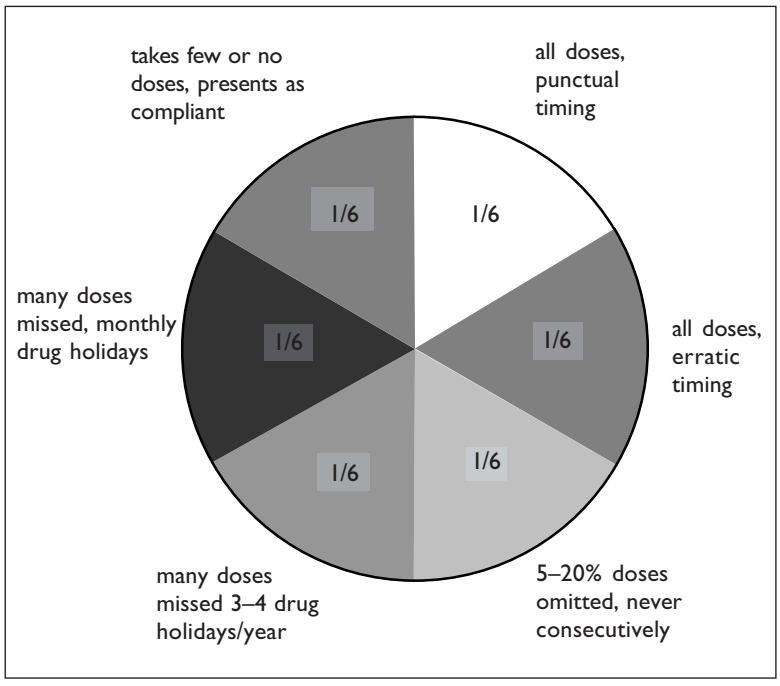

FIGURE 3
The 'rule of sixes' for patterns of compliance among medically unselected patients.

and all-patient averaging is becoming increasingly questionable. An increasing number of more powerful new drugs are coming to the marketplace, and little data are available on drug response in compliant patients or on the effects of drug holidays in non-compliant patients. Caution is required in the interpretation of trial data lacking reliable assessment of compliance.

PHARMACOVIGILANCE: PICKING UP FAINT SIGNALS (Sir James Cameron Bequest Lecture)

One of the earliest systems for reporting adverse drug reactions was the Hyderabad Chloroform Commission, privately funded by Nazim (VI) Hyderabad following a series of chloroform-related hazards. Chloroform was first introduced in 1847, and the first death reported in January 1848 in a 15-year-old girl from County Durham. However, the drug remained in use until 1906 when it was eventually withdrawn. The Hyderabad Chloroform Commission was the first example of a post-marketing surveillance system, and it highlighted the need for legislation to ensure that drugs were as safe and efficacious as possible. Such a system may be useful in identifying adverse reactions and estimating risk-benefit.[21]

The antibiotic sulfanilamide dissolved well in diethylene glycol, which was a constituent of the drug excipient. In 1938, the drug caused 107 deaths in the US, 34 of whom were children, and all deaths occurred within one week of the commencement of treatment. Deaths were due to diethylene glycol toxicity and emphasised the importance of considering all of the constituent ingredients of marketed drugs, which should all be safe and efficacious. The 1938 US Federal Pure Food and Drug Act Amendment was created to ensure proper labelling and that all promotional claims should have supportive evidence. Despite awareness of the potential hazards of diethylene glycol in drug manufacture, it has accounted for a further seven childhood deaths in 1937, 14 deaths in 1986, 47 childhood deaths in 1990, 51 deaths in 1995 and 88 childhood deaths in 1998. Clearly, despite apparent advances in the methods of detecting such adverse reactions, lessons from history are not always being learned.

Distavel®, thalidomide, was an anti-emetic available in 1956, and in 1959 it was marketed as a treatment for morning sickness in pregnant women based on three years of clinical use. Phocomelia in babies was very rare between 1959–61; however, the number of cases increased dramatically towards the end of this period. By the time an association with thalidomide was made in 1961, and the drug withdrawn, over 4,000 patients had been exposed. Subsequently there were legislative amendments made to the US Federal Pure Food and Drug Act, and the 1968 UK Medicines Act, which demanded that safety and efficacy data be submitted before drug licensing was created. Surveillance systems were identified as essential in order to detect adverse drug reactions and thus estimate risk and benefit accurately.

A number of post-marketing reporting systems are currently in place in the UK.[22] These include case control studies, cohort studies and spontaneous reporting systems (including the Yellow Card Scheme, which is accessible to all prescribers). Currently there is gross under-reporting at less than ten per cent of all adverse events and two to four per cent of non-serious reactions. Several factors appear to influence reporting behaviour (Table 5).[23] A further limitation of the Yellow Card Scheme is that reactions are linked to the suspect drug through association rather than causation. Despite this, a number of important adverse drug reactions have been highlighted in this way, and recent examples include the links between terodoline and arrhythmia in 1991 and paroxetine and acute dystonia in 1993. Prescription event monitoring by the Green Card Scheme gives a clearer measure of absolute numbers of adverse events per absolute number of prescriptions issued. However, this is only available in a few countries and for a limited number of drugs and, therefore, the study cohort is smaller, and the drug indication is not recorded. Record-linkage systems such as the Medicines Monitoring Unit (MEMO) in Dundee link prescriptions with diagnosis and procedure codes. Other forms of record-linkage systems include links to GP databases and the General Practice Research Database (GPRD), which collates adverse events from specific drugs from over 400 practices and three million patients.

One of the more positive aspects arising from pharmacovigilance has been the shorter time taken to withdraw medications from the market after adverse event detection. For example, the recent withdrawal of troglitazone occurred within six weeks of its inital marketing because of hepatotoxicity. There is no room for complacency, however, and pharmacovigilance should be continued for the lifetime of any drug, i.e. 'we must think the worst in order to achieve the best'. To encourage greater reporting of adverse drug reactions, several regional monitoring centres have been formed which will allow better follow-up of drug safety issues and be

TABLE 5

Factors associated with poor reporting by GPs using the Yellow Card Scheme.

Factors influencing spontaneous reporting of adverse drug reactions via the Yellow Card Scheme among GPs in Wales.
• less likely to be UK/Irish graduate
• less likely to have MRCGP/FRCGP
• less likely to be GP trainers
• less likely to have reporting partners
• more likely to be in small practices

responsible for providing local education and training. The profile of pharmacovigilance programmes should be raised at both undergraduate and postgraduate levels, and closer collaboration between clinical pharmacologists and pharmacists has to be encouraged to make such systems more effective.

SESSION 4: NOVEL THERAPEUTIC STRATEGIES

INFLAMMATION AND PAIN IN ARTHRITIS – NEW CONCEPTS, NEW TREATMENTS

In models of inflammation, highly selective molecules successfully reduce 'adjuvant disease', but in clinical practice the situation is much more complex, reflecting the unpredictable nature of the effects and side-effects that might occur. Rheumatoid arthritis affects joints in a symmetrical fashion, and uncovering the pathological basis for this clinical observation is not only academically fascinating but could also give new insights that may lead to novel therapies. There is evidence of a neurogenic basis because patients with established rheumatoid arthritis show improvement in the opposite side of the body after a stroke. Several experiments show that the body can produce topographical mirror-image responses; for example, when a murine cutaneous nerve is sectioned the corresponding contralateral nerve begins to sprout. Indeed, when joint inflammation is induced experimentally, the contralateral joint shows a similar response, and this can be inhibited by agents that modify the nervous system.

The duration of symptoms is used in clinical practice as an indicator of disease activity and to monitor treatment effects. Some patients who have undergone the amputation of a limb continue to feel stiffness in the phantom limb, especially in the foot. The duration of phantom symptoms reflects disease activity elsewhere and is responsive to agents such as morphine or non-steroidal anti-inflammatory drugs over a similar time course. Similar findings have been reported in amputees with symptoms of painful spasms in their phantom limbs.[24] Patients instructed to place their normal limb into a box containing a mirror were given sight of their existing arm and its mirror image, creating the illusion that the amputated arm had returned. Movement of the normal limb whilst looking at its mirror image mimicked the sensation of movement in the phantom limb. In four out of five patients this technique relieved phantom limb spasms by using the mirror to facilitate extension of the phantom hand, and removal of the mirror resulted in immediate return of pain. Persistent use of the mirror box resulted in prolonged improvement of symptoms in some patients. The symptoms of patients with complex regional pain syndrome, also known as reflex sympathetic dystrophy, or causalgia, tend to be most overt in one limb. In a similar fashion, certain movements of the contralateral limb in these patients appear to be capable of reducing pain. Functional neuro-imaging studies reveal that when subjects move their arms in an incongruent fashion increased activity can be demonstrated in an area of the right parietal lobe, known as the incongruent pain centre, which may be relevant to mechanisms of disease symmetry.

The findings described above indicate that complex neurogenic mechanisms underlie symmetrical physiological and pathological responses, such as pain and inflammation, and understanding them might result in novel treatment approaches.

ANTISENSE BASED GENE THERAPY FOR HYPERTENSION

Hypertension is a major cardiovascular risk factor, and poor compliance with current antihypertensive drug regimens, in part due to side-effects, limits the effectiveness of the therapeutic agents currently available. An alternative approach to overcoming problems with compliance is to use genetic therapies[25] where beneficial genes, such as those coding endothelial nitric oxide synthase, might be over-expressed, or where antisense (AS) oligonucleotides might be used to selectively inhibit gene expression[26] (Table 6).

One of the major challenges of gene therapy has been determining how best to deliver hydrophilic DNA material across the hydrophobic cell membrane and into cells. The use of viruses as vectors is one option and the choice of virus will depend on the clinical application. For example, retroviruses are particularly suitable in the treatment of hypertension because of their potential for long-term modification.

The renin-angiotensin system (RAS) plays a central role

TABLE 6

Possible genetic approaches to the treatment of hypertension.

'Sense' approach
• Over-expression of vasodilator-related genes
• Atrial natiuretic peptide
• Kallikrein
• Endothelial nitric oxide synthase
• Angiotensin II type I receptor
'Antisense' approach
• Inhibition of vasoconstrictor-related genes
• Renin-angiotensin system
• Antisense oligonucleotides
• Viral vectors, adeno virus and retroviral vector
• Beta I adrenergic receptor

in blood pressure control, and drugs targeting the RAS, for example angiotensin converting enzyme (ACE) inhibitors and angiotensin II type-1 receptor (AT_1R) blockers, are effective antihypertensive agents. Therefore, the use of AS therapy in targeting the RAS has been explored in hypertension. Using retroviral delivery, both ACE-AS and AT_1R-AS were administered to spontaneous hypertensive rats (SHRs) at five days of age before the development of hypertension. After 200 days, both AS transgenes remained integrated within cellular DNA and actively expressed; blood pressure was lower in rats transfected with either transgene compared to those who were administered the virus alone, and no effects were shown on blood pressure in a non-hypertensive rat strain. The AT_1R blocker losartan was found to reduce blood pressure in SHRs but had no effect in those transfected with AT_1R-AS. Both ACE-AS and AT_1R-AS also reduced cardiac hypertrophy in SHRs but had no effects in a non-hypertensive rat strain (Figure 4).

The benefits of gene therapy in hypertension may extend beyond just blood pressure-lowering effects. For example, endothelial function, measured as acetylcholine-mediated vasodilatation, was improved in isolated rat arteries transfected with AT_1R-AS, and transfection by ACE-AS reduced neo-intimal hyperplasia associated with balloon injury in normotensive rat arteries. Cardiac hypertrophy, in response to chronic angiotensin II infusion, can be inhibited by AT_1R-AS therapy[27] which also prevents the development of insulin resistance and hypertension in response to a fructose-rich diet. These experiments indicate the potential of AS therapy in the long-term control of hypertension, improvement of endothelial function and vascular reactivity, as well as attenuation of cardiac hypertrophy and prevention of restenosis. However, there is considerable work still to be done before human trials of this therapy can be undertaken. Of interest is the potential for AS gene therapy to reverse established hypertension, and the degree to which transgene expression can be regulated will also be critical.

ANTIBODY TREATMENTS

In theory, a number of immune-modulation strategies could be employed in the treatment of autoimmune diseases. However, clinical experience has been less encouraging, for example in the use of monoclonal antibodies to deplete or inhibit migration and activation of white cells. In contrast, studies inhibiting tumour necrosis factor alpha (TNFα) have been more successful. Tumour necrosis factor alpha acts by cross-linking cell surface receptors and promotes various pro-inflammatory and adhesion molecules and can be inhibited by monoclonal antibodies to TNFα or its receptors. An open label trial found that anti-TNFα antibody administration in patients with rheumatoid arthritis was well tolerated and resulted in clinical and laboratory improvements.[28] A subsequent randomised double-blind trial confirmed the clinical potential of this approach using infliximab, a chimeric human-mouse anti-TNFα monoclonal antibody.[29] When a recombinant fusion protein consisting of the soluble TNFα receptor linked to the Fc portion of human IgG_1 was administered to 180 patients with refractory rheumatoid arthritis in a placebo controlled study, therapy was well tolerated and resulted in improved inflammatory symptoms.[30] The effects of adding infliximab to methotrexate therapy in rheumatoid arthritis was investigated in the ATTRACT study[31] which found that

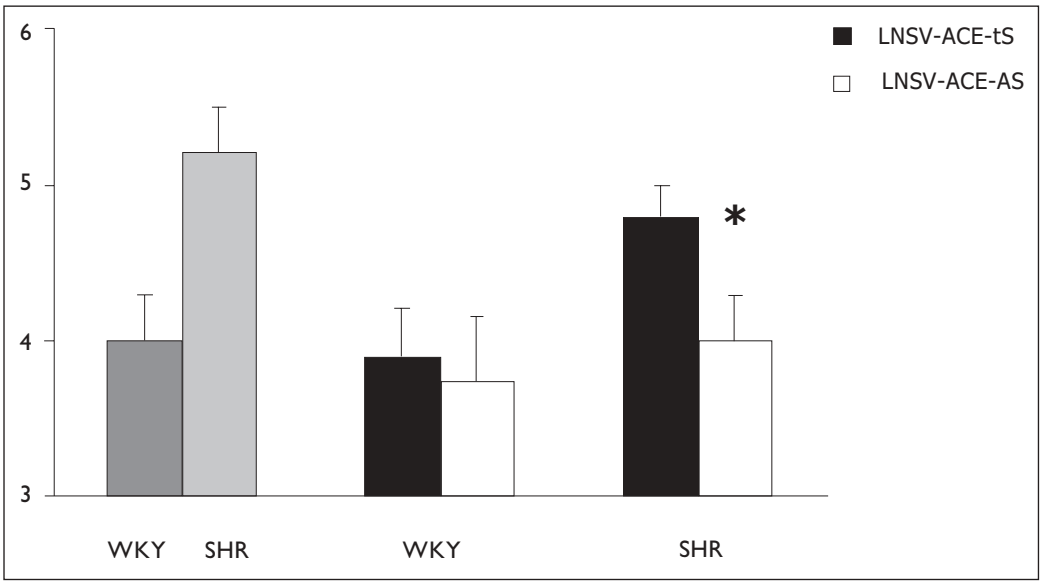

FIGURE 4

The ratio of heart to body weight of non-hypertensive rats (WKY) and spontaneously hypertensive rats (SHR). Untreated animals shown on the left, and effects of ACE-AS, or control ACE-tS, delivered by retroviral vector LNSV shown for WKY and SHR; *p <0·05.

combined therapy was more effective than methotrexate alone, and the improved clinical and radiographic responses persisted for at least two years.

Potential adverse effects of anti-TNFα therapy include infection, autoimmunity, allergy and injection site reactions; post-marketing surveillance of 170,000 patients has shown that sepsis occurs in 0·04%, and malignancy in 0·01% of patients. Reactivation of tuberculosis is a particular concern with anti-TNFα therapy; the greatest risk is within the first month of therapy, and screening prior to treatment is recommended. Although anti-TNFα therapy looks promising in the treatment of rheumatoid arthritis, questions remain about its long-term safety and efficacy given that repeated administration results in anti-human monoclonal antibody formation. Furthermore, therapy is expensive and the optimal dose is not known. Its place in relation to disease-modifying agents, other than methotrexate, needs to be clarified.

SESSION 5: GENOMICS IN DRUG TREATMENT AND DEVELOPMENT

GENE THERAPY FOR HUMAN DISEASES

Ion movement across respiratory epithelial cells determines the extent to which water, moving by osmosis, is present on the airway surface, which in turn is critical for effective mucociliary clearance. The cystic fibrosis trans-membrane regulator (CFTR) protein is a chloride channel found on mucosal surfaces, including that of the airway. Patients with cystic fibrosis (CF) have a mutation of this protein that causes reduced chloride movement, reduced mucosal surface water content, impaired mucociliary clearance and a propensity to infection. The problem is compounded by increased movement of sodium into cells, further reducing mucosal surface water. Replacement of the dysfunctional CFTR with the normal protein by gene therapy is a promising future treatment for CF.

The effects of CFTR transgenes can be assessed functionally by measuring trans-membrane chloride ion transport, and early studies in mice demonstrate that CFTR gene delivery by a liposomal vector results in approximately 50% recovery of the chloride ion transport defect. The first human studies performed using nasal transfection resulted in around 20% improvement in chloride transport, which lasted for about seven days. Administration of the normal gene complexed to cationic liposomes in nebulised form to CF patients has subsequently been shown to improve the chloride transport defect in the lung.[32] Some success has also been achieved using adenoviral vectors; however, the thick mucus found in CF forms a barrier between the airway and the epithelium and inhibits the efficiency of gene transfer. A number of mucolytic agents are available, and perhaps the most useful is recombinant DNAse. Although it may seem illogical to administer DNA together with an enzyme that can break it down, liposomes are used to protect the DNA from enzymatic destruction, and DNAse partially improves gene transfer efficiency.[33] Overall, it is now possible to improve chloride transport in the lung towards 25% of normal values, and this response is sustained for several weeks.

Chronic respiratory tract infection with *Pseudomonas aeruginosa* accounts for much of the morbidity and mortality seen in CF. When added to cultured epithelium from CF patients the bacteria adhere to the cells more powerfully than to cells derived from normal subjects, and this effect is inhibited by CFTR gene transfection.[34]

Although gene therapy in CF appears capable of improving respiratory epithelial function, it remains limited by the efficiency of gene transfer. In this respect, the development of the recombinant Sendai virus is of interest. In the respiratory tract of mice and ferrets[35] and cultured human nasal epithelial cells, the Sendai virus results in efficient gene transfer that is significantly better than that achieved with liposomes or adenovirus techniques. Furthermore, airway mucus appears to have less effect on the efficiency of gene transfection, and it is hoped that this will provide a useful new vector for respiratory gene transfer in the future.

Recent years have seen encouraging progress towards the goal of effective gene therapy for CF, and further advances are expected. It is hoped that Phase 3 trials will be possible within the next five years.

PHARMACOGENOMICS AND DRUG DEVELOPMENT (Sydney Watson Smith Lecture)

Adverse drug reactions are responsible for major morbidity and mortality and contribute significantly to the overall cost of health care. It is generally difficult to predict which patients will experience clinically significant side-effects from drugs, and inter-individual genetic variability might hold the key to predicting those who are more likely to respond to a drug, therapeutically or adversely. Pharmacogenetics is concerned with identifying those patients who will derive maximum benefit from a particular agent and who will be least likely to develop side-effects.

A wide number of genes are relevant to drug action, for example those influencing drug targets, metabolising enzymes and clearance mechanisms. Prior to the availability of data from the Human Genome Project (HGP) there were essentially two approaches applied to the investigation of genes thought responsible for clinically important variation in drug responses. Specific hypotheses could be generated about genes causing differential drug responses, which could be tested in responders and non-responders. For example, the PRESTO trial investigated the effects of tranilast, which

interferes with vascular medial smooth muscle proliferation and migration induced by platelet-derived growth factor and transforming growth factor beta-1.[36] In this double-blind placebo-controlled study of 11,500 patients undergoing percutaneous transluminal angioplasty, raised bilirubin concentrations occurred in four per cent of those who received tranilast and were found to have Gilbert's syndrome, a benign condition in which mild chronic hyperbilirubinaemia occurs secondary to impaired hepatic glucuronidating activity. Gilbert's syndrome occurs in patients who are homozygous for 7 rather than 6 TA repeats at a specific section of the 5' promoter region of the bilirubin UDP-glucuronosyltransferase-1 gene.[37] All of those in whom transilast was associated with a rise in serum bilirubin were found to be homozygous for the 7 TA repeat genotype.

An alternative method of investigating genetic variation in drug responses is to study single nucleotide polymorphisms (SNPs). At certain chromosomal locations there is significantly greater variation of nucleotides across the normal population, and these loci are said to contain SNPs. Although they may themselves result in functionally heterogeneous gene products they can also be used to map other gene variants associated with particular phenotypes. The use of SNP analysis can be illustrated by the relationship between Alzheimer's disease and apolipoprotein E (APOE) genotype, where five common APOE genotypes are related to the age at onset of Alzheimer's disease; in particular, early onset is particularly likely in homozygotes for APOE4. Comparison of patients with Alzheimer's disease to controls reveals distinct SNP differences between them and is one example of how SNP analysis can be used to detect highly variable genes with important clinical consequences.

The Wellcome Trust, along with several pharmaceutical companies and academic centres, founded the SNP Consortium with the aim of identifying 300,000 SNPs and mapping at least half of these within two years. Advances in sequencing technology have enabled the project to actually identify 2·5 million SNPs and map 2 million of them already. Single nucleotide polymorphisms analysis has been used to identify genes relevant to both psoriasis and migraine and can be applied to search for genes relevant to drug side-effects. For example, the anti-retroviral agent abacavir causes hypersensitivity reactions in five per cent of those in whom the drug is subsequently contraindicated because of the risk of future anaphylaxis. A major study started three years ago, due to be completed by the end of 2002, is applying 200,000 SNP maps to DNA samples taken from patients with hypersensitivity reactions and non-hypersensitive controls. Although the cost of this proof-of-principle study is of the order of £20 million, the results may mean that hypersensitivity risk can be predicted and the potential market for the drug massively expanded. The widespread use of SNP data has the potential to reduce drug related adverse events by 100-fold, in addition to a number of other potential advantages (Table 7). It might be speculated that in 20 years it will be possible to choose the most appropriate therapy for a patient based on that individual's unique complement of SNPs – the right medicine for the right patient.

TABLE 7

Areas where SNP data has the potential to improve drug utilisation.

The potential for SNPs to improve drug use.
• Improved identification of patients at risk
• Improved drug safety
• More informed treatment decisions
• Improved confidence of both physicians and patients in drug safety
• Improved compliance with therapy (as a result of the above)

SESSION 6: AFFORDING NEW DRUGS

EVALUATING NEW THERAPIES

A number of reasons have been put forward to determine why it is important to measure the health benefits and outcomes of interventions, including the need to inform professional practice, for example, with appraisal, revalidation and performance management. It facilitates informed choice and provides a basis for consumer protection. Furthermore, the information can be used for rationing, determining in some cases who will live in what degree of pain and discomfort, or die, whether by depriving patients of effective, but expensive, or desirable, but ineffective, treatments. By measuring benefit, treatments can be targeted to give the greatest health care benefit per unit of cost.

Health benefits can be assessed in a number of different ways, many of which have significant limitations. Routine NHS mortality data have limited accuracy, and there must be some account taken of increased risks taken on by centres that offer treatment to more challenging patients. Indeed, there is evidence that such data can change behaviour, with certain centres becoming less willing to take on high-risk cases. Case volume may also affect overall mortality figures, particularly in surgical care, where there is an inverse relationship between the number of procedures performed and the overall mortality.

Quality of life and assessment of social, physical and psychological function are alternative measures of health benefit, and include the EURO-QoL and SF36, which have been used in many randomised controlled trials.

Although they have limited validity and sensitivity across all populations they are generally considered reliable. The British United Provident Association (BUPA) has assessed all patients on admission and three months after surgery using the SF36, as well as documented variation in reported outcomes, both between patients and between clinicians. More specific quality of life measures are also available, for example the Oxford Scale for orthopaedics. The National Institute of Clinical Excellence (NICE) is increasingly grading interventions according to cost per Quality Adjusted Life Year (QALY); one QALY equates to one year of good quality of life, and those interventions costing less than £30,000 per QALY are more likely to be recommended. One notable recent exception to this is β-interferon for multiple sclerosis, for which the cost per QALY exceeds £30,000. It is inevitable that generic and specific measures of quality of life will be increasingly used; therefore, it is important that the data are as relevant and as accurate as possible.

What are the immediate challenges in the field of evaluating new interventions? The first is determining the cutoff point at which health technologies should be accepted or rejected so that it becomes possible to choose between competing technologies. Whereas £30,000 per QALY has been used in the UK, in Australia, for example, the equivalent of £15,000 per QALY has been used. These cutoff levels are rarely discussed openly and the current level adopted by NICE has no definitive rationale in scientific or policy terms. Cost per QALY assessment alone will not be sufficient to control expenditure as additional control of volume will also be needed. A further challenge is to promote acceptance of the ubiquitous nature of rationing and the profession as the rationing agent. As Groucho Marx said: 'The secret of life is honesty and fair play. If you can fake that you have made it!'. There will also be increasing debate on who should regulate the introduction of new technologies and, whereas doctors have traditionally fulfilled this role, increasing demand for transparency will necessitate greater involvement from patients who are likely to become increasingly well informed on the benefits of different interventions and the priority of each. However, patients can only make well informed choices when there is a good evidence base to which they can refer.

INTERACTIVE DEBATE

THIS HOUSE BELIEVES THAT ECONOMIC ANALYSIS SHOULD REMAIN A SECONDARY CONSIDERATION IN THE DEVELOPMENT OF CLINICAL GUIDELINES

Prior to the debate, 59% of the audience voted in favour of the motion and 42% voted against it.

Speaking for the motion, Professor Lowe first suggested that the authors of guidelines should address two fundamental questions. Firstly, on what authority do they tell patients and professionals what should be done? Secondly, what is the explicit evidence that the recommendations are reasonable? He then suggested that the ownership of guidelines should be by stakeholders rather than health care purchasers who say what they can and cannot afford, or by specialists emulating 'Good old boys sat around a table.'

The Scottish Intercollegiate Guidelines Network (SIGN) national guidelines are professional- and patient-led. They are peer reviewed in Scotland and worldwide and concentrate on 'the right thing to do' across the whole journey of care. Explicit links are made with evidence, experience and common sense, and they are medicolegally and professionally defensible. The guidelines also have an economic appendix; thus, health technology assessments by the Health Technology Board for Scotland might be included, for example in the development of the diabetic retinopathy screening guideline.

In economic terms the implementation of SIGN guidelines appears to be cost neutral. Whilst they promote best practice, they also condemn ineffective practice. To date, neither trusts nor an economic advisor have raised many financial concerns. However, as a pilot, a health economist is involved with three guidelines that are currently under preparation. Concerns regarding financial guidelines include too much emphasis on 'value for money', leading to the distortion of funding priorities and questionable medicolegality and clinical governance.

The SIGN guidelines are intended to promote clinical audit and the development of local protocols which reflect local disease prevalence within the national guideline. Local ownership is considered essential to successful implementation, allowing for local choices to be made according to local experience and preference. Furthermore, it can be argued that economic issues are considered more relevant to local rather than national development.

In summary, Professor Lowe concluded that the right way to produce guidelines is on a national basis, through professionals and patients, making explicit links with evidence and experience and allowing for local protocol development. Although useful, economic evaluation should be of secondary importance and should inform what has to be spent rather than dictate the priorities.

Opposing the motion, Professor Maynard agreed that SIGN has produced some excellent work and that it is important that best evidence guide clinical practice. However, although SIGN guidelines make some assessment of expenditure, they do not assess cost effectiveness. In contrast, NICE takes account of both clinical and cost effectiveness. This information is needed in order to make

difficult rationing choices, which the SIGN approach does not address. If an intervention is considered cost effective then it can be assumed that it is also clinically effective. However, the reverse, that because an intervention is clinically effective it is also cost effective, is not necessarily true.

Whatever guidelines are adopted it is also crucial that volumes are monitored and controlled. Without this information the total expenditure related to an intervention will not be known and, therefore, will be difficult to control. Indeed, although NICE assesses interventions according to cost effectiveness criteria, it makes expenditure predictions that are not accurate because there is no volume control. The Scottish Intercollegiate Guidelines Network makes no attempt to assess or control volumes. It is also important that once an intervention is made generally available, adherence to the relevant guideline is adopted. The successful implementation of guidelines is a constant challenge. For example, there are known to be differences in the implementation of guidelines according to social class. Thus, although β-blockers are known to be cost effective, those from lower social classes are less likely to be prescribed them. In conclusion, Professor Maynard suggested that economics has an equal footing with clinical evidence in informing the right decisions regarding which interventions may be reimbursed.

A number of points were raised during discussion. The conclusions contained within guidelines will depend on the point on the learning curve at which assessments are made. The speakers were asked to comment on when guidelines should be reassessed, and on how much of the health budget should be spent on intervention assessment. Professor Maynard commented that guidelines should be continually revised as new evidence becomes available. With regard to how much should be spent on assessment he suggested that more money than is currently spent should be made available, and that approximately one per cent of the health care budget might be appropriate. Professor Lowe stated that the Royal College of Physicians of Edinburgh is implementing proficiency measures and that adequate Information Technology is particularly important in this regard.

Concern was raised that guidelines tend to concentrate on what can be relatively easily measured, but may neglect important areas where measurement is more difficult. Professor Lowe agreed, citing the example that the effects of drugs may be more easily assessed than other interventions. He further commented that guidelines that assess the entire journey of care, such as the SIGN guidelines, partly begin to address this problem.

Professor Maynard commented that often what is considered unmeasurable can actually be measured in some way, especially in surgery, although this can be more difficult in general practice. Although rationing is a reality, one clinician noted that some patients perceive that decisions about their care are affected by rationing when there is no such influence. Professor Maynard agreed and commented that media portrayal of NHS issues is highly influential of public perception of the service and that a more mature approach from the media would be valuable.

Following the discussion a further vote on the motion was conducted. Two-thirds agreed with the motion, with one-third disagreeing.

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