The 1995 Advanced Medicine Conference was held at the College from 13 to 16 February. All four days contained excellent talks from leaders in the field which usefully balanced science, research data, clinical overview and practical information. Topics included cardiovascular disease prediction and prevention, nitric oxide in disease, emerging applications of growth factors and anti-TNF therapy in rheumatoid arthritis. This report highlights information from 20 of the 50 contributions.

Professor Stafford Lightman (Bristol), the organiser, had selected an impressive panel of speakers for the conference and the standard of talks was very high indeed. The result was a useful blend of good British science, practical information and clear overviews of the state-of-the-art.

We have chosen to give the flavour of this conference by describing a limited number of the contributions in some detail rather than listing all the topics covered. This means having to exclude many equally excellent talks owing to lack of space, but all speakers’ contributions to the conference will be published in the Horizons in Medicine series later this year.

Cardiovascular disease

Professor D J P Barker (Southampton) reviewed the accumulating data linking fetal nutrition and development with disease in later life. There are different ‘critical windows’ of development for organs and metabolic systems during which nutritional deficiency and the fetal adaptation to it may lead to lifelong metabolic abnormalities and susceptibility to later disease. This has been shown in animal models, eg the systolic blood pressure (BP) in adult rats is related to maternal protein intake during pregnancy. In humans, low birth weight predicts adult hypertension and greater standardised mortality rate for cardiovascular disease. Infants who have a low birth weight in relation to their length (who have sacrificed muscle to maintain growth in utero) are more likely to have an impaired glucose tolerance test in adult life, possibly as a result of persistent abnormal muscle metabolism. There is also an inverse relationship between the newborn infant’s abdominal circumference and adult mean serum low density lipoprotein (LDL) levels. However, babies born small but in proportion are not at greater risk of coronary artery disease later in life. How these insights can be used for primary prevention of cardiovascular disease has yet to be seen.

Dr J R Seckl (Edinburgh) reviewed the factors that regulate birth weight. Among them, exposure to glucocorticoids in utero retards fetal growth, affects fetal tissue development and maturation, has direct hypertensive effects and ‘programmes’ metabolic responses. Experimentally, rats given dexamethasone in utero weigh 14% less at birth and have a higher BP in adulthood than controls. In humans, deficiency in a key enzyme, 1β-dehydrogenase, which normally protects the fetus against high levels of maternal glucocorticoids, may thus retard fetal growth and be important in the programming of hypertension in later life.

In the Lord Rayner Lecture, Professor M F Oliver (London) presented an overview of the wealth of published lipid lowering studies. The recently reported multicentre anti-atheroma study (MAAS) [1] achieved a 23% reduction in total cholesterol and a 31% reduction in LDL cholesterol in simvastatin treated patients, and was associated with significantly slower progression of coronary artery atheroma than in placebo treated patients; overall there were 13.4% vs 24.4% new lesions and 4.5% vs 18.4% new occlusions. However, although there was a (non-significant) reduction in the number of patients undergoing angioplasty or revascularisation in the simvastatin group, there was no benefit in terms of overall mortality. The ‘4S’ (Scandinavian Simvastatin Survival Study) [2] trial published last year represents an important landmark in secondary coronary disease prevention: using large enough numbers of patients (4,444) followed for a sufficient period of time (median 5.4 years) it was at last possible to show an overall improvement in survival in patients given lipid lowering therapy after a myocardial infarct. This study showed that improvement in mortality rates occurs between two and three years after treatment with active drug versus placebo. An overview of several trials suggests that the degree and duration of reduction of cholesterol determine the degree of reduction of coronary events, ie the cholesterol level needs to be low enough for long enough. HMG CoA reductase inhibitors (statins) may maximise this benefit.

The message from primary prevention trials is less clear-cut. Overall, such studies have produced disappointingly small degrees of cholesterol reduction (eg with diet) and so far no statin trials have been published. For primary prevention, the present strategy should be to treat only higher risk patients, for example those with total cholesterol > 6.5 mmol/1 or LDL > 4 mmol/1. In the light of present knowledge, Professor Oliver believes that there is currently undertreatment of patients at high risk for coronary artery disease and over-treatment of individuals with minimal or no risk.
Respiratory medicine

Nitric oxide (NO) plays an important role in the control of pulmonary vascular resistance and distribution of blood flow, probably by acting as a vasodilator on the precapillary arteriole. Dr T Higenbottom (Cambridge) described the results of studies of this control in the pulmonary vasculature of patients with chronic obstructive airway disease (COAD) and primary pulmonary hypertension (PPH)—they show similar changes in pulmonary vascular resistance when NO is inhaled. In severe PPH, however, there is impaired baseline release of NO which may be an important pathophysiological factor in this disease. NO is potentially a useful inhaled treatment for the adult respiratory distress syndrome. Preliminary studies have shown reduced shunt fraction and improved pulmonary artery oxygen pressure in this situation. A multicentre study is currently underway.

Dr R A Knight (London) provided an update on the genetics of cystic fibrosis (CF). The CF gene is located on the long arm of chromosome 7 and codes for a cellular chloride channel—the cystic fibrosis transmembrane conductance regulator (CFTR). The most common mutation of this gene—a mutation at amino acid number 508 (ΔF508)—accounts for 70% of cystic fibrosis genes in northern Europe and North America, but more than 500 other mutations have been recognised (the next most common of which accounts for 2%) and there are over 100 phenotypically silent polymorphisms. The genetics can be used to predict the severity of pancreatic disease in CF—homozygotes for ΔF508 have severe pancreatic disease whereas compound heterozygotes are more mildly affected. Unfortunately, no such prediction can as yet be made for the severity of the lung disease which may be related to additional (unrecognised) genetic determinants or to environmental factors. Since the respiratory problems are primarily responsible for the impaired lifespan and quality of life, this restricts the value of prenatal screening for CF at present.

Renal medicine

The majority of patients who have a systemic vasculitis involving the kidney have a positive anti-neutrophil cytoplasmic antibodies (ANCA) test. The ANCA titre correlates with disease activity and may predict relapse if a rising titre is seen while patients are in remission. ANCA is not exclusive to these systemic vasculitides and may also occur in endocarditis, HIV infection, amoebic abscesses, sclerosing cholangitis, inflammatory bowel disease and malignancies such as carcinoma of lung, leukaemia and lymphoma.

Professor A J Rees (Aberdeen) reviewed this group of diseases. Treatment of renal vasculitis is divided into two phases—induction with steroids and cyclophosphamide, and maintenance with steroids and azathioprine or methotrexate. In controlled trials plasma exchange has been shown to be of additional benefit in severely affected (dialysed) patients. Other novel treatments such as anti-T cell antibodies and cyclosporin remain under investigation. Most patients become ANCA negative after induction treatment; treatment may be successfully withdrawn after one year but patients who remain ANCA positive may require continuing therapy. Relapse is more common in patients who are cANCA (cytoplasmic ANCA) positive (1 per 50–60 months, mostly Wegener’s granulomatosis) than in those who are pANCA (proenzyme ANCA) positive (1 per 500 months—includes polyarteritis nodosa).

‘Renal failure—largely a problem of the elderly’ was the theme emphasised by Dr T Feest (Bristol). In this age group many changes are acute and remediable; diagnosis is therefore mandatory since the prognosis of acute renal failure is good. In general, there is under-referral of elderly patients to renal specialists in the UK in contrast to other parts of Europe. Renal support should be carefully considered—in France and Germany haemodialysis is the preferred method of choice in the elderly and this has been shown to offer a better quality of life. Renal transplantation may be offered since good quality five-year survival between 68% and 80% has been reported; rejection is less frequent but there is greater risk of perioperative death and poor rehabilitation. Age-matching of donor and recipient may increase the use of this treatment.

Biochemical medicine

Professor M B Pepys (RPMS, London) reviewed the clinical features and biochemistry of amyloid. There are five major types of amyloid—reactive, monoclonal gammopathy associated, haemodialysis associated, cerebral and pancreatic islet cell. All consist of protein fibrils coated with serum amyloid P (SAP) component. Labelling of SAP with 125I can be employed in diagnosing and quantifying amyloid deposits, and may be used to follow its natural history and response to treatment. A current hypothesis is that SAP protects the protein fibrils from degradation by proteinases. The use of agents such as MODG, a sugar which inhibits the binding of SAP to the protein fibrils and may make them accessible to proteinases, is a potential future strategy in the treatment of this disease.

Pharmacology

Professor Moncada (Wellcom Research Laboratories, Beckenham, Kent) referred to the 12,000 or so papers that have been published on nitric oxide (NO) since he identified it as the endothelium derived relaxation factor in 1988. The new biology of NO, which includes a critical role in vascular tone, a probable role in killing of pathogens by phagocytic cells and a possible
role in long-term potentiation (and hence memory) via glutamate/NMDA receptors in the central nervous system, is likely to lead to many therapeutic applications. The ability of L-NMMA, a nitric oxide synthase inhibitor, to reverse the vascular changes in septic shock and improve outcome is being tested in a multicentre clinical trial.

Growth factors

Dr J M P Holly (Bristol) elegantly introduced the expanding field of growth factors (GFs) which currently fall into six families—epidermal (EGF), transforming GFβ (TGFβ), platelet-derived (PDGF), fibroblast (FGF), insulin-like (IGF) and neurotropic (NGF). The regulation of GF action is very different from that of classical hormones. GFs are secreted continuously, without regulation, by a large variety of cell types resulting in very high concentrations (1,000 x that of peptide hormones) both in the circulation and extracellular compartment. However, the majority are either complexed to an array of binding proteins (six in the case of IGF), attached to cell surfaces or to glycosaminoglycans of the extracellular matrix itself. The size of the bioactive pool is then carefully regulated by the secretion of activating proteases by the target cells and fluctuations in binding protein levels. GFs are thus stored ‘extracellularly’ in contrast to the intracellular storage granules of peptide hormones. Dr Holly illustrated this by the diurnal variation in IGF bioactivity seen in some individuals which is fully accounted for by variations in IGF-binding protein levels, the total IGF concentration remaining constant through the day.

A metabolic application of GFs was provided by Dr D Dunger (Oxford), who showed that daily IGF-1 injections suppress the inappropriately high growth hormone levels seen in pubertal insulin dependent diabetics. The result is a lowering of insulin resistance, abolition of the ‘dawn phenomenon’ and an overall improvement in diabetic control. Side-effects appear minimal at the doses used and benefits were sustained over one month. Long-term clinical studies are beginning and Dr Dunger believes that beneficial effects on growth in diabetic children will also be seen.

A dramatic clinical application of growth factors was described by Professor M W J Ferguson (Manchester). He showed that topically administered antibodies to TGFβ 1 and 2 (both are required), or TGFβ 3 peptide itself, can alter the direction of collagen deposition in wound healing such that there is almost no scarring. After preliminary studies on volunteers, including Professor Ferguson himself, clinical trials in wound healing with TGFβ 3 and mannose-6-phosphate, an inhibitor of TGFβ 1 and 2 activation, are now under way. If modulation of the TGFβ system is successful, Professor Ferguson hopes that it will prove of value in other processes involving the formation of fibrous tissue, such as cirrhosis and scleroderma.

Immunology

In the Croonian lecture, Professor R N Maini (Kennedy Institute of Rheumatology, London) described the first successful application of an anti-cytokine monoclonal antibody therapy in the treatment of rheumatoid arthritis (RA). His group targeted the cytokine tumour necrosis factor (TNF) using an antibody from the biotechnology company, Centocor originally (but unsuccessfully) designed for use in septic shock. An initial open study showed clinical and biochemical responses in severe RA within days of the first infusion of antibody, swollen joint counts falling from 16–20 to 4–8 and C-reactive protein levels staying low for 6–8 weeks after infusion. A dose-finding study showed a plateau at 10 mg/kg (no further benefit at 20 mg/kg). No significant side-effects were observed although infections were slightly more common than in a placebo group. Interestingly, two patients developed anti-double-stranded DNA antibodies after treatment which disappeared without being associated with symptoms. The place of anti-TNF therapy in RA remains to be established, since all patients eventually relapsed. Whether it will play a role in modifying the course of early disease, in maintaining remission with repeated doses, or as third-line therapy in severe disease we do not yet know but its success does appear to support a key role for TNF dysregulation in this disease.

Professor M Feldmann (Kennedy Institute of Rheumatology, London) reviewed his group’s work on identifying sites for intervention in the cytokine cascade of RA. They provided the first evidence for TNF as a possible site of intervention but their attention is now directed to interleukin-10 (IL-10) which appears to be the main endogenous anti-inflammatory cytokine in the joint. Clinical trials of IL-10, and perhaps even local gene therapy with IL-10 generating constructs, are now under consideration.

A link between stress and reduced immune responses has long been suspected but the exact mechanism has been difficult to define. Attention has concentrated on raised levels of corticosteroid which may be immunosuppressive, but Professor G A W Rook (University College London) reviewed the evidence in favour of a role for dehydroepiandrosterone-dione (DHEA). DHEA, a weak androgen produced by the adrenal, is the most abundant circulating steroid. It appears to block the immunosuppressive actions of dexamethasone on the thymus and improve responses when applied topically at the site of immunisations. Furthermore, in T cells it switches the balance in favour of delayed-type hypersensitivity reactions (‘Th1 responses’) and away from supporting antibody production (‘Th2 responses’). The marked fall in DHEA levels seen in US rangers undergoing stressful military training exercises, in patients with tuberculosis and in the elderly may account for the reduced T cell immunity and skin test responses observed in these groups. In the elderly, DHEA administration apparently...
induces a sense of well-being, making it a particularly attractive therapeutic option.

Neurology

Professor W I McDonald (Institute of Neurology, London) began his talk with dramatic MRI time-lapse video footage of evolving multiple sclerosis (MS) lesions. Unlike CT scans, MRI shows lesions in the white matter in 98% of patients with clinically definite MS. Serial scans at up to weekly intervals over nine months have shown that new lesions produce enhanced images after gadolinium injection (indicating the acute inflammatory phase) for around a month (range one week to three months). Such lesions are surrounded by a larger non-enhancing area and both areas shrink over the subsequent months. Using a technique known as short echo time proton spectroscopy to detect lipid in the brain, Professor McDonald's team found that demyelination occurs early in new lesions (during the inflammatory phase). Recovery of function is accounted for not by remyelination but by conduction in unmyelinated fibres. Persistent (irreversible) neurological deficits are therefore due to axonal degeneration, ie actual neuronal loss, not simply demyelination. MRI detects 10 times more MS lesions than are clinically apparent, presumably because they are occurring in 'silent' areas of the periventricular white matter. As a result, MRI appearances correlate poorly with clinical status. However, if the MRI scan is normal in acute optic neuritis, progressive MS develops in only 8% of patients over the following five years compared with 82% of those with abnormal scans.

Endocrinology and metabolism

With the publication of the results of the large (1,441 patients) American Diabetes Control and Complications Trial (DCCT) in 1993, tight metabolic control in diabetes has once again become an issue. Professor D R Hadden (Belfast) admitted that failure to obtain such information earlier was embarrassing; previous trials pointing to the same conclusion had been too small, too short or uncontrolled. A meta-analysis in 1993 had found only 271 patients properly randomised in six previous studies from Scandinavia and none from the UK. The DCCT along with the previous trials have now established that very good diabetic control—mean blood glucose 8.6 mmol/l, glycated haemoglobin (HbA1) around 7.0%—reduces the development of retinopathy, neuropathy and nephropathy by over 50% and significantly slows progression in those with complications. The initial worsening of established retinopathy associated with tight control in the first one to two years seen in previous studies was confirmed by the DCCT, but the longer-term outcome was improved (mean 6.5 years). Indeed, one prediction suggests that intensive control at diagnosis could reduce the mean delay to significant retinopathy from 15 years to 68 years! The trade-off is a three-fold increase in severe hypoglycaemic events and a 10 lb weight gain with intensive therapy.

Dr A Hattersley (Royal Devon and Exeter Hospital) elegantly described the search for genetic abnormalities underlying the rare dominantly inherited form of type II diabetes, maturity-onset diabetes of the young (MODY). MODY is characterised by mild hyperglycaemia that remains easy to control throughout life, is present from early adulthood (? or childhood), is not associated with obesity or insulin resistance and is rarely associated with complications. Distinction from insulin-dependent diabetes (IDDM) and avoidance of unnecessary insulin therapy is important for the clinician. The early age of onset and 100% penetrance has allowed extended pedigrees of three generations to be identified; amongst affected individuals only 46% have 2 hour blood sugars in the diabetic range. In series from different countries, 5-50% of MODY families have a mutation in the gene for glucokinase (GCK), the rate-limiting enzyme in glucose uptake and sensing in the beta cell. This is consistent with the reduced insulin response to glucose infusion and apparent 'resetting of the glucose sensor' in these patients. However, GCK mutations do not account for the remaining MODY families (who have a higher rate of diabetic complications) and such mutations are present in only 1-2% of type II diabetics overall. It is hoped that genetic analysis of non-GCK MODY may now identify genes more relevant to the majority of late-onset diabetics.

The distinction between osteoporosis and osteomalacia may not be as clear-cut as previously emphasised. Professor K-T Khaw (Cambridge—one of only two women speakers at the conference) described how her study in Cambridge had correlated lower 25-OH vitamin D levels and higher parathyroid hormone (PTH) levels (within the standard 'normal range') with reduced bone density. Since changes in bone density even within the normal range correlate with the risk of hip fracture, the variations seen in the Cambridge study could have considerable significance for the hip fracture rates in the population as a whole. The ideal daily vitamin D intake is unknown but toxicity appears not to develop under 5,000 iu/day. Professor Khaw currently recommends 400 iu/day, but has tried 100,000 units as a single winter dose and believes this to improve compliance and reduce cost while being equally safe.

The title of Professor H S Jacobs' (University College London) talk, 'Polycystic ovaries can kill', emphasised that in research, even though all the initial data point in one direction, the end result has still to be directly demonstrated. His group found that women with polycystic ovaries (PCO) (ultrasonically defined as 10 or more cysts 2-8 mm in diameter) who represent around 23% of random volunteers and 92% of those who present with hirsutism, have raised fasting
insulin levels and reduced high density lipoprotein (HDL) levels. This suggested that they may have a form of ‘syndrome X’, described by Reaven, of increased insulin resistance with increased cardiovascular risk. Indeed, in a long-term follow-up study by Dahlgren [3] of women who had had wedge resections for PCO, hypertension was three times as common as in controls and the estimated risk of myocardial infarction over six times higher. Professor Jacobs’ report of his own long-term follow-up study concerned 1,028 women with a histological diagnosis of PCO made at surgery prior to 1970 who were identified from pathological records and followed in the NHS registry until death, age 75 or 1994, whichever came first. Their average age at diagnosis was 25.7 years and duration of follow-up 28.1 years; 82% of the records were traced. To his admitted surprise, the risk of death, and in particular cardiovascular death, in this large PCO group was the same as that expected for the population as a whole, with a trend in favour of survival in the PCO group! Professor Jacobs suggested that the higher oestrogen levels in PCO women may be responsible for changing the outcome from that predicted by the surrogate markers of cardiovascular risk (HDL etc).

Concluding comments

The conference was well attended through all four days by consultants and junior doctors, a number of them from Europe and the USA. Everybody came away with useful facts for present practice and with exciting views of the future. Fourteen junior doctors and thirteen medical students were also able to attend the conference through the generous support given by the Foulkes Foundation. One student suggested that many of her colleagues were turning away from the thought of pursuing careers in hospital medicine/research even as early as the third undergraduate year. The 54 speakers at this conference showed that we are not yet short of successful scientist-clinician role models in Britain.

References

1 MAAS Investigators. Effect of simvastatin on coronary atheroma; the Multicentre Anti-Atheroma Study (MAAS). Lancet 1994;344:633-8.
2 Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-9.
3 Dahlgren E, Johansson S, Lindstedt G, Knutsson F, et al. Women with polycystic ovary syndrome wedge resected in 1956-65: a long term follow-up focussing on natural history and circulating hormones. Fertil Steril 1992;57:505-13.

Clinical computing: friend or foe?

A conference on various aspects of clinical computing was held at the Royal College of Physicians on 23 January 1994. The aim was to draw together experts in the field to review current progress and experience, showing the benefits for patient care, education, training and research. Systems currently in use were reviewed and their benefits and problems outlined. It was hoped that this would inspire those not currently using such systems and help them avoid the pitfalls of those with previous experience.

The conference was opened by Sir Leslie Turnberg who stated that clinicians had previously been reluctant and slow to take advantage of new computer technology. He thought that this might be due to two reasons, first that too much had been claimed for systems and they had failed to deliver these promises and second that system failures had put people off. Recently, however, there had been huge increases in computing power, combined with decreasing costs and increased computer literacy. He felt that we were on the brink of changes in attitude.

Dr J D Read (NHS Centre for Coding and Classification, Loughborough) spoke on terming, encoding and grouping. He pointed out that the importance of information was increasing and that the management dataset should be an expansion of the clinical dataset. Currently the patient record could be encoded to form clinical datasets and management datasets, eg ICD-10/OPCS 4; these could then be formed into groups, eg health care resource groups, for costing purposes. Read codes are a dictionary of clinical terms that attempt to use natural clinical language. They can also be used to record symptoms, test results and patients’ skills and functional abilities. ICD-10/OPCS 4 follow definitions of conditions. The latest version of Read codes relates to ICD-10 via a ‘coding frame’, which allows the Read code to be encoded. A Read code may lead to more than one ICD-10/OPCS code, but will produce a default ICD-10/OPCS code that may only be altered with the addition of extra detail; eg if a 25 year old hypertensive becomes pregnant, Read codes allow this to be essential hypertension, whereas ICD-10 changes the diagnosis to hypertension of pregnancy.

Dr O H B Gyde (Birmingham Heartlands Hospital) outlined the ways in which standards were set. They may be issued by authorities, bodies or institutions,