considerable problems in the UK during summer. Although the universal use of lead-free petrol will reduce the number of lead particles in the ambient air, the rapid proliferation of diesel fuelled vehicles will still generate PM\textsubscript{10} to pollute the atmosphere.

Solutions

Professor Phillip Goodwin (University College, London) looked at ways of preventing some of the problems caused by outdoor pollution. Of the many sources of outdoor atmospheric pollution, motor traffic is the largest. The best way forward is to adopt measures to reduce the number of motor vehicles on the road and also reduce vehicle emissions. Moving from leaded to unleaded petrol will reduce the number of lead particles in the atmosphere. At times when there are unusually high concentrations of pollutants due to bad climatic conditions, local authorities should take measures to impose short-term bans on traffic, especially in city centres. It is still early days for 'pollution free fuels' but with rapid technological advancement this is something we can look forward to.

General comments

This conference brought together the multi-disciplinary scientific community working in environmental toxicology to consider the key issues relating to air pollution and health. There was a general consensus that motor vehicle emissions were the largest source of urban outdoor air pollution and that new legislation was urgently needed to reduce motor vehicle traffic in city centres in the UK. Research in environmental toxicology is necessary to develop better monitoring systems for estimating personal exposure, to understand mechanisms by which pollutants exacerbate mucosal inflammation in asthma and to investigate the potential protective role of dietary antioxidant supplementation in asthmatics during pollution episodes.

The speakers largely achieved the difficult task of making their presentations simple, precise and understandable to medical specialists and non-specialists, and to scientists.

### SCIENCE-BASED COMPLEMENTARY MEDICINE

**Wednesday 22 January 1997**

Topics will include ◆ randomised assessment ◆ placebo and controls ◆ homeopathy ◆ manipulative treatments ◆ complementary medicine in cancer ◆ Chinese herbal medicine and malaria ◆ acupuncture.

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**Epithelial cell biology—its clinical impact**

A conference entitled 'Epithelial cell biology—a science impacting clinically' was held at the Royal College of Physicians of London on 6 March 1996.

**Growth control in epithelia**

Professor W J Gullick (Royal Postgraduate Medical School, London) gave an overview of the regulation of epithelial growth by positive growth factors and its clinical implications. The combination of a growth factor and its receptor induces changes in the receptor such as dimerisation and phosphorylation which activate second messengers and hence initiate intracellular signals. In pathological states overexpression of growth factor receptors on the cell surface, or mutations of these receptors, can cause unregulated transmembrane signalling independent of ligand binding, driving the cell towards cancerous growth [1]. These receptor abnormalities have a causal role in epithelial carcinogenesis and are not just an epiphenomenon. Growth factor receptor mutations in cancer can be used to indicate prognosis and in future may be used as targets for chemotherapy with monoclonal antibodies.

Dr R Akhurst (University of Glasgow) made the point, using transforming growth factor beta (TGF\textbeta) as an example, that one growth factor can have many different actions on epithelium. At various times TGF\textbeta can act as a potent growth inhibitor, mitogen, stimulator of extracellular matrix production, immunosuppressor, inducer of apoptosis and both a stimulator and inhibitor of differentiation. TGF\textbeta is also implicated in multistage skin carcinogenesis acting at an early stage as a tumour suppressor but at later stage enhances the progression of skin papillomas to carcinomas [2].

Dr G I Evan (Imperial Cancer Research Fund, London) gave an intriguing talk about the control of apoptosis and its relevance to carcinogenesis [3]. There is a dynamic equilibrium between cell proliferation, differentiation with consequent growth arrest, and cell death. Tumour production can arise from deregulation of cell proliferation or inhibition of cell loss. Apoptosis is a rapid, energy dependent form of controlled cell death. The c-myc proto-oncogene encodes for a central component of the cell proliferative machinery and deregulation of c-myc expression is implicated in carcinogenesis [3]. However, it can also
act as a potent inducer of apoptosis in cells deprived of growth factors or in the presence of cytostatic drugs. Survival factors modulate c-myc activity and protect the cell from apoptosis; they can be external growth factors, for example insulin-like growth factor 2 (IGF-2) and platelet-derived growth factor (PDGF), or internal, as in the case of the BCL-2 oncogene. A knowledge of these mechanisms is fundamental to our understanding of conditions featuring cellular over-proliferation or degeneration.

Epithelial repair and neoplastic change

Professor N Wright (Royal Postgraduate Medical School, London) presented a review of trefoil peptides, which are a family of peptides expressed in gastrointestinal mucus cells in both healthy and diseased tissue. These proteins share a structural motif and their compact secondary structure may protect them from enzymatic degradation [4]. In animal models of acute ulceration they have a cytoprotective effect and in the early phase of repair stimulate the migration of epithelium across the ulcer base. They also have a role in chronic ulceration, for example they are highly expressed at the edge of duodenal ulcers and are widely distributed in the intestine in inflammatory bowel disease [5]. Trefoil peptides may potentially be used with epidermal growth factor (EGF) to stimulate healing of non-infectious gastro-intestinal ulcers.

Professor J L Rees (University of Newcastle upon Tyne) reviewed his work on ultraviolet light induced carcinogenesis in squamous epithelia. Melanin pigmentation protects against this. There are two types of melanin, red and black melanin, the black form being more photoprotective. The proportion of black to red melanin is controlled by melanocyte stimulating hormone, which acts via its receptor, melanocyte 1 receptor (MC1R), on melanocytes to stimulate black melanin synthesis. The gene which codes for MC1R has variants in humans and these variants are commonly found in people with fair skin and red hair who tan poorly and are prone to skin cancer, but they are rarely found in people who tan easily and are resistant to skin cancer [6]. Polymorphic microsatellite markers have been used to determine the pattern of chromosome loss in skin cancers; in basal cell carcinomas there is usually loss confined to chromosomal arm 9q but in squamous carcinomas the chromosomal loss is more widespread and hence these chromosomal regions may contain genes important in squamous cell carcinogenesis [7].

Professor C Paraskeva (University of Bristol) spoke about the early events leading to colorectal carcinogenesis. This is a multistage, multifactorial event with both genetic and environmental factors [8]. Genetic factors include mutation of the APC and MCC genes, activation of the k-ras oncogene and loss of the tumour suppressor genes p53 and DCC. The Western diet, low in fibre, is an environmental factor which is linked epidemiologically to colonic cancer. Biological explanations for this association are emerging; for example, dietary fibre is fermented by colonic bacterial flora to the short-chain fatty acids butyrate, propionate and acetate, these compounds can induce apoptosis of benign and malignant cell lines at physiological concentrations in vitro in a p53 independent manner. This may explain the hypothesised anti-tumour effect of fibre on the bowel by killing potential tumour cells at an early stage [9].

Controlling epithelial growth

Professor I M Leigh (St Bartholomew’s and the Royal London Hospital School of Medicine and Dentistry) reviewed epithelial repair mechanisms. The stem cells in the dermis reside mostly around hair follicles. Following a skin injury they migrate into the wound bed and proliferate. Terminally differentiated keratinocytes produce many positive and negative growth factors. This biological function, including the upregulation of some of these factors in hyper-proliferative skin conditions, is not yet fully understood. Current tissue culture techniques make it possible to culture epithelial sheets from small skin biopsies and to regraft them on to wounds; in vivo models of skin wounding and keratinocyte transfer allow the detailed study of the regenerative process necessary to produce a fully functional replacement for the dermal elements of skin [10].

Professor C E M Griffiths (University of Manchester) gave an overview of the retinoid family, derived from vitamin A and widely used in dermatology. They mediate their actions through nuclear retinoic acid receptors and cellular retinoic acid binding proteins (CRABP-I,II); they are important in controlling cellular growth, proliferation and differentiation, and their potential for cancer treatment is being studied [11]. Synthetic retinoids and retinoid-mimetic compounds are being investigated; for example, liarozole is a compound which inhibits the p450 metabolism of all trans-retinoic acids, has retinoid-like effects in vivo and has anti-tumour effects, but has fewer side effects and a shorter half-life than retinoic acid [12].

Dr S G O'Brien (Hammersmith Hospital, London) reviewed antisense strategies in epithelial cell malignancy. Oligonucleotide sequences of DNA or RNA can be synthesised which are complementary to (ie are antisense to) a target gene’s product. When introduced into the cell they downregulate that gene’s product either by physical disruption of the ribosome mechanism or by inducing ribonuclease H. Ideally, an antisense molecule should enter the appropriate compartment of the cell efficiently, resist intra- and extra-cellular nucleases and be accessible to the target molecule. Potential epithelial cell targets to modulate cell growth and behaviour include EGF, PDGF, TGFβ, c-ERB2 and the ras oncogene [13].
The epithelium as a target for gene replacement

Dr D Geddes (Royal Brompton Hospital, London) argued that the ideal gene therapy for cystic fibrosis may be short lasting and easily repeatable. Because of their low toxicity and immune reactivity, liposomes have been chosen as the vector to carry the cystic fibrosis transmembrane receptor gene in the phase 1 clinical trial currently being conducted in Britain. In this trial, limited to the nasal epithelium of cystic fibrosis patients, no inflammation has been detected and in the majority of recipients there is partial correction of the electrophysiological abnormality which lasts one week. Low efficiency of transfection is a major problem, partly due to the mucus barrier on airway epithelium, but new types of liposomes are being developed to overcome this [14].

Professor G Y Wu (University of Connecticut School of Medicine) gave examples of his laboratory’s attempts to target therapeutic genes to the liver. The asialoglycoprotein receptor is highly specific for hepatic parenchymal cells, and ligands which attach to this receptor are endocytosed into liver hepatocytes. When DNA is attached to a ligand for the asialoglycoprotein receptor, the proportion of DNA reaching the liver following injection into a peripheral vein is increased from 17% to 85%. In a rat model of familial hyperbilirubinaemia (glucuronyl transferase deficiency) the DNA for glucuronyl transferase can be transfected into the liver and its protein detected for 72 hours, and if the rats are pretreated with colchicine to disrupt the endosomal degradative pathway of hepatocytes, the protein can be detected in the liver for 8 weeks and causes a significant reduction in serum bilirubin for 50 days. The relevant point was made that gene therapy for human disease will only be safe and effective when we fully understand the cellular mechanisms underlying it [15].

Professor D R Garrod (University of Manchester) gave the Watson Smith Lecture in which he outlined his work on desmosomes [16]. They are a widely distributed type of intercellular junction characterised by the presence of specific transmembrane glycoproteins and cytoplasmic plaque proteins. Autoimmunity to desmosomes in the skin is thought to cause certain types of pemphigus, a condition characterised by reduced cell to cell adhesion. In squamous and transitional cell carcinomas of the head and neck there is down-regulation of desmosomal expression which correlates with metastatic ability. This downregulation is not seen in colorectal carcinomas but temporary modulation of adhesiveness may play a part in the invasiveness and metastasis of the tumour [17].

Conclusion

The theme of this conference included basic research from the diverse specialities of gastroenterology and dermatology. The mechanisms that determine epithelial growth and regulation in the normal and diseased states are becoming understood. Gene targeting provides an opportunity to correct disease processes at an early stage and a potential cure for disease, but gene therapy techniques are still in their infancy. Many clinical trials are proceeding but as yet little clinical benefit has been demonstrated. The speakers at this conference emphasised that progress will be made through basic science research. Overall this was a well-attended conference which highlighted areas of promise for the future.

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