health affairs, but many aspects of the commission's work impinge on health.

This has necessitated the development of representative European medical organisations, usually from a coming together of national associations or specialty groups. These bodies communicate with the European Commission through the Standing Committee of Doctors of the European Community. The standing committee's agenda is wide ranging, recent meetings having considered regulating access to medical studies, specialist training, quality assurance in health care, product liability, regulating pharmaceuticals, ethical issues (AIDS, transplantation, and genome analysis), care of the elderly, and informatics in medicine. Some of these have been debated for 20 years without resolution. A working party has recently proposed ways of making the standing committee more effective.

The fragmented and partial involvement of the European Community in health matters is, however, largely responsible for the slow progress. The existence of substantial unemployment among doctors in the European Community (perhaps over 100 000 doctors) and the inability of some states to regulate access to medical studies for legal reasons have distorted the market for doctors and jeopardised standards of training. The commission has shown little understanding of this problem and no readiness to act. Standards of medical training, both basic and specialist, vary greatly between member states, but again, despite a succession of reports from the commission's advisory committee on medical training (a body made up of doctors), no attempt to tighten the minimal provisions set out in the medical directives has been made. Last year the BMA's annual representative meeting reaffirmed its support for a new directive on numbers of medical students and for adopting stricter controls on standards of training. The association's European Communities committee will be pursuing these policies in discussions with the Department of Health this year, but rapid progress seems unlikely without a restructuring of the European Commission and the creation of a health directorate, something which is not even under consideration at present.

Increasing medical migration does, however, raise several issues for consideration at a national level. Trainers who are responsible for doctors who have qualified in other European Community countries need to be aware of the different educational systems in the various countries. In particular, few continental medical schools provide as much clinical teaching as is usual in Britain, and trainees from the European Community may need some coaching in clinical skills at the beginning of their appointments. Occasionally, a trainer may

doubt the adequacy of a doctor's basic training. The BMA and the General Medical Council both have a role in monitoring standards of training in Europe but need to be made aware of trainers' anxieties if they are to fulfil it.

Freedom of migration within the European Community offers an opportunity for closer contact and valuable cross fertilisation of ideas between doctors in different countries, and it is desirable that the traffic should be two way. Several schemes exist to help British doctors wishing to train in other European Community countries, and these should be encouraged. At the same time, there is concern that training opportunities for European Community doctors in Britain are unnecessarily restricted by their ineligibility for visiting registrar posts and the requirement for them to compete for career registrar posts, even though most do not intend to make a permanent career here. A third category of registrar post needs to be devised that would cater for European Community trainees without destroying the principles underlying *Achieving a Balance*.

Although 1992 will not bring with it any new regulations directly affecting doctors, important decisions on matters affecting health care are increasingly being taken in Brussels. The BMA and the medical profession generally need to be aware of this and to respond accordingly. The recent decision by the BMA council to spend £12 500 of the association's funds to establish a permanent secretariat in Brussels for the Standing Committee of Doctors of the European Community is encouraging.¹ Recent moves to strengthen the association's international affairs division must continue, and inevitably more staff will have to be committed full time to monitoring and organising events and lobbying in Europe. The medical profession in Britain could have an important role in shaping European medicine in the twenty first century, but it will succeed in doing so only by developing the necessary awareness and commitment.

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Genetics and lung disease

Advances our understanding of emphysema, cystic fibrosis, and asthma

The delicate structure of the lung is frequently exposed to inhaled environmental insults. The body has an array of defences against them, including the mucociliary escalator of the bronchi, the scavenging macrophages of the alveolus, and the mechanisms for developing immunity, mediated by T and B lymphocytes. Disease ensues if environmental insults overwhelm initial barriers, when inflammatory pathways and the specific immune response may contribute to tissue damage. Infections of the lung have an enormous impact on mortality and morbidity worldwide, organic dusts can "drive" bronchial disease such as asthma or alveolar disease, inorganic dusts

produce the pneumoconioses, and cigarette smoke destroys lung tissue (emphysema) and causes lung cancer. Previously overshadowed, the role of genetic factors in lung disease is now becoming more evident with changing patterns of disease and as a result of the molecular genetic "revolution." Such developments are offering improved understanding of emphysema, cystic fibrosis, and asthma and also hopes for their more effective treatment and prevention.

Though most cases of emphysema are attributable to the overwhelming effects of heavy cigarette smoking, one distinct group of patients is unduly susceptible to the destructive

effect of cigarette smoke and hence to premature emphysema. They have deficiency of α_1 antitrypsin.¹ In the lung this globular protein inhibits the excessive actions of neutrophil and macrophage elastase, which cigarette smoke promotes.² When the lung is heavily exposed to cigarette smoke the protective effects of α_1 antitrypsin may be overwhelmed by the amount of elastase released or by a direct oxidative action of cigarette smoke on the α_1 antitrypsin molecule. Free elastase then digests and destroys the supportive tissue and walls of the alveoli to cause emphysema, the common and disabling disorder of smokers in their 60s. The subgroup of people who develop premature emphysema in their 30s and 40s have inherited defects of α_1 antitrypsin which are described using the protease inhibitor nomenclature, in which S and Z stand for important mutant forms causing significant deficiency of α_1 antitrypsin protein. Inheritance is autosomal recessive; one in 20 Britons may have a single copy of a gene associated with deficiency and one in 1000 have two such genes (often ZZ or SZ), and this leads to critical lowering (less than 40%) of serum α_1 antitrypsin concentrations and therefore premature emphysema in smokers.³ The diagnosis of premature emphysema should lead, with consent, to screening of younger siblings for deficiency of α_1 antitrypsin and hence to forceful recommendations on cigarette smoking. Antenatal diagnosis of a deficient genotype is possible with oligonucleotide probes that specifically recognise the S and Z variant genes.⁴ α_1 Antitrypsin protein, produced by recombinant genetic methods, when inhaled may adequately replenish concentrations in the lungs,⁵ but the effect of such treatment in preventing disease requires further research.

Cystic fibrosis is a disease of the exocrine glands in which viscid secretions of low water content cause gastrointestinal and pancreatic disorder and, by disrupting the bronchial mucociliary escalator, recurrent bronchial infection, progressive bronchiectasis, and respiratory failure.⁶ The prevalence of cystic fibrosis has increased owing to the availability of pancreatic enzyme supplements and powerful antibiotics, which allow more prolonged survival. Recent success in identifying the defect underlying this lethal, autosomal, recessively inherited disease by a programme of molecular genetic research,⁷⁻⁹ has vindicated the method of "reverse genetics."¹⁰ In this, the molecular pathology of inherited disease is investigated not by analysis of pathophysiological phenomena but by direct identification of the gene, based on chromosomal localisation or "geography."

Localising a gene locus is possible by observing genetic linkage—the phenomenon in which alleles from different genetic loci are co-inherited because of their proximity on a chromosome. In cystic fibrosis, genetic linkage was detected to a series of genetic markers (including restriction fragment length polymorphisms of DNA) located on the long arm of chromosome 7.¹¹ The application of diverse molecular genetic methods—including gene walking, jumping, cloning, hybridisation, and sequencing—finally identified a structural gene normally expressed in tissues affected in cystic fibrosis that showed a specific mutation (gD 508) in 70% of the cystic fibrosis chromosomes; three DNA base nucleotides were deleted from the gene and one amino acid, phenylalanine 508, from its protein product.⁹ The product has now been characterised as a membrane protein,⁸ the cystic fibrosis transmembrane conductance regulator, which controls the transmembrane transfer of an, as yet, unrecognised molecule. Cystic fibrosis transmembrane conductance regulator protein has been produced by genetic engineering methods,¹² and the

transfer of normal gene into cystic fibrosis cells corrects recognisable abnormalities—for example, impaired membrane transport of chloride ions.^{13,14} Antenatal diagnosis of cystic fibrosis by direct identification of D508 and other more recently recognised mutations is now becoming available,¹⁵ though the ethics and practicalities of screening couples for carriage of the cystic fibrosis gene have yet to be confronted. One approach to secondary prevention of the disease may be to replace the gene or protein product in affected tissue; progressive bronchiectasis is the predominant cause of death, and preliminary studies of transferring by viral particles normal cystic fibrosis transmembrane conductance regulator gene into bronchial epithelial cells have been reported.¹⁶

Asthma has long been recognised as having a familial component, most obviously in people with "extrinsic" asthma who may also suffer from rhinitis and eczema as a result of an allergic response (atopy) to common antigens such as the house dust mite or grass pollens. Reactions between such antigens and IgE, bound to mast cells in the respiratory mucosa, lead to intense local inflammation and hence the symptoms of asthma and rhinitis. Though the dosage of inhaled antigen and other factors (including cigarette smoke and pollutants) must influence the likelihood of clinical disease, recent family studies suggest that atopy (that is, allergic responsiveness to one or more common antigens) is dominantly inherited¹⁷; molecular genetic linkage studies indicate that the "atopy" gene locus is on chromosome 11.¹⁸ If this gene and its protein product can be successfully identified by the "reverse genetics" method so successfully used for cystic fibrosis, our understanding of allergic response in respiratory disease and the prospects for improved prevention and treatment of asthma should be greatly enhanced.

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