Eritreans in Asmara

male circumcision—rather like comparing rape with masturbation.

Educate families first

Female genital mutilation affects girls, often too young or scared to fend for themselves, who are almost invariably subjected to vigorous social and family pressure. It is those families that must be educated first, with discretion and sensitivity, and preferably by women from within their own communities. The only way that this harmful and mindless practice will be eradicated—both here and abroad—will be when parents wish to provide their daughters with the freedom, status, and physical safety that they deserve. For this to happen, women within those communities, many of whom will have been subjected to female genital mutilation themselves, must be empowered to speak out for what they want rather than that which they have come to expect.

Legislation against female genital mutilation may well have contributed to the practice going “underground” in this country, but it has not made it disappear. Declarations, discussion, and increasing media interest are making a valuable contribution to the understanding of female genital mutilation, but it will be those who are affected most who will eventually make the choice to eradicate the mutilation on our doorsteps.

Recent Advances

Respiratory medicine

R M du Bois

Clinical and molecular technological advances have transformed our understanding and knowledge of the complexities of respiratory disease over the past 20 years. Set against this background of rapid advances, this review will highlight some of the key recent developments during the past 12 months that are likely to influence clinical practice.

Asthma

Asthma is an important medical and social issue in the community, which will probably continue to have an impact on hospital resources throughout the 1990s. The number of admissions in England and Wales rose exponentially from just under 20 000 a year in the 1960s to about 100 000 in the 1980s.¹ Although the rate now seems to have stabilised, no evidence exists for a decreasing trend in hospitalisation or mortality.

Death rates continue to cause concern. Lang and Polansky reported patterns of mortality in Philadelphia and found an increase in the rate of death from asthma, from 1.68/100 000 population in 1969 to 2.41/100 000 in 1991.² Contrary to common belief, this increase was not related to air pollution, measures of which showed a substantial improvement over the same period. The most important risk factors for death from asthma were being poor and being black. A second study, in contrast, found no increase in the expected number of deaths associated with asthma in residents of Rochester, Minnesota, a community in which 96% are predominantly middle class and white.³ The geographical variation in the prevalence of asthma has been too pronounced and the population increase too rapid for these to be attributable to genetic factors,

suggesting that important environmental influences may be operating. Although multiple factors such as quality of health care, health education, and living conditions are likely to be important, the studies raise important questions about predisposition and causation.

RELEVANCE OF ENVIRONMENTAL FACTORS

If pollution is not the cause of the increased prevalence of asthma then what is? Do environmental factors have any relevance? Studies of asthma caused by agents inhaled at work support the influence of environmental factors.⁴ An investigation of staff working with laboratory animals found a direct relation between the measured concentration of allergens in the air and the incidence of new respiratory symptoms and positive results to skin prick tests for rats' urinary protein.⁵ In particular, there seems to be a “window of susceptibility” of 1-2 years, during which the manifestation of hypersensitivity develops and the modifying effects of smoking (enhancing the likelihood of developing an allergy) are at their peak. These observations are consistent with the knowledge that infant sensitisation may also occur within a critical period after first exposure to ambient allergens. A good example of the value of identifying cause is the prevention of asthma induced by soy beans in Barcelona. The unloading of soy beans in the port caused outbreaks of asthma; identification of the cause resulted in filters being installed in the silos, and this eliminated outbreaks that had previously caused major morbidity including admissions to an intensive care unit.⁶

In the context of an increase in asthma and in deaths

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BMJ 1995;310:1594-7

from asthma it is crucial that we learn more about causation. Increasing our understanding of the nature of the inherited predispositions and their interaction with environmental influences are central to any strategy designed to reduce the incidence of asthma.

Molecular genetics

Molecular science has provided clinical scientists with powerful tools to dissect and understand mechanisms of disease, particularly the chronic inflammatory diseases. Techniques such as micro-satellite mapping and restriction fragment length polymorphism analysis can be used to identify individuals at risk of disease. With single gene defects such as α_1 antitrypsin deficiency and cystic fibrosis this task is now fairly easy, and the means are being developed to correct deficiency by administering the protein (in the case of α_1 antitrypsin) or replacing the defective gene with a functional one (in cystic fibrosis) (see below). The issues are more complex for diseases that are not due to single gene defects, but genetic susceptibility factors are being identified.

A series of studies on asthma have now confirmed that several gene loci are involved in susceptibility to atopy and occupational asthma. A polymorphism for the gene encoding the β subunit of the high affinity receptor for IgE (*FcER1- β*) on chromosome 11q has been shown to be associated with atopy.⁷ In recent studies the same group of researchers has now shown that the transmission of the polymorphism is maternal.⁸ In this regard, two specific amino acid substitutions (at positions 181 and 183) of the IgE receptor β chain (isoleucine to leucine; valine to leucine respectively) were found to be associated with atopy and high serum IgE concentration when maternally transmitted. The importance of this polymorphism in atopy and asthma can be estimated only by investigation of its frequency and expression in community populations.

Marsh *et al* have found an association between high serum IgE concentration and five markers on chromosome 5q in the region of the interleukin 4 gene cluster: T_H2 driven immune responses which are now known to be important in the eosinophilic bronchitis of asthma are interleukin 4 dependent.⁹

Several studies have shown more specific gene relations between the antigens in the class II major histocompatibility complex responsible for the recognition of non-self and asthma. An HLA-DR2 linked haplotype was found to be associated with patients with asthma, but not rhinitis, caused by ragweed pollen¹⁰; alleles at the DQ locus (QB1*0503; DQB1*0201/0301) related to susceptibility to occupational asthma due to exposure to isocyanate whereas different DQ related haplotypes conferred protection; and predisposition to specific IgE induced by acid anhydride was associated with HLA-DR3 in another study of occupational hypersensitivity.¹¹⁻¹⁴

These studies, taken together with work that has shown a relation between class II major histocompatibility complex and diffuse lung disease in systemic sclerosis and rheumatoid arthritis, provide evidence of immunogenetic factors that predispose to chronic pulmonary inflammatory disorders. Although the mechanisms of chronic inflammation are complex, recognition of these genetically determined predispositions can lead to identification of at risk groups and focus studies on the inductive stages of disease, particularly when concepts of causation become clearer (see above). Future strategies for managing asthma will involve studies of polymorphisms and their relation to disease in populations (molecular epidemiology) and evaluation of outcome to determine the efficacy of any intervention.

Cystic fibrosis

Although rates of death from cystic fibrosis have improved considerably over recent years, largely owing to better treatment of lung infection and better nutrition, the average life span remains only about 30 years, with most patients dying from lung disease. Two new treatment approaches hold promise: aerosolised human recombinant DNase and gene therapy.

AEROSOLISED HUMAN RECOMBINANT DNASE

Airway secretions are viscous in cystic fibrosis; a significant component of the viscosity is DNA from inflammatory cells which are recruited to the bronchi. Endogenous DNases normally degrade DNA in extracellular sites but in cystic fibrosis the burden is too great. Against this background, human recombinant DNase was developed for administration with a nebuliser to patients with cystic fibrosis. Previous studies in vitro and pilot studies in vivo suggested that the approach was sound.¹² The findings of a multicentre, randomised, double blind, placebo controlled study in which 968 patients were enrolled provide further support for the use of the drug in cystic fibrosis. Comparisons of once and twice daily administrations of DNase for 24 weeks showed that the rate of exacerbations decreased, the measurements of forced expiratory volume in one second improved by on average 6%, and the drug was well tolerated.¹³ The findings have important implications. The cost effectiveness of human recombinant DNase is unknown—the cost of recombinant products is high—and long term efficacy must be shown through evaluative studies of outcomes.¹⁴ Current evidence, however, seems to support the use of DNase.

GENE THERAPY

Gene therapy involves the correction of an underlying pathophysiological defect through the transfer of genes. Since the gene for cystic fibrosis was first identified and cloned in 1989, remarkable strides have been made in applying molecular technology to the gene transfer for cystic fibrosis in humans. The gene is transferred in a "carrier" (in either a cationic lipid envelope known as a liposome or in an adenovirus). Adenovirus vectors are constructed such that the E1 region of the genome (needed for viral replication) is deleted and have been used to transfer a functional gene capable of protein production and correction of the cell's functional deficiency in vitro¹⁵⁻¹⁶; they have also been transferred efficiently in vivo.¹⁷⁻²⁰

These approaches are not without complications: the adenovirus can stimulate an inflammatory response due, at least in part, to local anamnestic immune responses to adenoviral protein.²¹⁻²² More recently, Caplen *et al* have used cationic liposomes to transfer the gene for cystic fibrosis to human nasal epithelium.²³ The deficit was partly restored temporarily, but, importantly, the transfer did not provoke a local inflammatory response.

Gene transfer will clearly be an important future therapeutic option, although much is still to be learned about the targeting and transfection efficiency of the vector and increasing the duration of gene expression.²⁴⁻²⁵

Adult respiratory distress syndrome

Overall mortality from acute lung injury severe enough to result in the adult respiratory distress syndrome is roughly 50%, although some recent studies show a figure nearer 40%. This depressing situation has stimulated considerable research aimed at improving mechanical ventilation or oxygenation through extracorporeal devices and at reversing or modulating the inflammatory responses that

amplify local injury and provoke subsequent fibrosis.

The findings of many of these studies have been disappointing, including the preliminary results from an international study of exogenous surfactant. Although the final report has not been published, a large international, randomised, placebo controlled trial of aerosolised surfactant in the adult respiratory distress syndrome induced by sepsis was reported to have been abandoned because of lack of efficacy.²⁶

In contrast, a study of the use of human recombinant interleukin 1 receptor antagonist was more positive.²⁷ Interleukin 1 is a proinflammatory cytokine released by several cell types, including the alveolar macrophage, during the early phases of inflammation. The use of a recombinant compound that inhibits interleukin 1 binding to its receptor is logical. Results from this placebo controlled multicentre study showed that interleukin 1 receptor antagonist reduced the death rate from 44% to 16% in patients receiving the highest test dose (133 mg/h) of active compound at 28 days. Further, larger clinical studies are needed to confirm this encouraging observation.

Imaging

Computed tomography, particularly with a high spatial resolution bone algorithm, has been used increasingly over the past 5-10 years to define lung disease with greater precision than is possible with conventional imaging techniques. Previous studies have concentrated on descriptive series of disease patterns and have concluded that high resolution computed tomography is more sensitive and specific than chest radiography in diagnosing diffuse lung disease. The result is that computed tomography has now replaced lung biopsy in the diagnosis and staging of selected cases of diffuse lung disease, and this is highly cost effective.

A recent study from Remy-Jardin *et al* of a large group of patients with rheumatoid arthritis confirmed that apparently occult and potentially life threatening disease can be identified and that computed tomography can readily discriminate the different forms of lung disease that may be present in this condition.²⁸ Further prospective studies on prognosis similar to those published on systemic sclerosis^{29,30} are needed to assess the prognostic value of computed tomography in rheumatoid arthritis and other rheumatological diseases.

LOW DOSE COMPUTED TOMOGRAPHY

Despite the major advance in imaging information provided by computed tomography, radiation burden has always been a concern. Muller's group in Vancouver has shown that low dose, thin section computed tomography can provide images that compare well to conventional dose computed tomography in diagnosis and are superior to chest radiographs.³¹

FIG 1—Large plugs of mucus in bronchiectatic airways in periphery of lower lobe; surrounding lung is of lower density because of reduced ventilation and thus perfusion (reproduced with permission³¹)

FIG 2—Top: Computed tomogram obtained during full inspiration shows mild bronchiectasis confined to posterobasal segment of left lower lobe and areas of minimally decreased attenuation (reproduced with permission³¹). Bottom: Computed tomogram obtained at end of expiration shows areas of decreased attenuation in left lower lobe and air trapping in a few secondary pulmonary lobules in right lower lobe (reproduced with permission³¹)

A high confidence rating for diagnosis was obtained in only 42% of radiographs but in 61% of low dose and 63% of conventional dose computed tomograms.

FUNCTIONAL ASSESSMENT

Other recent studies of computed tomography of the lung have continued to move from anatomical description to functional assessment, including evaluation of activity and prognosis. In sarcoidosis, unlike the correlations in fibrosing alveolitis, computed tomograms do not predict outcome, although some patterns—most notably, “ground glass” attenuation—reflect functional impairment.³²

Airways diseases can also be assessed functionally with computed tomography. In an investigation of 70 patients producing chronic purulent sputum, areas of decreased attenuation, indicative of small airways disease (fig 1), were seen in areas of lung with severe bronchiectasis but also in 69 of 406 lobar observations in areas of lung with no bronchiectasis (fig 2).³³ This suggests that small airways disease may be an early feature of bronchiectasis, which leads to more progressive injury and bronchiolar distortion. Longer term studies are needed to clarify this, but if confirmed as an early marker of disease, these changes shown with computed tomography could form the basis of the design of studies to prevent progression of disease.

OTHER IMAGING

Although conventional computed tomography is now well established, spiral computed tomography is rapidly becoming the standard way to image the thorax.³⁴ The advantages of truly contiguous sections is that totally seamless reconstructions are possible that may ultimately be used, for example, for virtual reality bronchoscopy imaging.

Magnetic resonance imaging continues to wait in the wings. The tantalising prospect of a non-ionising radiation means of imaging the lung parenchyma is

Recent advances in respiratory medicine

- Susceptibility to atopy and occupational asthma has been shown to involve gene loci: interrelations between such predispositions and environmental triggers are likely to provide insight into the causation of asthma
- Social factors are important determinants of increased rates of death from asthma
- The successful transfer of genes to human epithelium is a major breakthrough for the long term management of cystic fibrosis
- The introduction of recombinant DNase improves lung function and is likely to increase life span in patients with cystic fibrosis
- Cytokine antagonists reduce death rates from the adult respiratory distress syndrome
- High resolution computed tomography is transforming discrimination and prognosis in different forms of diffuse lung disease and can assess functional airways disease
- Spiral computed tomography produces seamless reconstructions of pulmonary structure that may herald virtual reality imaging

hindered by formidable technical problems in producing satisfactory images, although magnetic resonance imaging is as good as computed tomography in staging lung cancer.

Conclusion

The lung has several unique attributes. Combined, these have enabled striking advances in management to be made by harnessing huge technological advances to clinical problems, an approach which must continue if we are to use our limited health care resources most effectively and efficiently.

- 1 Office of Population Censuses and Surveys. *Hospital admissions for asthma, males and females combined, England and Wales 1962-91*. London: HMSO, 1994.
- 2 Lang DM, Polansky M. Patterns of asthma mortality in Philadelphia from 1969 to 1991. *N Engl J Med* 1994;331:1542-6.
- 3 Silverstein MD, Reed CE, O'Connell EJ, Melton LJ, O'Fallon M, Yunginger JW. Long-term survival of a cohort of community residents with asthma. *N Engl J Med* 1994;331:1537-41.
- 4 Newman Taylor AJ. Environmental determinants of asthma. *Lancet* 1995;345:296-9.
- 5 Cullinan P, Lawson D, Nieuwenhuijsen MJ, Gordon S, Tee RD, Venables KM, et al. Work related symptoms, sensitisation, and estimated exposure in workers not previously exposed to laboratory rats. *Occup Environ Med* 1994;51:589-92.
- 6 Anto JM, Sunyer J, Reed CE, Sabria J, Martinez F, Morell F, et al. Preventing asthma epidemics due to soybeans by dust-control measures. *N Engl J Med* 1993;329:1760-3.
- 7 Sandford AJ, Shirakawa T, Moffatt MF, Daniels SE, Ra C, Faux JA, et al. Localisation of atopy and the β subunit of the high affinity IgE receptor (Fc ϵ R1) on chromosome 11q. *Lancet* 1993;341:332-4.
- 8 Shirakawa T, Li A, Dubowitz M, Dekker JW, Shaw AE, Faux JA, et al. Association between atopy and variants of the β subunit of the high-affinity immunoglobulin E receptor. *Nat Genet* 1994;7:125-9.
- 9 Marsh DG, Neely JD, Breazeale DR, Ghosh B, Freidhoff LR, Ehrlich-Kautzky A, et al. Linkage analysis of IL-4 and other chromosome 5q31.1 markers and total serum immunoglobulin E concentrations. *Science* 1994;264:1152-6.
- 10 Blumenthal M, Marcus-Bagley D, Awdeh Z, Johnson B, Yunis EJ, Alper CA. HLA-DR2, (HLA-B7, SC31, DR2), and (HLA-B8, SC01, DR3) haplotypes distinguish subjects with asthma from those with rhinitis only in ragweed pollen allergy. *J Immunol* 1992;148:411-6.
- 11 Young RP, Barker RD, Pile KD, Cookson WOCM, Newman Taylor AJ. The association of HLA-DR3 with specific IgE to inhaled acid anhydrides. *American Journal of Respiratory and Critical Care Medicine* 1995;151:219-225.
- 11a Bignon JS, Aron Y, Lu LY, Kopferschmitt M, Garnier R, Mapp C. HLA class II alleles in isocyanate-induced asthma. *American Journal of Respiratory and Critical Care Medicine* 1994;149:71-5.
- 12 Ranasinha C, Assoufi B, Shak S, Christiansen D, Fuchs H, Empey D, et al. Efficacy and safety of short-term administration of aerosolized human DNase I in adults with stable stage cystic fibrosis. *Lancet* 1993;342:199-202.
- 13 Fuchs HL, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, et al for the Pulmozyme Study Group. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *N Engl J Med* 1994;331:637-42.
- 14 Davis PD. Evolution of therapy for cystic fibrosis. *N Engl J Med* 1994;331:672-3.
- 15 Zabner J, Couture LA, Smith AE, Welsh MJ. Correction of c-AMP-stimulated fluid secretion in cystic fibrosis airway epithelia: efficiency of adenovirus-mediated gene transfer in vitro. *Hum Genet* 1994;5:585-93.
- 16 Rosenfeld MA, Chu CS, Seth P, Danel C, Banks T, Yoneyama K, et al. Gene

transfer to freshly isolated human respiratory epithelial cells in vitro using a replication-deficient adenovirus containing the human cystic fibrosis transmembrane conductance regulator cDNA. *Hum Gene Ther* 1994;5:331-42.

- 17 Wilson JM, Engelhardt JF, Grossman M, Simon RH, Yang Y. Gene therapy of cystic fibrosis lung disease using E1 deleted adenoviruses: a phase I trial. *Hum Gene Ther* 1994;5:501-19.
- 18 Zabner J, Couture LA, Gregory RJ, Graham SM, Smith AE, Welsh MJ. Adenovirus-mediated gene transfer transiently corrects the chloride transport defect in nasal epithelia of patients with cystic fibrosis. *Cell* 1993;75:207-16.
- 19 Welsh MJ, Smith AE, Zabner J, Rich DP, Graham SM, Gregory RJ, et al. Cystic fibrosis gene therapy using an adenovirus vector: in vivo safety and efficacy in nasal epithelium. *Hum Genet* 1994;5:209-19.
- 20 Boucher RC, Knowles MR, Johnson LG, Olsen JC, Pickles R, Wilson JM, et al. Gene therapy for cystic fibrosis using E1-deleted adenovirus: a phase I trial in the nasal cavity. *Hum Gene Ther* 1994;5:615-39.
- 21 Yei S, Mittereder N, Tang K, O'Sullivan C, Trapnell BC. Adenovirus-mediated gene transfer for cystic fibrosis: quantitative evaluation of repeated in vivo vector administration to the lung. *Gene Therapy* 1994;1:192-200.
- 22 Yang Y, Nunes FA, Berenski K, Furth EE, Gonczol E, Wilson JM. Cellular immunity to viral antigens limits E1-deleted for gene therapy. *Proc Natl Acad Sci USA* 1994;91:4407-11.
- 23 Caplen NJ, Alton EFWF, Middleton PG, Dorin JR, Stevenson BJ, Gao X, et al. Liposome-mediated CFTR gene transfer to the nasal epithelium of patients with cystic fibrosis. *Nature Medicine* 1995;1:39-46.
- 24 Grubb BR, Pickles RJ, Ye H, Yankaskas JR, Vick RN, Engelhardt JF, et al. Inefficient gene transfer by adenovirus vector to cystic fibrosis airway epithelia of mice and humans. *Nature* 1994;371:802-6.
- 25 Crystal RG. The gene as the drug. *Nature Medicine* 1995;1:15-7.
- 26 Anzueto A, Baughman R, Guntupalli K, De Maria E, Davis K, Weg J, et al. An international, randomised, placebo-controlled, trial evaluating the safety and efficacy of aerosolised surfactant in patients with sepsis-induced ARDS. *American Journal of Respiratory and Critical Care Medicine* 1994;149:A567.
- 27 Fisher CJ Jr, Slotman GJ, Opal SM, Pribble JP, Bone RC, Emmanuel G, et al for the IL-1RA Sepsis Syndrome Study Group. Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: a randomized, open-label, placebo-controlled multicenter trial. *Crit Care Med* 1994;22:12-21.
- 28 Remy-Jardin M, Remy J, Cortet B, Mauri F, Delcambre B. Lung changes in rheumatoid arthritis: CT findings. *Radiology* 1994;193:375-82.
- 29 Wells AU, King AD, Rubens MB, Black CM, Hansell DM, du Bois RM. Functional impairment in fibrosing alveolitis after matching for CT findings, demographic factors, and smoking: a comparison between cryptogenic fibrosing alveolitis and the fibrosing alveolitis of systemic sclerosis [abstract]. *Thorax* 1994;49:395P.
- 30 Wells AU, du Bois RM. Prediction of disease progression in idiopathic pulmonary fibrosis. *Eur Respir J* 1994;7:637-9.
- 31 Soo Lee K, Primack SL, Staples CA, Mayo JR, Aldrich JE, Muller NL. Chronic infiltrative lung disease: comparison of diagnostic accuracies of radiography and low- and conventional-dose thin-section CT. *Radiology* 1994;191:669-73.
- 32 Remy-Jardin M, Giraud F, Remy J, Wattinne L, Wallaert B, Duhamel A. Pulmonary sarcoidosis: role of CT in the evaluation of disease activity and functional impairment and in prognosis assessment. *Radiology* 1994;191:675-80.
- 33 Hansell DM, Wells AU, Rubens MB, Cole PJ. Bronchiectasis: functional significance of areas of decreased attenuation at expiratory CT. *Radiology* 1994;193:369-74.
- 34 Paranjpe DV, Bergin CJ. Spiral CT of the lungs: optimal technique and resolution compared with conventional CT. *American Journal of Roentgenology* 1994;162:561-7.

ANY QUESTIONS

Does snuff dipping affect bronchial reactivity?

Snuff dipping is the regular use of snuff. Such regular use carries a risk of carcinoma of the oral mucosa. Cardiovascular risk factors and myocardial infarction are affected less by smokeless tobacco than by cigarettes. The association between cigarette smoking and bronchial reactivity has been hotly debated. There is now evidence that even passive exposure to cigarette smoke increases bronchial reactivity in people with and without asthma who have noticed symptoms after exposure to cigarette smoke. Seven out of 39 people without asthma who had reported upper respiratory tract symptoms after exposure to cigarette smoke showed an increase in non-specific reactivity six hours after exposure to tobacco smoke for four hours in an environmental chamber.¹ The changes are probably produced by products of the burning tobacco such as oxidants and particulates.

Given the difficulty in showing increased bronchial reactivity with inhaled cigarette smoke containing multiple constituents in a breathable form, it is unlikely that smokeless tobacco, chewed or sniffed, would be associated with demonstrable effects on the airways.² JOHN REES, consultant physician in London

- 1 Menon P, Rando RJ, Stankus RP, Salvaggio JE, Lehrer SB. Passive cigarette smoke—challenge studies in increase in bronchial hyperactivity. *J Allergy Clin Immunol* 1992;89:560-6.
- 2 Rao NM. Cardio-vascular and respiratory manifestations in tobacco chewers. *J Assoc Phys India* 1993;41:223-4.