The more acute problem is the distance that doctors are from their patients. Although most people report that distance is not an obstacle to access, for those most in need, including elderly and disabled people and those dependent on public transport, distance is often an important constraint. The negative effect of distance on the use of general practice services, both at the surgery and at home, has been repeatedly documented over the past 20 years.^{4,5} Knox has described how the changes in the locations of general practices in Aberdeen between 1950 and 1973 reinforced the geographical patterns of disadvantage.⁶ (Their amalgamation into group practices and their failure to devolve from city centre to peripheral housing estates made access more rather than less difficult.) Most general practitioners breathe a sigh of relief when new premises are built. Siting, however, is often a parochial affair, dependent on personal preference, the availability of a site, and the location of the list rather than on any wider considerations of geographical equity.

Under the present system some measure of social planning is at least conceivable. Patch and locality planning is beginning to emerge, adapting services to the needs of local populations and their providers.⁷ Whether this option to rationalise primary care services will remain is questionable. Perhaps we should be thankful for two things: firstly, that each patient does not have 87 different doctors as may happen in market driven systems that have abandoned gatekeepers, generalists, and continuity, instead favouring primary access to a multiplicity of specialists.⁸ And we should also be thankful that general practice is not yet beset by the problems of the education service, with basic provision limited by distance in the state sector and choice limited by ability to pay in the private sector. Equity, of either access or quality, does

not appear on the agenda of a government currently bent on establishing such a two tier service for primary care.⁹

Even forward thinking administrative authorities are floundering. There are neither adequate structures nor policies capable of dealing with coherent planning for primary care. In many places the destabilisation of hospital services has compounded the problem, and fewer managers and planners at district and regional levels are likely to add to the chaos.

Additional payments for deprivation have improved some unacceptably low medical incomes. But more substantial measures will be needed to prevent the widening divergence in access to and quality of primary care services, which is increasingly apparent both locally and regionally.¹⁰ Efficient distribution of resources is inextricably related to equity. Current policy does not address this, and, as Murray *et al* point out, the problems have not gone away.

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Clonality in Langerhans' cell histiocytosis

Women are more informative than men

Most human tumours are monoclonal, which suggests that they originate from a single cell. "Clonality" can be investigated by several techniques. In plasma a dominant monoclonal class of immunoglobulin suggests a neoplasm derived from a single altered plasma cell, which gives it a survival and growth advantage over non-neoplastic cells. In lymphoid malignancies, studies on rearrangements of genes coding for antigen receptors provide an excellent system of clonal markers, with consistent rearrangement of clonal immunoglobulin heavy chains (in B cell leukaemias and lymphomas)¹ and T cell receptor β chains (in T cell tumours). In other tumours careful cytogenetic and molecular analysis has shown consistent reciprocal chromosomal translocations and partial and complete chromosomal deletions or duplications which reflect tumour clonality as well as indicating stretches of altered sequences of DNA that may have a role in the initial neoplastic change. Cytogenetic and DNA analysis has not yet, however, provided clonal markers for many solid tumours.²

An alternative approach, applicable only to females, is to take advantage of the phenomenon of "X-inactivation" (X inactivation mosaicism).^{3,4} Early in the development of female embryos one X chromosome of each pair is randomly inactivated in each somatic cell. Some enzymes occur in two forms (isoenzymes)—if they are encoded by the X chromosome one form but not the other is represented in each cell.

The result of clonal expansion of a tumour cell reflects this event—only one form of the isoenzyme is expressed, as shown by Fialkow by using isoenzymes of glucose-6-phosphate dehydrogenase.³ These X inactivation studies have now been extended by molecular techniques, including polymerase chain reaction,⁵ and examination of very small samples of tissue is now possible.

Applying this approach, Willman and colleagues have clearly shown the clonal nature of Langerhans' cell histiocytosis (histiocytosis X).⁶ The disorder, first described over 100 years ago,⁷ had previously been known as Hand-Schüller-Christian disease, eosinophilic granuloma of bone, Letterer-Siwe disease, and self healing reticulocytosis. Abnormal Langerhans-like cells are pathognomonic of the condition, and they and their normal counterpart (the Langerhans histiocyte, which presents antigen) are rare in expressing the CD1a antigen. The clinical presentation and course of Langerhans cell histiocytosis vary from a spontaneously regressing solitary lytic lesion of bone to an intermediate form with lesions in bone, skin, mucous membranes, liver, and spleen with variable organ dysfunction to a lethal leukaemia-like disorder most often seen in infants.⁸

This variation has led to much speculation about the nature of the condition. A viral cause has been suggested, but ultrastructural and serological studies yield negative results,^{9,10} and no consistent evidence for an immune

deficiency or an abnormal immunological response has been found. The unexpected and intriguing finding of Willman and colleagues was that all 10 lesions from patients with Langerhans' cell histiocytosis whom they studied contained clonal populations of cells, with the proportion of clonal cells corresponding to the proportion of lesional Langerhans-like cells, whether from solitary lesions or extensive multisystem disease. The clonal nature of Langerhans' cell histiocytosis from the initiation of the disease process suggests that this is a true tumour and not a non-specific condition that predisposes to the development of neoplasia. The initial lesion may provide the necessary clues to the primary molecular event leading to tumorigenesis. Yu *et al* last year reported similar findings in tissues enriched by flow sorting of CD1a positive cells from three patients.¹¹ Sequential studies, to show that the "clonality" pattern is constant throughout the course of the disease, are needed, but these observations still provide the first solid clue to defining the aetiology of the condition in 100 years.

Somatic mutation

The hypothesis that Langerhans' cell histiocytosis arises from somatic mutation of DNA in a normal Langerhans' cell or precursor cell, leading to a neoplastic phenotype, must now be seriously considered, even though studies of clonality have not shown mutation. A single mutation that provides a growth advantage does not necessarily equate with malignancy, but the increased proliferation of cells may predispose to additional somatic mutations¹² and evolution in some cases to cancer.

Throughout this process the abnormal Langerhans'-like cells would retain the same X linked clonal marker. Varying clinical outcomes would depend on the number of mutations acquired, possibly on the role of immune surveillance and on the micro environment where the mutated cells are sited or to which they migrate. Additional gene mutations might cause clonal evolution of the disease from a benign to a more malignant invasive form.

Alone, monoclonality is necessary but not sufficient to define neoplasia. Benign parathyroid adenomas may be clonal,¹³ and lymphoproliferation associated with immunodeficiency may move through a benign polyclonal proliferative

disease to a monoclonal process, as shown by rearrangements of immunoglobulin heavy chains, eventually progressing to a malignant phenotype.¹⁴

Molecular technologies for examining complex genome changes, such as fluorescent in situ hybridisation and comparative genome mapping,¹⁵ are now at a stage at which they could be applied to Langerhans' cell histiocytosis and provide clues to the molecular pathology of this disorder. Willman and her colleagues have presented a powerful demonstration of the use of clonal analysis and an important direction for future research into Langerhans' cell histiocytosis.⁶ Application of X linked analysis to other disorders of histiocytes will be informative. In research to improve the prediction of prognosis and to suggest treatments samples of female tissue will be at a premium.

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Nutrition and lung health

Should people at risk of chronic obstructive lung disease eat more fruit and vegetables?

In striking contrast to the relation between diet and cardiovascular disease, the relation between diet and lung disease has not received much attention. Standard texts on nutrition make little or no reference to the respiratory system.¹ Two reasons help to explain this relative neglect. Firstly, the most common fatal diseases of the respiratory system—lung cancer and chronic obstructive pulmonary disease—are so clearly related to tobacco smoking that other factors have had little scrutiny. Secondly, even in those respiratory diseases in which nutrition is believed to play an important part (for example, cystic fibrosis and emphysema), the relation between nutrition and the disease is not directly causal. This has made investigation of the place of nutrition in the pathological process unattractive. Interesting new evidence is, however, beginning to emerge from sources as varied as

molecular biology laboratories and epidemiological units. This suggests that a relation may exist between intake of certain dietary elements and lung disease—and that the links may have a practical importance.

In 1990 an analysis of data from a representative sample of adults in the United States suggested that a high dietary intake and a raised serum concentration of vitamin C had a protective effect against respiratory symptoms.² Independent of cigarette smoking, an inverse relation was shown between bronchitis diagnosed by a doctor and dietary intake of vitamin C. Strachan *et al* compared 1502 non-smokers and 1357 smokers with no history of respiratory disease and found that consumption of fresh fruit in winter (and by implication habitual consumption of fruit) was related to ventilatory function not only in current smokers but also in lifelong