letters on the chart and the lack of an accurate or standardised scoring system. The variation in the ratio of the sizes of the letters between successive lines is somewhat arbitrary. The relatively large gaps between acuity levels at the lower end of the acuity scale on a Snellen chart (6/60-6/24) can result in gross overestimation and underestimation of visual acuity. This makes the assessment of change in visual acuity difficult. An irregular progression in the sizes of the letters also introduces changes in the scaling factor of the chart at reduced test distances that can alter the acuity score. The tradition of scoring Snellen acuity as the smallest line at which a majority of letters is correctly identified has recently been shown to restrict the sensitivity of the test to detecting changes over time.⁴

New charts

These problems⁵⁻⁷ have led to the development of alternatives to the Snellen chart.^{8,9} The most notable innovations are the use of a geometric progression in the size of the letters (that is, the change between lines occurs in uniform steps) and the introduction of an equivalent task for all acuity levels, ensuring that the only variable is the change in the angular size of the letter. This is achieved by using a set of letters that are equally legible and by presenting the same number of letters on each line of the chart.

These charts have been shown to provide accurate and reliable measures of visual acuity¹⁰ and have become the gold standard for measuring visual acuity in research.¹¹ Furthermore, their design allows the use of interpolated scoring systems that significantly improve doctors' ability to detect changes in acuity.⁴ In such systems equal weighting is given to every letter on the chart, and the score for each letter is incorporated in the overall acuity score. An important advantage of this type of chart is that it allows low levels of acuity to be measured with the same precision as higher levels

of acuity—a feature that the Snellen chart lacks. Indeed, a reliable measure of visual acuity may be more important in patients with reduced vision as they are likely to require treatment.

Gibson and Sanderson reported that the repeatability of measurements of visual acuity made with a Snellen chart was extremely poor, with up to 13% of subjects displaying discrepancies of two lines or more on repeated testing.⁶ Taking these results into consideration, doctors must be extremely cautious when assigning clinical importance to changes in acuity of two lines or less as these differences may simply reflect the inherent variability of the Snellen chart.

PAUL MCGRAW
Research fellow

Department of Vision Sciences,
Glasgow Caledonian University,
Glasgow G4 0BA

BARRY WINN
Professor

DAVID WHITAKER
Senior lecturer

Department of Optometry,
University of Bradford,
Bradford BD7 1DP

- 1 Pandit JC. Testing acuity of vision in general practice: reaching recommended standard. *BMJ* 1994;309:1408.
- 2 Flom MC, Heath G, Takahashi E. Contour interaction and visual resolution: contralateral effects. *Science* 1963;142:979-80.
- 3 Bennett AG. Ophthalmic test types. *British Journal of Physiological Optics* 1965;22:238-71.
- 4 Bailey I, Bullimore MA, Raasch T, Taylor HR. Clinical grading and the effects of scaling. *Invest Ophthalmol Vis Sci* 1991;32:422-32.
- 5 Lovie-Kitchin JE. Validity and reliability of visual acuity measurements. *Ophthalm Physiol Opt* 1988;8:363-70.
- 6 Gibson SA, Sanderson HF. Observer variation in ophthalmology. *Br J Ophthalmol* 1980;64:457-60.
- 7 Wick B, Schor CMA. Comparison of Snellen chart and S-chart visual acuity assessment in amblyopia. *J Am Optom Assoc* 1984;55:359-61.
- 8 Bailey IL, Lovie JE. New design principles for visual acuity letter charts. *Am J Optom Physiol Opt* 1976;53:740-5.
- 9 Ferris FL, Kassoff A, Bresnick GH, Bailey IL. New visual acuity charts for clinical research. *Am J Ophthalmol* 1982;94:91-6.
- 10 Elliot DB, Sheridan M. The use of accurate visual acuity measurements in clinical anti-cataract formulation trials. *Ophthalm Physiol Opt* 1988;8:397-401.
- 11 Sheedy JE. Standards for visual acuity measurement. In: *Eye care technology forum proceedings*. Bethesda, Maryland: National Institutes of Health, 1993.

Genetic traits in common diseases

Support the adage that autoimmunity is the price paid for eradicating infectious diseases

An important current topic of medical research is the localisation of genes implicated in the susceptibility to common chronic diseases such as insulin dependent diabetes, rheumatoid arthritis, and multiple sclerosis. This has been greatly facilitated by the use of the polymerase chain reaction to characterise polymorphic microsatellite markers and the advent of automated technology and computer software to construct high resolution genetic maps covering the entire genome.

A recent example of the success of these methods occurred in the genome-wide search in families for genes conferring susceptibility to insulin dependent diabetes.¹ Population studies, based on epidemiological principles, test the association of disease with specific genetic markers, and recent advances have also been made with this approach.

Most of these common diseases are clearly polygenic, involving several loci, and many population association studies leave little doubt that an appreciable genetic component of immunopathology lies in the major histocompatibility complex. This is a four megabase stretch of DNA (about 0.1% of the human genome) located on the short arm of chromosome 6 and containing up to 200 genes, many of which

are immunologically relevant. Within the major histocompatibility complex lies the gene for tumour necrosis factor α , a potent proinflammatory cytokine implicated in the pathogenesis and clinical manifestations of many inflammatory and infectious conditions.² In view of its chromosomal location and biological effects there has been speculation that polymorphism within the gene for tumour necrosis factor α may play a part in the genetic association of the major histocompatibility complex with at least some of these diseases.³

A biallelic polymorphism has been described in the gene for tumour necrosis factor α in a region that controls transcription.⁴ The rarer allele, TNF2, is part of the HLA A1-B8-DR3-DQ2 haplotype,⁵ which is associated with many autoimmune diseases.^{6,7} A preliminary study in coeliac disease, which is strongly associated with HLA-DQ2, found carriage of TNF2 in 96% of patients compared with 21% of controls, suggesting that a second susceptibility locus on this haplotype may lie close to, or within, the locus for tumour necrosis factor.⁸

In malaria high plasma concentrations of tumour necrosis factor α are associated with more severe disease, with the highest concentrations occurring in fatal cases of cerebral

malaria.⁹ A study of genotypes for tumour necrosis factor α in west African patients with malaria has shown that homozygosity for the TNF2 allele is associated with a sevenfold increased risk of death or severe neurological complications due to cerebral malaria.¹⁰ Furthermore, the TNF2 allele in gene assays directs higher levels of transcription of the gene compared with the common allele, suggesting that this polymorphism directly affects production of tumour necrosis factor α .¹¹

Malaria or systemic lupus erythematosus?

An interesting observation is the apparent protection from autoimmune diseases in areas of west Africa where malaria is endemic,¹² in contrast to the high incidence of systemic lupus erythematosus in Afro-American populations, who are mostly of west African descent.¹³ This has led to speculation that high concentrations of tumour necrosis factor α induced by malaria in west Africa may protect against systemic lupus erythematosus. In support of this idea, protective effects of recombinant tumour necrosis factor α in the (NZB $\times$ NZW)_{F1} mouse model of lupus have been cited,¹⁴ and infection of this strain with *Plasmodium berghei* prevents the development of the lupus-like disease.¹⁵ The TNF2 allele may be responsible for the lower incidence of lupus in Africa, resulting from endemic malaria, while the absence of this stimulant of the production of tumour necrosis factor α allows for the increased incidence of this disease in Afro-Americans. If this is correct it would be a good example of the old clinical adage that "autoimmunity is the price paid for eradicating infectious diseases."

Despite the adverse effects of homozygosity in malaria, TNF2 is maintained at a similar frequency in west African and northern European populations, which suggests that compensatory pressures in Africa exist to maintain the allele. Perhaps it has beneficial effects in other important infectious diseases such as measles, meningococcal disease, leprosy, or tuberculosis. There may also be heterozygous advantages.

The efficacy of treatment with antibodies to tumour necrosis factor α is being investigated in several diseases and has been shown to be beneficial in rheumatoid arthritis.¹⁶ Determining patients' genotype for tumour necrosis factor

before starting treatment may permit the selection of patients who are genetically predisposed to produce high concentrations of this cytokine and who might therefore benefit most from this treatment. The prospect of targeting treatment at those predicted to gain most therapeutic benefit clearly has important clinical and economic consequences, particularly in diseases of high prevalence such as malaria. Clinical benefits may result from this research by the end of the decade.

ANTHONY G WILSON
Senior registrar

GORDON W DUFF
Florey professor of molecular medicine

Section of Molecular Medicine,
Department of Medicine and Pharmacology,
University of Sheffield,
Royal Hallamshire Hospital,
Sheffield S10 2JF

- 1 Davies JL, Kawaguchi Y, Bennett ST, Copeman JB, Cordell HJ, Pritchard LE, *et al.* A genome-wide search for human type 1 diabetes susceptibility genes. *Nature* 1994;371:130-5.
- 2 Beutler B, Cerami A. The biology of cachectin/TNF—a primary mediator of the host response. *Ann Rev Immunol* 1989;7:625-5.
- 3 Jacob CO. Tumour necrosis factor α in autoimmunity: pretty girl or old witch? *Immunol Today* 1992;13:122-5.
- 4 Wilson AG, di Giovine FS, Blakemore AIF, Duff GW. Single base polymorphism in the human tumour necrosis factor alpha (TNF α) gene detectable by NcoI restriction of PCR product. *Hum Mol Genet* 1992;1:353.
- 5 Wilson AG, de Vries N, Pociot F, di Giovine FS, van de Putte LBA, Duff GW. An allelic polymorphism within the human tumour necrosis factor alpha promoter region is strongly associated with the HLA A1, B8 and DR3 alleles. *J Exp Med* 1993;177:557-60.
- 6 Pociot F, Wilson AG, Nerup J, Duff GW. No independent association between a tumour necrosis factor, a promoter region polymorphism and insulin-dependent diabetes mellitus. *Eur J Immunol* 1993;23:3050-3.
- 7 Tiwari JL, Teraski PI. *HLA and disease associations*. New York: Springer Verlag, 1985:5.
- 8 Mansfield JC, Holden H, Wilson AG, Holdsworth CD, Duff GW. Coeliac disease associates with a polymorphism in the promoter region of the TNF α gene and further defines the coeliac haplotype [abstract]. *Gut* 1993;34:S23-20.
- 9 Kwiatkowski D, Hill AVS, Sambou I, Twumasi P, Castracane J, Manogue KR, *et al.* TNF concentrations in fatal cerebral, non-fatal cerebral, and uncomplicated *Plasmodium falciparum* malaria. *Lancet* 1990;336:1201-4.
- 10 McGuire W, Hill AVS, Allsopp CEM, Greenwood BM, Kwiatkowski D. Cerebral malaria is associated with a polymorphism in the promoter region of the human TNF- α gene. *Nature* 1994;371:508-11.
- 11 Wilson AG, Symons JA, McDowell TL, di Giovine FS, Duff GW. Effects of a tumour necrosis factor (TNF α) promoter base transition on transcriptional activity [abstract]. *Br J Rheumatol* 1994;33:89.
- 12 Greenwood BM. Autoimmune disease and parasitic infections in Nigerians. *Lancet* 1968;i:380-2.
- 13 Ballou SP, Kahn M, Kusher A. Clinical features of systemic lupus erythematosus. Differences related to race and age of onset. *Arthritis Rheum* 1982;25:55-60.
- 14 Jacob CO, McDevitt HO. Tumour necrosis factor- α in murine autoimmune "lupus" nephritis. *Nature* 1988;331:356-7.
- 15 Greenwood BM, Herrick EM, Voller A. Suppression of autoimmune disease in NZB and (NZB $\times$ NZW)_{F1} hybrid mice by infection with malaria. *Nature* 1970;226:266-7.
- 16 Elliott MJ, Maini RN, Feldmann M, Long-Fox A, Charles P, Katsikis P, *et al.* Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumour necrosis factor α . *Arthritis Rheum* 1993;36:1681-90.

Health care rationing

The British approach seems likely to be based on guidelines

The recent decision of Cambridge Health Authority not to fund a second bone marrow transplant operation for a 10 year old girl has brought to public attention what has long been clear to doctors, managers, and politicians. Rationing or priority setting is an inherent feature of decision making in health care. This applies not only to Britain but to health services around the world.¹

A recent inquiry by the all party House of Commons health committee has reviewed the experience of purchasers in setting priorities and has made a series of recommendations to the government.² In its response the government has accepted the broad thrust of the committee's report and has set out how it intends to approach rationing in future.³

Experience in different countries suggests that there are two main approaches to rationing. Firstly, there is what might be described as rationing by exclusion. This is the approach

taken in Oregon, where the state health commission drew up a long list of condition-treatment pairs and ranked them in order of priority. With the resources available it has been possible to include 565 out of 696 treatments in the government funded Medicaid programme. The remaining treatments have been excluded from funding thus far, although this may change as the Oregon scheme evolves.

The second approach is to ration by guidelines. This is the approach taken in New Zealand, where a core services committee appointed by the government decided that rationing by exclusion, Oregon style, was neither helpful nor desirable. Instead the committee has staged a series of consensus conferences to draw up guidelines for the treatment of specific conditions and the provision of different services. New Zealand's approach is based on the belief that priorities are best set by ensuring that patients who can clearly benefit