iodine deficiency disorders when urinary iodine is measured.

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- 1 Valeix P, Zarebska M, Preziosi P, Galan P, Pelletier B, Hercberg S. Iodine deficiency in France. *Lancet* 1999; **353**: 1766-67.
- 2 Aghini-Lombardi F, Antonangeli L, Martino E, et al. The spectrum of thyroid disorders in an iodine-deficient community: the Pescopagano survey. *J Clin Endocrinol Metab* 1999; **84**: 561-66.
- 3 Delange F, Benker G, Caron P, et al. Thyroid volume and urinary iodine in European schoolchildren: standardization of values for assessment of iodine deficiency. *Eur J Endocrinol* 1997; **136**: 180-87.
- 4 Vermiglio F, Lo Presti VP, Castagna MG, et al. Increased risk of maternal thyroid failure with pregnancy progression in an iodine deficient area with major iodine deficiency disorders. *Thyroid* 1999; **9**: 19-24.
- 5 Berghout A, Wiersinga W. Thyroid size and thyroid function during pregnancy: an analysis. *Eur J Endocrinol* 1998; **138**: 536-42.

Corneodesmosin (MHC S) gene in guttate psoriasis

Sir—Psoriasis is strongly associated with the HLA-C region in different populations.¹ We have previously reported the association between chronic plaque psoriasis and an allele of the S (corneodesmosin) gene (position +1243),² located 160 kb telomeric to HLA-C.³ Michael Allen and colleagues (May 8, p 1589)⁴ show involvement of an S gene haplotype (allele 5) in chronic plaque psoriasis with the transmission disequilibrium test in 152 parent-offspring trios.⁴ Guttate psoriasis is a clinical subtype of psoriasis, characterised by showers of small round lesions occurring after acute streptococcal infections, which predominately affects children and young adults.

We did an association analysis of the same S gene haplotype and HLA-Cw6 in 103 patients with guttate psoriasis and 501 matched healthy controls. The results show a significant increase of the S gene haplotype and HLA-Cw6 in the guttate psoriatic cohort. The presence of HLA-Cw6 conferred a high relative risk of the disease (odds ratio 19.2 [95% CI 11.0-33.6], $p < 0.0001$). A weaker but significant association was found between S gene allele 5 and guttate psoriasis (odds ratio 6.2 [3.8-10.1], $p < 0.0001$). These findings indicate a role for the

HLA-C/S region in guttate psoriasis, as previously reported in chronic plaque psoriasis,^{2,4} and suggest that the Cw6/S locus is important in the pathophysiology of both forms of the disease.

To assess whether the effect of the S gene allele 5 was independent of Cw6, we stratified patients and controls according to their Cw6 status. The results showed that there was a weak but significant effect of the S gene haplotype in both the presence (odds ratio 2.7 [1.4-5.1], $p = 0.0033$) and absence (odds ratio 3.6 [1.1-11.8], $p = 0.0229$) of Cw6. This finding indicates that the S gene may be having an effect in guttate psoriasis that is independent of Cw6, supporting the conclusion of the studies in chronic plaque psoriasis.^{2,4}

Corneodesmosin is processed during keratinocyte differentiation by cleavage in its amino and carboxy terminal domains, which is thought to be a prerequisite for desquamation.⁵ Substitutions at positions +619 and +1243 give aminoacid changes P186S and L394S, respectively. These substitutions might interfere with the processing of the S gene product, thus contributing to the disruption of epidermal differentiation, which is a feature of psoriasis.

Other candidate genes in this region may be important and the S gene allele 5 could be acting as a marker for the susceptibility locus.

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- 1 Bhlerao J, Bowcock AM. The genetics of psoriasis: a complex disorder of skin and immune system. *Hum Mol Genet* 1998; **7**: 1537-45.
- 2 Tazi Ahnini R, Camp NJ, Cork MJ, et al. Novel genetic association between the corneodesmosin (MHC S) gene and susceptibility to psoriasis. *Hum Mol Genet* 1999; **8**: 1135-40.
- 3 Zhou Y, Chaplin DD. Identification in the HLA class I region of a gene expressed late in keratinocyte differentiation. *Proc Natl Acad Sci USA* 1993; **90**: 9470-73.
- 4 Allen MH, Veal C, Faassen A, et al. A non-HLA gene with the MHC in psoriasis. *Lancet* 1999; **353**: 1589-90.
- 5 Simon M, Montézin M, Guerrin M, Durieux JJ, Serre G. Characterization and purification of human corneodesmosin, an epidermal basic glycoprotein associated with corneocyte-specific modified desmosomes. *J Biol Chem* 1997; **272**: 31770-76.

From effect size into number needed to treat

Sir—Toshi A Furukawa (May 15, p 1680)¹ presents a conversion table that links the number needed to treat (NNT) with the effect size (ES). NNT is viewed as an intuitive and simple way to summarise the investment of time, energy, and resources that clinician and patients must make to achieve a specific therapeutic goal.^{1,2} However, we would like to point out that the magnitude of NNT, the reciprocal of absolute risk reduction, may not correctly reflect the clinical significance of a new treatment over the conventional ones.

For example, a randomised trial shows that a new treatment provides a 60% survival compared with 50% survival under the conventional therapy, so treating 100 patients with the new treatment will prevent (50-40=10) death. In other words, for every ten patients treated with the new treatment, one death is prevented, so NNT is ten. However, this calculation of NNT does not take account of the magnitude of the baseline mortality rate, which is an important factor in any interpretation of the clinical significance of a new treatment. If a new therapy can reduce the mortality of deadly variant Creutzfeldt-Jakob disease from 100% to 90%, this will be an important breakthrough. But for hospital-acquired pneumonia with 50% mortality under the current treatment, a new broad-spectrum antibiotic that reduces the mortality to 40% has much less impact. But in both situations, NNT will equally be ten. With NNT, the different clinical significance will not be appreciated appropriately.

The use of odds ratio of survival can overcome this pitfall. The odds ratio proportionally reflects the chances of both survival and death in both conventional and new treatment groups. Intuitively, the odds ratio is the comparison of two odds, ratio of probability of survival over death, between the new and the conventional treatment. A better treatment has a higher odds of survival. When there is no difference between two treatments, the odds ratio equals 1. A higher odds ratio away from 1 implies a higher superiority of the new treatment. In the previous example, in the case of 90% versus 100% mortality, the odds ratio is 23.3; whereas in the case of 40% versus 50% mortality, it is 1.5. The magnitude of the odds ratio clearly points out the difference hidden under NNT.

The odds ratio has long been used in case-control studies and multivariate logistic regression, but infrequently

used in randomised trials, apart from in meta-analyses.² The odds ratio is not favoured by many epidemiologists, who insist risk is the basic measurement in epidemiology and that this ratio is not directly linked to risk.³ But the odds ratio itself is a valid measure of treatment effect in randomised trials, with distinct statistical property.² From a clinician's point of view, the advantage of the odds ratio (a superior indicator of clinical significance) outweighs its disadvantage (not directly linked to risk). The NNT is actually not so informative as it promised to be; for clinical readers the odds ratio is a more suitable way to summarise the results of randomised trials.

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- 1 Furukawa TA. From effect size to number needed to treat. *Lancet* 1999; **353**: 1680.
- 2 Laupacis A, Sackett DL, Robert RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med* 1988; **318**: 1728-33.
- 3 Sinclair JC, Bracken MB. Clinically useful measures of effect in binary analyses of randomized trials. *J Clin Epidemiol* 1994; **47**: 881-89.

Sir—In meta-analysis, effect sizes are used for combining results of individual studies in which the same construct (eg, depression) is measured with different instruments or scales. The effect size (the difference of the mean effect of treatment and control group over the pooled SD) expresses the treatment effect in standard units (instead of original units) and the results of all studies can be combined by calculating a pooled effect size.

Interpretation of effect sizes, however, is difficult. Toshi Furukawa¹ presents a table to convert effect sizes into numbers needed to treat, which are easier to understand. Continuous data, however, will then be degraded to dichotomous data (with potential loss of information) and assumptions must be made regarding the cut-off value for

the calculation of the response rate of, for example, the control group, which may be arbitrary. Cohen's guideline that effect sizes of 0.2, 0.5, and 0.8 correspond to a small, medium, and large effect, respectively, is also arbitrary.^{1,2} Moreover, the clinical relevance of a treatment effect cannot be deduced from Cohen's interpretation.

A third means of facilitating the interpretation of effect sizes is to back-transform the pooled effect size by multiplying it with a typical SD of one of the instruments of interest.³ In this way the treatment effect can be interpreted in the units of that instrument. The result of this back-transformation, however, depends on which SD is judged typical. The table shows an example of three meta-analyses (by the fixed effects method)⁴ of studies with fictitious data comparing the effect of drug A and B for the treatment of high blood pressure. Let us assume that each study involved two groups of 100 patients and that drug B is more effective than drug A, leading to a 5 mm Hg lower mean blood pressure after treatment. Study 1 and 2 investigated homogeneous study populations (eg, with respect to age), indicated by small SDs, whereas studies 3 and 4 represent more heterogeneous study populations (with larger SDs). The pooled effect sizes would be 1.0, 0.3, and 0.6, respectively. Note that these figures roughly correspond with a large, small, and medium effect, respectively,² although a constant mean difference of 5 mm Hg was present. In the third meta-analysis (pertaining to all studies with varying SDs), back-transformation of the pooled effect size with various typical SDs produces treatment effects ranging from 3.2 mm Hg to 9.7 mm Hg (table). Only an SD of 7.7 would have given a correct back-transformed mean difference of 5 mm Hg, but there is no way of finding this required SD post hoc. Because methods for deriving a correct typical SD are lacking, back-transformation of effect sizes produces incorrect and confusing results.

Study	Mean (SD)		Mean difference	Effect size	Typical SD	Back-transformed mean difference
	Drug A	Drug B				
1	95 (5.0)	90 (5.0)	5.0	1.0		
2	105 (5.0)	100 (5.0)	5.0	1.0		
1+2			5.0	1.00	5.0	5.0
3	100 (15.0)	95 (15.0)	5.0	0.3		
4	110 (15.0)	105 (15.0)	5.0	0.3		
3+4			5.0	0.33	15.0	5.0
					5.0	3.2
Pooled results of studies 1-4			5.0	0.65	10.0	6.5
					15.0	9.7

All data (except effect size) are mm Hg. (data are fictitious).

Meta-analyses of various sets of studies

Translation of effect sizes into clinically meaningful units is a hazardous endeavour. Assessment of the clinical relevance of a treatment effect, based on effect size values only, continues to be a challenging undertaking.

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- 1 Furukawa TA. From effect size into number needed to treat. *Lancet* 1999; **353**: 1680.
- 2 Cohen J. Statistical power analysis in the behavioral sciences. Hillsdale, NJ: Erlbaum, 1988.
- 3 Gotzsche PC, Hammarquist C, Burr M. House dust mite control measures in the management of asthma: meta-analysis. *BMJ* 1998; **317**: 1105-10.
- 4 Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. *Stat Med* 1991; **10**: 1665-77.

Transit-time analysis in hepatic cirrhosis

Sir—Thomas Albrecht and colleagues (May 8, p 1579)¹ report the diagnosis of hepatic cirrhosis by transit-time analysis of ultrasonography. The investigators injected a contrast agent into a peripheral vein and did simultaneous ultrasound detection of the signal in a central hepatic vein. The short transit times seen in patients with cirrhosis could have a hepatosplanchnic origin, and be caused by the hyperdynamic central circulation, the presence of pulmonary shunts, or a combination of these, but the investigators were unable to elucidate these aspects.

Central circulation time (CCT) is reduced in cirrhotic patients, as shown by the indicator dilution technique with injection of radiolabelled albumin and sampling at the aortic bifurcation.² Furthermore, in a multivariate Cox regression model, CCT proved to have an independent prognostic significance in a population of consecutively referred cirrhotic patients who underwent hepatic venous catheterisation.³ Pulmonary arteriovenous shunts could shorten the central transit time. However, in a large consecutive study, Møller and colleagues⁴ saw only a small number of patients with cirrhosis (22%) who showed signs of decreased arterial oxygenation, which suggests that the reduced central transit time is mainly explained by a hyperdynamic circulation without pulmonary shunts.

We analysed data for 41 patients with alcoholic cirrhosis, whose cardiac output was measured by the indicator