Cystic fibrosis, breath pentane, and lipid peroxidation

SIR,—Dr Weitz and colleagues (April 20, p 933) report the value of breath pentane analysis as an index of increased lipid peroxidation in vivo. However, Weitz et al fail to indicate the potential shortcomings of the method, as we are beginning to see in the context of cystic fibrosis.

We have found that techniques involving hydrocarbon-contaminated inspired air, as used by Weitz et al, produce unreliably high results for breath pentane analysis. Increased quantities of breath pentane do not provide a specific marker of increased lipid peroxidation since they may accompany infection of the small intestine by colonic bacteria. Reassessment after one week of neomycin helps to assess the contribution of this possible artefact in our patients.[1] In addition, isolated measurement of breath pentane does not give a global view of free-radical oxidation of lipids in vivo because pentane is only one of several end-products in the lipid peroxidation pathway, and this method takes no account of the alternative lipid isomerisation pathway.[2] For these reasons some suggest that a panel of free-radical markers should be adopted, including those that reflect free-radical damage to non-lipid constituents of blood and tissues. With this approach we have found evidence for oxidative stress in patients with cystic fibrosis: increased quantities of the lipid isomerisation marker 9-cis, 11-trans linoleic acid (9,11 LA) are present in relation to concentrations of the natural fatty acid (9,12 LA) in both nasal epithelia and sera,[3] and there is a reduced ratio of bioactive ascorbic acid to total vitamin C in plasma.[4]

Increased amounts of pentane are unlikely to be of major pathogenetic importance. By contrast, other end-products of lipid oxidation such as hydroxy alkenals (involved in signal transduction and which are powerful chemotactins) and 9,11 LA (which could be expected to reduce membrane fluidity) may be more important. These effects could be relevant to the epithelial transport defects associated with cystic fibrosis.[5] Despite our reservations, breath hydrocarbon analysis does allow changes in lipid peroxidation as part of the disease process to be monitored. The dynamic nature of the investigation and its non-invasiveness are major assets.

Studies have been supported by the Cystic Fibrosis Research Trust.

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Epidermal ICAM-1 in psoriasis after long-term cyclosporin

SIR,—Dr Barker and colleagues (Jan 26, p 211) suggest that cyclosporin could act in psoriasis partly through the expression of epidermal adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1). This is a reasonable assumption because intralesional cyclosporin reduces expression of ICAM-1 in parallel with plaque regression.[1] Two weeks of oral cyclosporin reduces ICAM-1 endothelial cell expression if psoriasis has responded.[2] When oral cyclosporin was given in alopecia areata, terminal hair regrowth could be correlated with a fall in ICAM-1 expression by follicular epithelium.[3] However, the effect of long-term oral cyclosporin on ICAM-1 expression of keratinocytes in chronic plaque psoriasis has not been reported.

Keratinocyte staining for ICAM-1 with a monoclonal antibody (RR-1; gift of Prof T. Springer) was measured in 14 patients with psoriasis. 6 mm punch skin biopsy samples were taken before and after a three-month course of either 2·5 or 5 mg/kg per day cyclosporin. Clinical response was very good, with a fall in mean PASI (psoriasis area severity index) from 13 (SEM 1·8) to 2·7 (0·7). ICAM staining usually decreased, but in two patients there was a considerable increase, despite a satisfactory clinical response as shown by a fall in PASI score to under 20% of baseline. Both patients had relapsed to about 60% of their baseline PASI score, especially around the face, within a month of stopping cyclosporin. This compares with a relapse of 42% of baseline PASI for the whole group.

It seems that ICAM-1 expression in psoriasis can still arise despite a good clinical response, and that it is not essential to the action of cyclosporin. Variable staining for ICAM-1 in inflammatory diseases suggests that on its own it is not sufficient for leucocyte-mediated cytotoxicity to occur and that ICAM-1 expression is unlikely to be the "final common pathway" in the pathogenesis of such diseases.[4] Cyclosporin may be acting through other mechanisms such as interference with the activation of T lymphocytes, which is needed for their adhesion to ICAM-bearing epidermal cells. This corroborates experience in renal allografts where tubular expression of ICAM-1 can occur despite adequate treatment with cyclosporin to prevent rejection.[5] We are presently looking at other integrin molecules to see if better markers for the action of cyclosporin can be found.

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Growth references

SIR,—We are often asked about growth references for specific populations—for example, country, race, or disease specific growth curves. We describe here minimum criteria for such reference curves and discuss the complexity and cost of such development. We focus on weight and height reference curves but some of the arguments may also be applicable to other anthropometric measurements. The differences between a "reference" and a "standard" have been described elsewhere.[1] This letter focuses on the development and use of growth references that provide a point of comparison but do not necessarily define optimum growth.

Ideally, growth reference curves should be based on a representative sample of the population. Growth curves should not be developed from convenient sample data, such as clinic records. The representativeness (relative to the general population) of such data are questionable, and the accuracy of the weight, height, and age information generally cannot be verified. Longitudinal data are appealing, because of the potential for the determination of growth velocity, but collecting such data on a representative population is likely to be prohibitively expensive.

The sample size for developing reference curves must be adequate to ensure smooth and consistent extreme centile estimates. Because of distinct growth patterns, separate curves for males and females should be developed, with at least 100 males and 100 females at each month of age (at least for those less than 5 years of age).

Once the information has been collected and computerised, complex statistical software is necessary to smooth the data. There is always the potential to "oversmooth" or "undersmooth", a question that relates to whether irregularities in the unsmoothed curves are due to biological processes or to sampling variation. Creating normalised curves allows the results to be expressed as standard deviations (Z-scores) and percentiles.[2] To make the reference curves accessible to researchers and public health workers, new computer software should be produced to incorporate the new curves.

Data collection, smoothing, normalisation, and computerisation of new reference curves is expensive and time-consuming. Moreover, in countries where local growth curves have been developed through collecting information on well-nourished children, the curves generally have differed little from the existing Centers for Disease Control/World Health Organisation reference curves.[1] The use of local standards can also make it difficult to compare nutrition status between countries. Any secular changes in the growth of a population would necessitate updating the local standard.[1]

These practical and theoretical considerations obviate creating race or ethnic specific curves. Although race and ethnic groups may differ somewhat in average growth, the differences do not generally become apparent until mid-childhood. Furthermore, they are usually not substantial[1] and do not have a large effect on the prevalence of anthropometric abnormality (such as more than 2 SD below the median).

Disease-specific growth curves—for example, for children with AIDS or cystic fibrosis—present the above complexities plus others, such as varying disease severity. Advances in the detection and treatment of disease over time would also necessitate updating the reference. Disease-specific growth curves may not be practicable in most settings.

Although the current CDC/WHO international reference is not without limitations,[3] it is adequate and allows researchers to evaluate the growth pattern of individuals and assess the nutritional status of populations. We recommend that this reference be used in the nutritional assessment of individual children and populations. In developing countries the resources needed to produce a local growth reference might be more effectively used to meet other public health needs.

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Screening for congenital hip dysplasia

SIR,—Your April 20 editorial draws attention to the confusion surrounding congenital hip dysplasia.

The failure of clinical screening is not surprising in view of Leck's[1] estimate that there are twenty-two false-positive tests and one false-negative test for each true positive. Ultrasonography offers the possibilty of more accurate screening, but expense, difficulty of use, and variable results with this method have been given as reasons for persisting with clinical screening.[2] Ultrasound equipment is in regular use in departments of radiology, cardiology, and obstetrics. If use of the equipment available is rationalised, ultrasound screening for congenital hip dysplasia would not be expensive. Radiologists experienced in ultrasonography do not regard such examination of the infant hip as difficult.[3] A large pilot study of ultrasound screening of congenital dislocation of the hip

has been done in the UK, with one radiologist scanning 1001 infant hips.[4] It led to a substantial reduction in the number of hips requiring splinting and demonstrated hip abnormalities in two babies with normal physical examinations.

Clarke et al[5] who were quoted in the editorial as strong proponents of a selective approach to ultrasound screening concluded "We consider that a prospective long-term trial of ultrasound screening of all births is required". The diagnosis and managment of congenital dislocation of the hip could be greatly improved by such a trial.

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Percutaneous ethanol injection of parathyroid adenomas in primary hyperparathyroidism

SIR,—Dr Monzani and colleagues (March 23, p 743) report successful treatment of autonomous thyroid nodule with percutaneous ethanol injection. Ultrasonically guided percutaneous ethanol injection, which seems to be an efficient technique for inducing tumour necrosis,[1] has also been successful in the treatment of parathyroid tumours in secondary hyperparathyroidism.[2] We report that ultrasonically guided percutaneous ethanol injection can also be effective in primary hyperparathyroidism.

6 patients (mean age 79 years) with a confirmed diagnosis of primary hyperparathyroidism and contraindications for surgery (severe heart failure in 3, recent myocardial infarction in 2, and recent stroke in 1) underwent ultrasonically guided percutaneous ethanol injection of parathyroid adenoma. After the parathyroid adenoma had been located by echography, 0·5–1 ml ethanol (95%) was injected with a fine needle, leading to necrosis of the tumour. 5 of the 6 patients were successfully treated by one to three ethanol injections, with plasma calcium and phosphorus concentrations becoming normal during follow-up of 6–21 months. In 3 patients, calcium values were not completely normal after the first ethanol injection, suggesting an incomplete necrosis of the parathyroid adenoma and leading to one or two further ethanol injections several days later, until normal calcium values were achieved. Mean plasma calcium and parathyroid hormone (PTH) (PTH intact assay; normal range 20–80 ng/l) were significantly reduced and phosphorus was significantly higher after ethanol injection (table).

MEAN PLASMA CALCIUM, PHOSPHORUS, AND PTH BEFORE AND AFTER PERCUTANEOUS ETHANOL INJECTION OF PARATHYROID ADENOMA IN 5 SUCCESSFULLY TREATED PATIENTS

—	Before injection	After injection:				
		2 h	6 h	24 h	48 h	1 mo
Mean plasma calcium (mg/dl)	125 (17)	106 (4)	105 (2)	100 (5)	97 (3)	96 (7)
Mean plasma phosphorus (mg/dl)	21·6 (3·5)	..	27 (3·6)	28 (6·3)	34 (6)	34 (4·8)
Mean PTH (ng/l)	195 (70)	..	..	..	..	62 (17)

PTH = parathyroid hormone.
p < 0·01 (before vs after) for all three variables