Unicef, the Church of England, and the Royal College of Midwives, are calling on this company to change its practices. Can we all be wrong?

PATTI RUNDALL

Baby Milk Action,
Cambrige CB2 3AX

1 Fookes GA. Nestlé supports international code. *BMJ* 1993;**307**: 324-5. (31 July.)
2 Dillner L. Coffins greet Nestlé shareholders. *BMJ* 1993;**306**: 1563-4. (12 June.)

Functional hypoglycaemia postulated as cause of chronic fatigue syndrome

EDITOR,—In discussing the various causes of the chronic fatigue syndrome P K Thomas fails to mention one syndrome—namely, functional hypoglycaemia. We do not believe that such a syndrome exists, but in the Netherlands it has become a popular diagnosis among "alternative doctors," who claim that chronic fatigue is caused by inappropriately increased postprandial insulin concentrations with subsequent hypoglycaemia. This disease is linked to a so called allergy to endogenous glucose.

It is clear from this description that there is no scientific basis for this syndrome, and this is confirmed in the literature. Unfortunately, doctors and dietitians who recognise this syndrome have burdened their patients with complicated diets, requiring the elimination of all simple carbohydrates. When we asked an alternative doctor why we never see hypoglycaemia in these patients we were told that we do not measure glucose concentrations at the right moment. The diagnosis should be made after a standard oral glucose tolerance test with measurement of glucose concentrations three and five hours after glucose intake. "Overproduction" of insulin is thus shown by reactive hypoglycaemia.

The use of this non-physiological test to diagnose this syndrome has no scientific basis whatsoever.[2,3] Nevertheless, tens of thousands of patients are treated for this syndrome in the Netherlands.

LIESBERTH HEUFT
BERT BRAVENBOER
CATHARINA ZIEKENHUIS

Eindhoven,
Netherlands

1 Thomas PK. The chronic fatigue syndrome: what do we know? *BMJ* 1993;**306**:1557-8. (12 June.)
2 Zelissen PMJ, Erkelens DW. Zin en onzin bij de diagnostiek van spontane hypoglycemie. *Ned Tijdschr Geneesk* 1989;**133**: 1536-8.
3 Palardy J, Havrankova J, Lepage R, Matte R, Belanger R, D'Amour P, *et al.* Blood glucose measurements during symptomatic episodes in patients with suspected postprandial hypoglycemia. *N Engl J Med* 1989;**321**:1421-5.

Thyroid function in elderly people

Thyrotrophin releasing hormone test is useful

EDITOR,—In the management of patients with raised plasma or serum thyroid stimulating hormone concentration, with no history of thyroid disease, and not taking drugs known to influence thyroid function, Peter Rae and colleagues state that if after four to six weeks thyroid stimulating hormone concentration is <10 mU/l then the measurement of thyroid autoantibodies will help distinguish between those with underlying thyroid disease and those without.[1] This may not on its own be adequate as about 12% of most populations are positive for thyroid autoantibodies.[2]

The thyrotrophin releasing hormone test can be a useful dynamic function test to combine with the measurement of autoantibodies in identifying those patients to consider for replacement therapy. The test has been used to identify elderly patients with subclinical thyroid dysfunction that was not recognised by basal thyroid stimulating hormone values alone.[3] In another study the test had a positive predictive value of 81%.[4]

We performed thyrotrophin releasing hormone tests on 26 patients who had serum thyroid stimulating hormone concentrations between 4·3 and 10 mU/l on two separate occasions at least three months apart. Sixteen (62%) of them had a hypothyroid response, and the remaining 10 (38%) had a euthyroid response, and there was no correlation with basal concentration of the hormone. We have previously shown that response to the thyrotrophin releasing hormone test is not predicted by thyroid autoantibodies in a group of patients with subclinical hypothyroidism.[5] A hypothyroid response to thyrotrophin releasing hormone is a useful indication of the need for an early treatment in patients with positive results on thyroid autoantibody screens.

J BOLO-DEOKU
O A MOJIMINIYI
A H WILCOX
J L BARRON

Department of Chemical Pathology
and Metabolism,
St Helier Trust,
Carshalton,
Surrey SM5 1AA

1 Rae P, Farrer J, Beckett G, Toft A. Assessment of thyroid status in the elderly people. *BMJ* 1993;**307**:177-80. (17 July.)
2 Prentice LM, Phillips DIW, Sarsero D, Beever K, McLachlan SM, Smith BR. Geographical distribution of subclinical autoimmune thyroid disease in Britain: a study using highly sensitive direct assays for autoantibodies to thyroglobulin and thyroid peroxidase. *Acta Endocrinol* 1990;**123**:493-8.
3 Targum SD, Marshall LE, Magac-Harris K, Martin D. TRH tests in a healthy elderly population. Demonstration of gender difference. *J Am Geriatr Soc* 1989;**37**:533-6.
4 Brown CA, Hennessey JV. Clinical significance of mildly elevated thyrotropin levels with normal thyroxine levels. *South Med J* 1989;**82**:681-5.
5 Mojiminiyi OA, Wilcox AH, Rege VP, Barron JL. Use of the TRH test and thyroid autoantibodies in subclinical hypothyroidism. *Proc ACB National Meeting* 1992:82. (Abstract.)

Take account of iodine supply

EDITOR,—In their article on the assessment of thyroid status in elderly people Peter Rae and colleagues present diagnostic algorithms that seem to be useful in the management of elderly people living in areas that are not deficient in iodine.[1] We believe, however, that a different approach is required in areas that are deficient in iodine (for example, large parts of continental Europe).

Iodine deficiency leads to hyperplasia of the thyroid gland.[2] This could explain the greater frequency of clinical and subclinical hyperthyroidism compared with hypothyroidism (3·7% and 2·8% versus 1·7% and 2·0%) in screening studies of elderly patients from iodine deficient areas.[3] The prevalence of goitre in these studies was about 50%.[4] Autonomously functioning thyroid tissue was detected by suppressive quantitative technetium scintigraphy in about half of elderly patients with goitre.[5] The findings suggest that in these areas the probability of a low thyroid stimulating hormone concentration caused by autonomously functioning thyroid tissue but not by non-thyroidal illness of elderly people is greater than that in areas with a good supply of iodine. Even under these circumstances we agree that healthy elderly people without palpable goitre should not be screened for thyroid dysfunction. Nevertheless, we propose general screening of long term patients in geriatric hospitals.

We also agree that an elderly patient with a normal thyroid stimulating hormone concentration should not be investigated further for thyroid dysfunction. In a long term patient in a geriatric hospital who does not have palpable goitre, however, we would not regard a suppressed thyroid stimulating hormone concentration and normal thyroxine and triiodothyronine concentrations as indicating non-thyroidal illness; ultrasonography and, if necessary, radioisotopic scanning of the thyroid have to be performed to rule out or detect autonomously functioning nodules. In addition, we believe that even in the case of a subnormal but not suppressed thyroid stimulating hormone concentration in elderly patients, autonomously functioning thyroid tissue should be ruled out either by repeated follow up studies of thyroid stimulating hormone or by a thyrotrophin releasing hormone test (we still use this test for this purpose).[3] In iodine deficient elderly patients a small amount of autonomously functioning thyroid tissue presenting only as a subnormal thyroid stimulating hormone concentration should not be interpreted as hyperthyroidism. It may, however, have clinical consequences if iodine is given (for example, on angiography, in drugs that contain iodine such as amiodarone, and possibly prophylactically as iodinated salt or milk) since it may provoke clinical hyperthyroidism.[6]

I SZABOLCS
M GÓTH
L KOVÁCS
O DOHÁN
G SZILÁGYI

Department of Endocrinology,
Postgraduate Medical School,
PO Box 112,
Budapest,
1389 Hungary

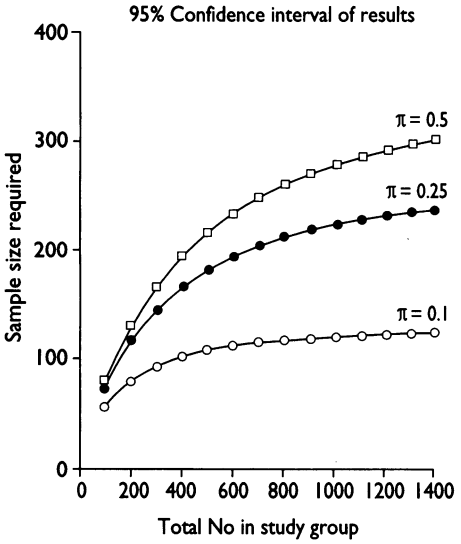
1 Rae P, Farrar J, Becker G, Toft A. Assessment of thyroid status in elderly people. *BMJ* 1993;**307**:177-80. (17 July.)
2 Stübner D, Gärtner R, Greil W, Gropper K, Brabant G, Permanetter W, *et al.* Hypertrophy and hyperplasia during goitre growth and involution in rats—separate bioeffects of TSH and iodine. *Acta Endocrinol* 1987;**116**:537-42.
3 Szabolcs I, Ploenes C, Bernard W, Herrmann J. Screening of geriatric patients for thyroid dysfunction with thyrotropin-releasing hormone test, sensitive thyrotropin and free thyroxine estimation. *Horm Metab Res* 1990;**22**:298-302.
4 Hintze G, Windeler J, Baumert J, Stein H, Robberling J. Thyroid volume and goitre prevalence in the elderly as determined by ultrasound and their relationship to laboratory indices. *Acta Endocrinol* 1991;**124**:12-8.
5 Baehre M, Hilgers R, Lindemann C, Emrich D. Thyroid autonomy; sensitive detection in vivo and estimation of its functional relevance using quantified high-resolution scintigraphy. *Acta Endocrinol* 1988;**117**:145-53.
6 Fradkin JE, Wolff J. Iodide-induced thyrotoxicosis. *Medicine* 1983;**62**:1-20.

Sample sizes in audit

EDITOR,—L Peter seems to anticipate the wish of every investigator by supplying a sample size chart for audit without asking any of the questions that statisticians usually ask—such as, what is the expected prevalence of a positive response?[1] An odd feature of the chart given is the unexplained kink in it. I wish to present a revised and expanded chart and to explain some limitations of using it.

When an investigator is sampling a nominal variable (such as whether or not a test has been carried out) he or she will obtain x positive responses out of n, and the ratio $p=x/n$ estimates a population prevalence π. Peter gives the example of a group of asthmatic patients registered with a practice and wishes to see what proportion have had their peak flow recorded in the past 12 months. The usual formula for a confidence interval has to be modified if the population from which the sample is taken is finite.[2] Peter's chart gives sample sizes so as to be able to estimate the 95% confidence interval to be five percentage points either side of the estimate.

The figure shows the revised sample sizes for $\pi=0{\cdot}1$, $0{\cdot}25$, and $0{\cdot}5$. Suppose that there were 400 patients with asthma in a practice and the proportion positive in the sample was expected to be $\pi=0{\cdot}5$. Then the required sample size, from the figure, is just under 200—that is, only about half of



Graph used to calculate sample size

the asthmatic patients would need to be sampled, at random.

The chart may seem counterintuitive in that the sample required to estimate $\pi=0{\cdot}1$ is smaller than that required to estimate $\pi=0{\cdot}5$ and yet one would expect a larger sample to be needed to estimate a smaller proportion. This arises because the variance of an estimated proportion is largest at $\pi=0{\cdot}5$. The width of the confidence interval, however, is fixed at 0·05, and so if $\pi=0{\cdot}1$ the allowable error is 50% of the estimate whereas if $\pi=0{\cdot}5$ the allowable error is only 10% of the estimate. The formula given by Machin and Campbell should be used for confidence intervals with other widths.[2]

This formula should not be used to test hypotheses. For example, to test the hypothesis that 50% of asthmatic patients had had their peak flow recorded in the past year one would use conventional tables, as described by Daly, in which the concept of the power of the test is also involved.[3]

M J CAMPBELL

Department of Medical Statistics and Computing,
University of Southampton,
Southampton General Hospital,
Southampton SO9 4XY

1 Peters L. Audit in primary medical care paediatrics. *BMJ* 1993;307:51-3. (3 July.)
2 Machin D, Campbell MJ. *Statistical tables for the design of clinical trials*. Oxford: Blackwell Scientific, 1987.
3 Daly LE. Confidence intervals and sample sizes: don't throw out all your old sample size tables. *BMJ* 1991;302:333-6.

Management of hyponatraemia

Differentiate between acute and chronic

EDITOR,—Allen I Arieff is correct to draw attention to the dangers of hypotonic fluids in the postoperative period.[1] He is incorrect, however, to state that neither the magnitude nor the rate of fall in serum sodium concentration is important in the genesis of brain damage. In his own series of 15 women who died or had permanent brain injury all had profound hyponatraemia and had been made acutely hyponatraemic.[2] Conversely, chronic severe hyponatraemia may be asymptomatic and minor perturbations of sodium do not cause damage.

Of most concern is Arieff's advocacy of hypertonic saline with loop diuretics for correcting hyponatraemia by up to 25 mmol/l in the first 24 hours. Sodium chloride is not innocuous, and correction of chronic hyponatraemia at a rate greater than 10 mmol/l/24 h risks long term neurological complications.[3] In addition, it is misleading to suggest that calculations of sodium deficit can be used to control the rate of correction accurately. Even in Arieff's own hands the rate of correction varied widely.[4] Rehydration with isotonic saline has resulted in rapid correction producing central pontine myelinolysis.[5] Even spontaneous correction can be rapid. Few authors would agree with Arieff that central pontine myelinolysis has nothing to do with hyponatraemia in most cases. In the 406 cases of central pontine myelinolysis that I identified in the literature severe hyponatraemia (≤120 mmol/l) had occurred in 179, moderate hyponatraemia in 69, normonatraemia in 12, and hypernatraemia in 24; the natraemic state was not recorded in the remaining 122.

Arieff fails to differentiate between acute and chronic cases in his treatment regimen or to address the underlying causes of the hyponatraemia. The opinion that "the rate of correction is not a factor in the genesis of hyponatraemic brain injury" is a minority view.

SIMON J ELLIS

Department of Clinical Neurology,
Radcliffe Infirmary,
Oxford OX2 6HE

1 Arieff AI. Management of hyponatraemia. *BMJ* 1993;307:305-8. (31 July.)
2 Arieff AI. Hyponatremia convulsions, respiratory arrest and permanent brain damage after elective surgery in healthy women. *N Engl J Med* 1986;314:1529-35.
3 Ellis SJ. The neurological complications of hyponatraemia [abstract]. *Neurology* 1993;43:A271.
4 Ayus JC, Krothapalli RK, Arieff AI. Treatment of symptomatic hyponatremia and its relation to brain damage: a prospective study. *N Engl J Med* 1987;317:1190-5.
5 Lundbom N, Laurila O, Laurila S. Central pontine myelinolysis after correction of chronic hyponatraemia. *Lancet* 1993;342: 247-8.

Author's reply

EDITOR,—Simon J Ellis's concerns seem largely to reflect anecdotally generated opinions rather than documented information. For example, data showing that either the magnitude or the rate of development of hyponatraemia correlates with brain damage do not exist. On the contrary, a recent prospective study of 739 patients who were hyponatraemic postoperatively clearly shows that neither factor has any relation to brain damage.[1]

Ellis expresses concern that treatment with hypertonic saline "risks long term neurological complications." Although earlier anecdotal reports speculated on this possibility, confounding variables, such as alcoholism and hypoxic brain damage, were not considered. Data are available on 164 consecutive hyponatraemic patients studied prospectively worldwide, in whom confounding variables were not present.[2] Rates of correction ranged up to 20 mmol/l/h. No patient suffered any neurological complication, which shows that the rate of correction is not a factor in the occurrence of brain damage.[2]

The contention that serum sodium deficit cannot be accurately controlled during correction of hyponatraemia is unsupported by any data. In over 200 consecutively treated patients the change in serum sodium concentration was essentially identical with that predicted from the suggested calculations,[3] and worldwide reports from virtually all other investigators over 40 years yield identical results.[3]

Ellis then suggests that treatment of hyponatraemia with hypertonic saline may cause central pontine myelinolysis. A few such anecdotal reports exist. Retrospective review of hyponatraemic patients diagnosed as having central pontine myelinolysis shows, however, that the diagnosis was incorrect about 85% of the time, while among patients with central pontine myelinolysis other conditions known to be associated with cerebral demyelination were present.[4] Central pontine myelinolysis has never occurred in any prospective trial of the treatment of hyponatraemia.[2] It is associated not with hyponatraemia but with other major medical illness, such as cirrhosis, alcoholism, cachexia, and burns.[2]

Ellis's belief that my statement that "the rate of correction [of hyponatraemia] is not a factor in the genesis of hyponatraemic brain injury" is a minority view is erroneous. In fact, when only controlled studies rather than anecdotal data are considered it is a unanimous view. All prospective studies have found no relation between the rate of correction of hyponatraemia and brain injury.[2] Ellis cites an unreviewed abstract in support of his undocumented claims.[5] The statistical test he used, however, is invalid for the available sample size, negating the conclusions.[5] Given that Ellis's overall mortality of 31% (26 of 84 patients died) is the highest ever reported worldwide,[5] I urge him to re-evaluate his nihilistic approach to the treatment of hyponatraemia.

ALLEN I ARIEFF

Geriatrics Research,
Veterans Affairs Medical Center,
San Francisco,
CA 94121, USA

1 Ayus JC, Wheeler JM, Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. *Ann Intern Med* 1992; 117:891-7.
2 Ayus JC, Arieff AI. Pathogenesis and prevention of hyponatremic encephalopathy. *Endocrinol Metab Clin North Am* 1993;22:425-46.
3 Arieff AI. Management of hyponatraemia. *BMJ* 1993;307:305-8. (31 July.)
4 Tien R, Arieff AI, Kucharczyk W, Wasik A, Kucharczyk J. Hyponatremic encephalopathy: is central pontine myelinolysis a component? *Am J Med* 1992;92:513-22.
5 Ellis SJ. The neurological complications of severe hyponatremia [abstract]. *Neurology* 1993;43:A271.

Generalised seizure due to terfenadine

EDITOR,—We recently reported on a 27 year old man who suffered his first tonic-clonic seizure while taking the antihistamine terfenadine.[1] In the absence of any other relevant precipitants or history, and in view of the temporal coincidence, we proposed a causal relation between the drug and the seizure. Twelve months later he has now had a second unprovoked seizure, which was not related to any drug use. It is therefore likely that he has primary generalised tonic-clonic epilepsy; terfenadine may not have been the cause of his original seizure.

This case illustrates the importance of long term follow up in the assessment of possible adverse drug reactions.

PHILIP TIDSWELL
ANNE E D'ASSIS-FONSECA

Pinderfields General Hospital,
Wakefield,
West Yorkshire WF1 4DG

1 Tidswell P, d'Assis-Fonseca A. Generalised seizure due to terfenadine. *BMJ* 1993;307:241. (24 July.)

Unexpected cardiac abnormalities in Lyme disease

EDITOR,—Evidence is growing that cardiac abnormalities may occur as a late complication of infection with *Borrelia burgdorferi* (Lyme disease).[1,2] We carried out detailed cardiac investigations on a series of patients with Lyme disease after a man developed reversible complete atrioventricular block and aortic valve regurgitation four and a half years after his initial, untreated illness.

We studied eight outpatients at the infectious diseases unit at Ruchill Hospital. The diagnosis of Lyme disease was based on clinical features of disseminated Lyme disease; a positive result of an