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Clinical economics

Although they may not be conversant with the methods of economic analysis, doctors are beginning to understand that there is a limit to what society should be asked to pay for the many benefits of modern drugs and other treatments, and that choices have to be made between medical interventions as well as between health and other equally deserving social services.[1]

In any system of health care financing the drug budget is a vulnerable item as it can be identified easily and always seems large. Other areas of health care delivery, such as laboratory tests and radiological and operative procedures, are not usually subject to similar scrutiny. The bureaucratic response to rising costs of drugs tends to be attempts to try to limit use by restrictions on the number of items that may be prescribed and by using an approach of cost minimisation, where the costs of different treatments are compared and the outcome measurement of effectiveness is simply forgotten. These policies run the risk of reducing cost-effective practices along with inappropriate ones and the resultant health service is a cheap instead of an efficient one. Cost-effectiveness rather than cost alone should be used to determine the content of medical care in most settings and not just in programmes for the poor.[2] The medical profession should promote this approach vigorously in order to influence the perspective of the decision-makers. It is important to maintain a broad range of drugs on the various formularies as long as they are reasonably cost-effective. Furthermore, tertiary care centres such as academic hospitals should at least have limited access to more expensive new products with improved side-effect profiles.

Some health interventions or treatments have been adopted on the basis of weak clinical evidence of effectiveness and without any formal economic evaluation. In fact, the office of technology assessment of the US Congress has estimated that 80-90% of the procedures implemented are not validated by randomised studies.[3] However, pharmaceuticals are well studied from an economic evaluation viewpoint since their approval is subject to the demonstration of efficacy and effectiveness. It is generally easier to withhold funding for a new technology than it is withdraw funding from an existing one. Now that universal precautions against HIV transmission to health care workers have been introduced in some hospitals, it will be very difficult to withdraw them, even though they cost $565 000 per additional life-year saved.[4] The ideal time to evaluate the cost-effectiveness of a technology is therefore before its widespread introduction into clinical practice. Arbitrary decisions to contain costs without taking into account cost-effectiveness are exemplified by the removal of effective gastric antisecretory drugs from formularies, which inevitably would result in a rise in hospital inpatient treatment for peptic ulcer disease.[5] Finally, economic analysis may prove to be an effective defence against direct political interference in the drug approval/listing process.[1]

Economic analysis is, however, still a developing science and there is a general lack of availability of people with the necessary skills either to undertake, or to scrutinise, economic evaluations, so that the range and quality of evaluations may be self-limiting.[6] Major areas of methodological inconsistency include measurement techniques used for utility or quality-of-life assessment and the methods used for estimating costs. Analysts who conduct the cost-effectiveness studies have to second-guess clinical judgement and may come up with results that run counter to conventional wisdom.[2] This may raise considerable scepticism within the medical profession. Some of the decision-makers have backgrounds in clinical pharmacology and the related basic sciences, and may regard clinical economics, with its reliance on assumptions and models, with suspicion. The particular objective of cost-effectiveness analysis is to maximise the net health benefit for a target population derived from a fixed budget. While its application is obvious from what may be called the societal or population viewpoint, it produces results that are counter-intuitive from the clinician's perspective. Individually clinicians are, appropriately, concerned solely with the effectiveness of a specific intervention for their patients and are not concerned with the benefit derived from spending those resources on other patients in the target population. This difference in perspective and objectives is important in understanding why many clinicians object to the use of cost-effectiveness analysis in setting policies.[2] Decisions that used to be the private domain of the medical profession must now be shared with individuals trained in mathematics and quantitative skills. With medical care there are crucial ethical issues to be taken into account. If resources are not limited the clinician's perspective works fine, because everyone gets everything anyway. If resources are limited, however, the societal perspective is correct, and the clinician's perspective will truly harm the health of the population.

The first government to set criteria for cost-effectiveness analysis that should be provided in support of applications for listing of new pharmaceutical products is that of Australia.[1] What is meant by the term cost-effectiveness analysis? Economic analysis is concerned with *how* to use resources, not *whether* to use them, i.e. how to allocate a budget to activities in a way that maximises the health of the population being served. The units for measuring the benefits and harms of a treatment are either natural units (e.g. life expectancy after oncotherapy) or some composite measure, such as quality-adjusted life-years or QALYs.[2] The latter is the most commonly used non-monetary measure of clinical outcome for economic evaluation. The QALY combines the person's length of life with their degree of well-being during that life, by using a health index, such as devised by Professor Rachel Rosser.[7] These indices appeal to economists because they produce specific numbers for the different states of well-being; each year of life can, therefore, be discounted by the amount of disability and distress suffered by the patient in that year. However, the QALY measure suffers from some limitations. In the field of mental health therapies QALYs are extremely difficult to measure; also in the elderly, due to their shorter life expectancy. When a disability constitutes a small proportion of a person's entire life, e.g. nausea, vomiting, postoperative recovery, and acute illnesses, QALYs are inappropriate.[8] The validity of the relationships between QALYs gained and intermediate health outcome measures remain to be established. Often the latter are non-linearly related to final health outcomes, e.g. changes in blood pressure or cholesterol in relation to a reduction in cardiovascular morbidity and mortality.[6] The techniques of economic evaluation and quality-of-life assessment are not as yet standardised, so that the calculated cost/QALY gained can vary considerably. It should also be noted that disease-specific utility scales are not acceptable for calculating QALYs as they do not permit comparison across programmes. Only instruments measuring the utility for general health states are acceptable. (Disease-specific utility scales may, however, allow comparison between different health interventions concerning the same disease; in these cases a general health index is not of great use because of poor sensitivity.) Finally, it is unlikely that data would be available

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on the effects of therapy on QALYs at the time listing decisions are made for new drugs.[1]

Cost-effectiveness ratios should be presented (e.g. cost per cure, cost per life-year, cost per QALY) and be calculated on an incremental basis, i.e. compared with the alternative, what extra unit of benefit is gained relative to the extra cost?.[9] Some suggest that the alternative product for comparison (or comparator) should be the least expensive currently available (e.g. generic price for alternative product used to treat the clinical problem), but the use of the most widely-used treatment as comparator is most likely to represent clinical work which a company might reasonably conduct.

Sophisticated economic evaluation adds costs to drug development. It considers not only the difference in the price of the pharmaceutical products themselves, but also all downstream events that result in differences in clinical outcome and costs. Furthermore, because most clinical trials of new medicines use, as comparator, placebo or baseline therapy, there may not be clinical trial results for the relevant 'head-to-head' comparisons. Thus, for the purpose of the economic evaluation, such comparisons will have to be synthesised using clinical data from a number of sources. Probably it would be more appropriate to restrict mandatory submission of cost-effectiveness analyses to 'breakthrough' drugs, i.e. those with which extension of life is a major outcome and for which significant premiums are requested versus current therapy. As such new chemical entities are becoming rarities, pharmaco-economics can then primarily be viewed from a medical perspective. Very often the acceptability of a particular procedure in economic terms is a matter of judgement. Economists cannot always say whether a particular treatment is desirable or not and medical input is essential to ensure that the comparisons made in submissions are reasonable and clinically relevant. It may also be necessary to revisit the economic analysis after a period of time to determine whether the predictions made before registration are fulfilled.[4]

Conventional medical wisdom aided by convincing peer-reviewed and published data should be able to gauge the relative cost-effectiveness of new drugs. Commonsense dictates that some health interventions are very cost-effective in increasing a patient's QALYs, e.g. simple preventive measures such as advice on diet or on cigarette smoking, and the reduction of blood pressure to prevent strokes. On the other hand, hospital haemodialysis for renal failure and brain surgery for malignant tumours are examples of very costly interventions bringing relatively small benefits. Economic analysis should be used for decision-aiding rather than decision-making.

Final decisions should continue to be made within a clinical rather than an economic framework. Evidence on comparative effectiveness and toxicity of new drugs in relation to the health needs of the community should be evaluated before considering the relative costs and the relationships between costs and effectiveness.[1] The medical profession has a social responsibility to ensure that limited resources available for health care yield the maximum benefit. Also in the private sector resources are becoming progressively more limited and time, tests and treatments will demand more and more economic decisions on a daily basis. Limitations imposed by the patient's insurance will increase his levels of co-payments. ('Willingness to pay', i.e. asking persons how much they would be willing to pay to receive a given health benefit such as avoiding pain or disability, is an example of cost-benefit analysis, where clinical effects are converted to financial units.) Patients who continue to demand that no cost be spared will simply have to pay the additional premium themselves.

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1. Henry D. Economic analysis as an aid to subsidisation decisions: the development of Australian guidelines for pharmaceuticals. *PharmacoEconomics* 1992; **1:** 54-67.
2. Eddy DM. Clinical decision making: from theory to practice: cost-effectiveness analysis. *JAMA* 1992; **267:** 1669-1675.
3. Goodman CS. The scope of US medical technologies assessment. In: *Assessing Medical Technologies — Institute of Medicine.* Chapt II. National Academic Press, 1985.
4. Stock SR, Gafni A, Bloch RF. Universal precautions to prevent HIV transmission to health care workers: an economic analysis. *Can Med Assoc J* 1990; **142:** 937-946.
5. Bulthuis R. Cimetidine and the cost of peptic ulcer in The Netherlands. *Effective Health Care* 1984; **1:** 297-309.
6. Drummond MF. Australian guidelines for cost-effectiveness studies of pharmaceuticals: the thin edge of the boomerang? Discussion Paper 88, Centre for Health Economics, University of York, 1991.
7. Rosser RM. A history of the development of health indicators. In: Teeling-Smith G, ed. *Measuring the Social Benefits of Medicine.* Office of Home Economics, 1984.
8. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *Can Med Assoc J* 1992; **146:** 473-481.
9. Detsky AS, Naglie IG. A clinician's guide to cost-effectiveness analysis. *Ann Intern Med* 1990; **113:** 147-154.

Frozen stored red blood cells and autologous transfusion

With the advent of human immunodeficiency virus (HIV) infection and the realisation that it may be transmitted by blood and its components, there is now a perception among many of the public that blood is unsafe despite rigorous screening for transmissible diseases. No medical procedure, however, has a 'zero risk' and blood and blood components are probably a great deal safer than most major surgical procedures provided proper precautions are taken in screening donors and their donations.

Nevertheless, requests for autologous transfusions have increased and blood transfusion services have introduced programmes to accommodate these requests. Autologous transfusion in the usual setting involves the withdrawal of a variable number of units (maximum of 4 - 5 over a 5-week period) from a patient prior to scheduled surgery, storage at 4 - 10°C, and reinfusion during and after surgery if necessary. In South Africa autologous transfusions comprise less than 1% of blood transfusions, although in the USA, by 1990, as much as 5% of all blood collected for transfusion was intended for autologous use.[1]

The Blood Transfusion Services in South Africa fully support the principles of autologous transfusion performed in this manner but do not recommend routine long-term storage of frozen blood for later autologous use, as advertised by a 'private' blood bank, and we should like to caution both the lay public and medical practitioners against the uncritical acceptance of this practice.

Techniques for the successful freezing and thawing of blood have been available since the 1960s. Blood designated for freezing is stored in special plastic packs and glycerol (as cryopreservative agent) is added, whereupon the packs are rapidly frozen. The frozen blood is then kept in liquid nitrogen or mechanical freezers with appropriate alarms. Provided that the blood is stored at –65°C or colder, the units may be stored for up to 10 years, and possibly longer.

To thaw the red cells the plastic pack is immersed

in a heated waterbath for 10 minutes, following which the cells are serially washed with saline solutions until all the glycerol is removed, otherwise the red cells will haemolyse on contact with the patient's plasma.

Processing time from the removal of the unit from the freezer to separation of the pack of deglycerolised cells from the washing apparatus requires an absolute minimum of 45 minutes. Quality control checks, transportation from the storage facility to the patient and grouping and crossmatch checks further delay issue of such a unit. The time required for these procedures plus transport to distant sites presents a major problem if frozen red cells are to be used in emergency situations. Furthermore, the red cells must be used within 24 hours of thawing; refreezing is not recommended. Of note is that approximately 20% of donated red cells are lost in the processing or are sufficiently damaged to allow for only a few hours' survival in the circulation after transfusion.[2]

Unless surgery is scheduled, the investment costs for possible later use of frozen blood is probably a waste of significant amounts of money. It is clear from the information given above that the chances are small that patients can receive frozen, thawed and washed red cells timeously following an emergency; the likelihood of success would diminish further with increasing distance between the emergency situation and the storage facility.

If elective surgery is required, most patients can more easily make arrangements to follow a standard programme to pre-deposit liquid red cell suspensions. This does not mean that frozen blood has no place in modern transfusion medicine. For those patients who have rare blood types or have been multiply allo-immunised, frozen blood is a necessity. Also for those rare persons who have experienced transfusion-associated anaphylactic reactions secondary to antibodies directed against IgA donor globulin, frozen stored red cells play a valuable role. For this reason, the Natal Blood Transfusion Service and the Western Province Transfusion Service have frozen blood storage facilities and patients who fall into these categories can obtain them from these services who keep an inventory of rare blood types. However, for routine speculative future need, frozen storage has a number of pitfalls and cannot be recommended.

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1. Silvergleid AJ. Pre-operative autologous donation: what have we learned? *Transfusion* 1991; **31:** 99-101.
2. Chaplin H. Clinical uses of frozen-stored red blood cells. In: Petz LD, Swisher SN, eds. *Clinical Practice of Transfusion Medicine.* 2nd ed. New York: Churchill Livingstone, 1989: 315-325.

Why fibrinogen should be measured as part of the coronary heart disease risk profile

Plasma fibrinogen was previously known only as a clotting factor and an acute-phase protein. Now, convincing evidence that raised levels of plasma fibrinogen are an independent risk factor for coronary heart disease (CHD) has come from six large prospective epidemiological trials.[1-6]

The Leigh study[2] in the UK followed a sample of 297 men, aged 40-69 years at entry, for a mean period of 7,3 years (range 0,1 - 16,1); new ischaemic events occurred in 40 of these men. In those with high total serum cholesterol levels, the incidence of ischaemic events was 6 times higher if fibrinogen levels were raised, and 12 times higher in those who had both high systolic blood pressures and elevated fibrinogen levels. The Northwick Park study[3] followed 1 511 white men aged 40 - 64 years at entry, for a mean period of 10 years (range 7,3 - 13,5), of whom 68 died as a result of an ischaemic event and 109 experienced a first major ischaemic event. This study demonstrated that a fibrinogen level elevated to one standard deviation above the mean increased the risk of an ischaemic episode within 5 years of entry by 85%, and that men with fibrinogen levels in the upper third of the population had a CHD risk 3 times higher than men with levels in the lower third. During the 12-year follow-up in the Framingham study[4] new cardiovascular events developed in 312 of the 1 315 subjects initially free of cardiovascular disease and for whom fibrinogen levels were available. Analysis of the results indicated that fibrinogen level was significantly related to CHD in both men and women. In the Caerphilly and Speedwell collaborative heart disease studies,[6] of the 4 860 middle-aged men who were followed for 5,1 years (Caerphilly) and 3,2 years (Speedwell), 251 developed a major ischaemic heart disease event. In this study the age-adjusted relative odds for ischaemic heart disease for men in the top 20% of the distribution compared with the bottom 20%, were 4,1 (95% confidence interval, 2,6 - 6,5) for plasma fibrinogen.

From the above it is clear that raised fibrinogen levels are a serious risk factor for CHD, and that they should be measured and treated. To do this successfully, an understanding of the factors influencing fibrinogen functions and of the determinants of plasma levels is necessary.

Plasma levels of fibrinogen will reflect the balance between synthesis and secretion on the one hand, and removal of fibrinogen from the circulation on the other; this will include catabolism, conversion to fibrin, uptake by platelets and possibly other tissues, and plasmin degradation of fibrin(ogen). Because fibrinogen is one of the acute-phase proteins, it is important when evaluating an individual's level, to exclude conditions which elicit the acute-phase response.

It seems that genetics may play a major role in determining fibrinogen concentrations. A Swedish study using Path analysis on 170 families showed that heredity accounted for 51% of the variations in plasma fibrinogen levels.[7] However, a number of studies support the contention that plasma levels are also influenced by lifestyle and other, probably in many instances unidentified, environmental factors.[8]

There is agreement in recent reviews[9] that smoking increase fibrinogen levels. Women tend to have higher levels than men, especially after menopause and when oral contraceptive drugs are used.[10] Levels are raised during pregnancy, and individuals who experience job strain or stress or who are from a lower social class tend to have high fibrinogen levels.[9]

Several abnormal physiological and disease states, in their own right independent risk factors for CHD, are associated with elevated plasma fibrinogen. These include diabetes mellitus, obesity, hypertension, renal disease, increased platelet aggregability, high low-density lipoprotein and low high-density lipoprotein cholesterol levels and hypertriglyceridaemia.[9] The effects

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of exercise, race or diet on fibrinogen levels are not clear. It is known that high levels of circulating free fatty acids and insulin-resistant states are associated with increased plasma fibrinogen.[11] It is therefore not inconceivable that dietary interventions which will reduce free fatty acid levels and improve insulin sensitivity could influence fibrinogen levels.

Definition of normal ranges for plasma fibrinogen, distribution in populations and standardisation of cut-off points where fibrinogen begins to contribute to CHD risk are areas which require urgent research. Values of 2,5 - 3,1 - 3,5 g/l are mentioned as 'normal'.[9] The methodology employed in determining fibrinogen levels influences results. Fibrinogen levels as low as 50% of 'normal', and even as low as 0,8 g/l, are sufficient for normal coagulation without bleeding tendencies. Levels usually observed are therefore well above those required for normal coagulation or optimal platelet function.[9] It seems that intra-individual or longitudinal variations in plasma fibrinogen are small, which suggests that a single determination may be sufficient (except when levels are raised because of an underlying inflammatory state).

There is as yet no universally accepted method of measuring fibrinogen. Of the different methods available, a number could satisfy requirements for standardisation, specificity, reliability and reproducibility. These include *inter alia* the total clottable gravimetric method, the functional methods of Clauss,[12] based on the rates of thrombin-induced clotting of Blombäck, and automated nephelometric determination. An enzyme-linked immunosorbent assay (ELISA) with a high specificity for intact fibrinogen has been developed.[13]

This method employs two monoclonal antibodies, one reacting with the N- and the other with the C-terminal domains of the Aα chain. It does not cross-react with the early products of fibrinogen degradation and will only detect fibrinogen molecules with at least one intact Aα chain. Additionally, viscometric, electrophoretic, colorimetric or radial immunodiffusion methods are in use in various research laboratories.

It therefore seems that definition and establishment of 'normal' ranges for plasma fibrinogen levels will only be possible after standardisation of methodology, or alternatively that normal ranges for a specific method should be indicated. The functional methods are presently the most widely used, but these methods are probably not as suitable as the ELISA for analysing samples from patients on fibrinolytic therapy. The cost-effectiveness of a particular method will further influence its suitability for a particular situation.

An important aspect of plasma fibrinogen determination is correct blood sampling procedures. Citrated or ethylenediaminetetra-acetic acid plasma from venous blood, obtained without stasis, is recommended. Because the relationship between clotting times and sample dilution is not linear, the functional methods are standardised on an exact 1:9 v/v (0,1 mol/l citrate: blood) dilution.

Because a high fibrinogen level increases the risk of atherogenesis and thrombus formation, and multiplies CHD risk in patients with high cholesterol levels or hypertension,[9] it seems reasonable to suggest that fibrinogen should be measured in high-risk patients and that raised levels should be treated. Non-pharmacological treatment such as cessation of smoking and a combination of diet and exercise seem to lower raised fibrinogen levels.[14] As yet there is no drug which selectively lowers plasma fibrinogen levels.[9] However, some lipid-lowering drugs, especially the fibrates[15] and drugs which lower triglyceride levels[9] also lower fibrinogen levels.

In South Africa we have a high incidence of CHD among several population groups. To improve prevention and treatment of the disease, we will have to increase research efforts to identify influences of lifestyle on fibrinogen levels, and to measure and treat raised levels in high-risk patients.

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1. Wilhelmsen L, Svärdsudd K, Korsan-Bengsten K, Larsson B, Welin L, Tibblin G. Fibrinogen as a risk factor for stroke and myocardial infarction. *N Engl J Med* 1984; **311:** 501-505.
2. Stone MC, Thorp JM. Plasma fibrinogen — a major coronary risk factor. *J R Coll Gen Pract* 1985; **35:** 565-569.
3. Meade TW, Mellows S, Brozovic M, *et al.* Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. *Lancet* 1986; **2:** 533-537.
4. Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and risk of cardiovascular disease: the Framingham study. *JAMA* 1987; **258:** 1183-1186.
5. Balleisen L, Schulte H, Assmann G, Epping P-H, Van de Loo J. Coagulation factors and the progress of coronary heart disease. *Lancet* 1987; **2:** 461.
6. Yarnell JWG, Baker IA, Sweetnam PM, *et al.* Fibrinogen, viscosity, and white blood cell count are major risk factors for ischemic heart disease: the Caerphilly and Speedwell collaborative heart disease studies. *Circulation* 1991; **83:** 836-844.
7. Hamsten A, Iselius L, De Faire U, Blombäck M. Genetic and cultural inheritance of plasma fibrinogen concentration. *Lancet* 1987; **2:** 988-990.
8. Ernst E. Regional variations in plasma fibrinogen levels. *Ann Intern Med* 1991; **115:** 329-330.
9. Cook NS, Ubben D. Fibrinogen as a major risk factor in cardiovascular disease. *Trends Pharmacol Sci* 1990; **11:** 444-451.
10. Ernst E. Oral contraceptives, fibrinogen and cardiovascular risk. *Atherosclerosis* 1992; **93:** 1-5.
11. Pickart LR, Thaler MM. Fatty acids, fibrinogen and blood flow: a general mechanism and hyperfibrinogenaemia and its pathological consequences. *Med Hypotheses* 1980; **6:** 545-547.
12. Von Clauss A. Gerinnungsphysiologische Schnellmetode zur Bestimmung des Fibrinogens. *Acta Haematol* (Basel) 1957; **17:** 237-246.
13. Hoegee-de Nobel E, Voskuilen M, Briët E, Brommer EJP, Nieuwenhuyzen W. A monoclonal antibody-based quantitative enzyme immunoassay for the determination of plasma fibrinogen concentrations. *Thromb Haemost* 1988; **60:** 415-418.
14. Nilsson P, Lindholm L, Scherstén B. Decrease of plasma fibrinogen by non-pharmacological treatment — a one-year study. *Perfusion* 1991; **4:** 437A.
15. Niort G, Bulgarelli A, Cassader M, Pagano G. Effect of short-term treatment with bezafibrate on plasma fibrinogen, fibrinopeptide A, platelet activation and blood filterability in atherosclerotic hyperfibrinogenemic patients. *Atherosclerosis* 1988; **71:** 113-119.

Brains and vitamins

'Upon what meat doth this our Caesar feed that he is grown so great?'

William Shakespeare, *Julius Caesar*

The practice of eating particular foods to produce euphoria, fan sexual desire, remedy impotence or obtain other desired effects, dates back thousands of years.

As children we were told of the unspeakable things that little boys are made of, and of the delectable viands from which little girls are fashioned. We were told to eat crusts to make our hair curl, beetroot to give colour to our cheeks, carrots to make our eyes sparkle, parsley and onions to promote breast development, fish to nourish brains, and an apple a day to keep the doctor away.

Are the messages given out by the media nowadays more explicit and telling than the folklore and anecdotal narratives of the past? Tony Smith[1] (Associate Editor, *British Medical Journal*) maintains that 'The messages is mainly: eat (or drink) this and you will enjoy it, or be happy or be seen to be successful, or beautiful, or sexually attractive: only very seldom is there any implication that the product will improve your health. And when the message does contain explicit nutritional comment, depressingly often the

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content is either false or nonsensical.'

There is currently tremendous interest and controversy surrounding the effect of various vitamins and mineral salts on the improvement of intelligence in schoolchildren. Early in 1988 the *Lancet* published a study by Benton and Roberts[2] which claimed that 90 Welsh schoolchildren aged 12 - 13 years experienced an improvement in non-verbal intelligence after 8 months of multivitamin and mineral supplementation. However, two subsequent studies, carried out in London and Dundee, failed to confirm these findings.

In the London study, 227 children aged 7 - 12 years were investigated.[3] The composition of their diets was determined. Each child completed tests of verbal and non-verbal intelligence, and was then randomly allocated to one of two groups after matching for age, sex, IQ and height. In a double-blind trial lasting 28 days, one group received a vitamin/mineral supplement daily, and the other group a placebo. On re-testing, there were no significant differences in performance between the two groups, nor consistent correlations between test scores and micronutrient intakes.

In Dundee, a randomised controlled trial was carried out for 7 months on the performance of 86 schoolchildren aged 11 - 13 in tests of reasoning.[4] A small, non-significant difference between the control and supplementation groups was found in a non-verbal test, although not in tests of reasoning.

In a study done in Belgium by Benton and Butts,[5] 167 13-year-olds received either a placebo or a vitamin/mineral supplement in a double-blind procedure. Pupils were sub-divided into groups according to the quality of their diets. Only the boys in the poor diet group (and not the girls) responded more positively in intelligence tests after supplementation.

In early 1991, a study sponsored by the scientific directorate of the Dietary Research Foundation was done on 410 American children, aged 10 - 12 years.[6] Sub-groups were fed either a placebo or increasing amounts of a multivitamin and mineral mixture. After treatment, both groups performed better. However, the response was not related to dose in linear fashion. In those children who were fed pills containing half or twice the recommended dietary allowances (RDA) for the USA, little response above placebo levels was elicited. It was only in the group receiving pills containing 100% of the RDA that anything of interest was observed. As an editorial in *Lancet* asked, 'Is it plausible that intelligence would be so precisely sensitive to a given vitamin intake?'[7]

Obvious drawbacks, as stressed by Whitehead,[8] include the short-term nature of the trial, the lack of details about subject exclusion from test groups and group comparability, inconsistencies between tests of non-verbal intelligence, and lack of follow-up tests once the subjects were taken off the supplements. Whitehead maintained that no physiological explanation exists for vitamin and mineral supplementation's affecting brain function in a well-nourished subject. As to other criticisms and comments, Cole and Whitehead[9] instanced 'the improvements (in IQ) which occurred in all of the schools sampled. Of the four schools studied, Riverbank is an economically depressed area in which a substantial proportion of the residents receive public assistance, while Oakdale contains students from among the most expensive homes in the country, with nearly half of them having IQs over 120. The suggestion that these two samples of children should have similar rates of vitamin deficiency is clearly unlikely.' Some might say preposterous.

Understandably, given the sensitivity of the topic, there has been considerable correspondence published in medical journals. Both the *Lancet* and the *British Medical Journal* have allowed ample space for argument,[10-13] and there has been lively discussion in *Nature*.[14-17] The authors of the various studies all agree, and certainly all the critics insist, that larger and better conducted clinical trials are mandatory.

What is the relevance of all these studies to local dietary intakes and intelligence levels? Interethnically, huge differences prevail with regard to socio-economic conditions, home environments, the calibre of school teachers, and numerous other respects. All parents wish fervently for a means to improve their children's IQ. Yet the intensity of the controversies mentioned certainly cautions them to go gently before purchasing expensive supplements. In the study by Schoenthaler *et al.*,[6] the improvements in poor and rich groups were much the same. This especially underlines the need for caution.

In our view, the general international dietary guidelines,[18,19] which recommend the eating of more plant foods, are very sound. Plant foods certainly supply more vitamins. Experts call for the doubling of bread consumption, principally wholemeal bread, the doubling of vegetable consumption, and an increase in the consumption of potatoes and fruit, each by half.[19-21] Adoption of these changes would go far, not only toward possibly increasing IQ levels in children, but also toward raising anti-oxidant levels in blood and tissues.[22] Future susceptibility to degenerative diseases, especially coronary heart disease, stroke, and diet-related cancers, would hence be reduced.

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1. Smith AJ. Nutrition and the media. In: Turner MR, ed. *Preventive Medicine and Nutrition*. London: Academic Press, 1981: 207-214.
2. Benton D, Roberts G. Effect of vitamin and mineral supplementation on intelligence of a sample of schoolchildren. *Lancet* 1988; **1:** 140-143.
3. Nelson M, Naismith DJ, Burley VJ, Gatenby SJ, Geddes N. Nutrient intakes, vitamin supplementation and intelligence in British schoolchildren. *Br J Nutr* 1990; **64:** 13-22.
4. Crombie IK, Todman J, McNeill G, Florey C du V, Menzies J, Kennedy RA. Effects of vitamin mineral supplementation on verbal and nonverbal reasoning of schoolchildren. *Lancet* 1990; **335:** 744-747.
5. Benton D, Butts JP. Vitamin/mineral supplementation and intelligence. *Lancet* 1990; **335:** 1158-1160.
6. Schoenthaler SJ, Amos SP, Eysenck HJ, Peritz E, Yudkin J. Controlled trial of vitamin-mineral supplementation: effects on intelligence and performance. *Personal Individ Diff* 1991; **12:** 343-362.
7. Anonymous. Brains and vitamins (Editorial). *Lancet* 1991; **337:** 587-588.
8. Whitehead RG. Vitamins, minerals, schoolchildren, and IQ. *BMJ* 1991; **302:** 548.
9. Cole TJ, Whitehead RG. Vitamins and IQ. *BMJ* 1991; **302:** 1206.
10. Schoenthaler S. Brains and vitamins. *Lancet* 1991; **337:** 728-729.
11. Yudkin J. Vitamins and IQ. *BMJ* 1991; **302:** 724-725.
12. Schoenthaler S. Vitamins and IQ. *BMJ* 1991; **302:** 1020-1021.
13. Peto R. Vitamins and IQ. *BMJ* 1991; **302:** 906.
14. Anonymous. Nature says: vitamins and IQ. *Nature* 1991; **350:** 2-3.
15. Aldous P. Publication ethics — IQ data controversy. *Nature* 1991; **350:** 5.
16. Blinkhorn S. A dose of vitamins and a pinch of salt. *Nature* 1991; **350:** 13.
17. Pauling L. Vitamins and intelligence tests. *Nature* 1991; **353:** 103.
18. Peterkin BB. Dietary guidelines for Americans. *J Am Diet Assoc* 1990; **90:** 1725-1727.
19. Panel on Dietary Reference Values of the Committee on Medical Aspects of Food Policy. *Dietary Reference Values for Food, Energy and Nutrients for the United Kingdom*. London: HMSO, 1991.
20. Bingham S. Dietary aspects of a health strategy for England. *BMJ* 1991; **303:** 353-355.
21. Report of a Study Group. Diet, nutrition, and the prevention of chronic disease. *WHO Tech Rep Ser* 1991; No. 803.
22. Diplock AT. Antioxidant nutrients and disease prevention: an overview. *Am J Clin Nutr* 1991; **53:** 189S-193S.