

An “ecological” approach to the obesity pandemic

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The increasing prevalence of obesity in many countries means that it should now be considered a pandemic.¹ One estimate from Australia suggests that over the past decade the average adult has been adding 1 gram a day to body weight.² This has occurred in the face of increasing knowledge, awareness, and education about obesity, nutrition, and exercise. It has been suggested that a paradigm shift is necessary if future progress is to be made.³

Traditionally, weight gain was thought of as caused by eating too much or exercising too little, or both (changes in weight = energy intake – energy expenditure). This led to the search for small deficiencies in energy metabolism such as a reduced thermic effect of food to explain obesity.⁴ Treatment was dominated by calorie counting, and public health messages extolled people to balance their intake and output. This paradigm has changed with the increasing understanding of the dynamic relations between energy stores, appetite mechanisms, and energy metabolism and of the wider recognition of nutrient partitioning.^{5,6} From studies which have shown that fat balance is equivalent to energy balance,⁷ the fat balance equation was developed (rate of change of fat stores = rate of fat intake – rate of fat oxidation).⁵ This equation is more dynamic than the original static equation and reflects energy balance under normal conditions of free access to foods. Because fat intake and oxidation are not closely balanced,⁸ this approach does not need metabolic abnormalities or genetic mutations to explain weight gain. Indeed, the differences in body fat between people living in the same environment could be better described as normal physiological variation. This paradigm is more helpful in explaining changes in body fat within an individual over time, but it does not account for the wider influences within and around individuals on obesity.

An ecological model

The model presented in figure 1 proposes three main influences on equilibrium levels of body fat—biological, behavioural, and environmental—mediated through energy intake or energy expenditure, or both, but moderated by physiological adjustments during periods of energy imbalance. The level of body fat is seen not as a “set point” like a thermostat fixed on an exact temperature but as a “settling point” that depends on the net effects of the other components of the model and that changes as they change. This places obesity in an ecological context which calls for more

Summary points

Current strategies are not containing the obesity pandemic

A shift is needed away from the traditional view of obesity as a personal disorder that requires treatment

An ecological approach regards obesity as a normal response to an abnormal environment, rather than vice versa

This approach resembles the classical epidemiological triad used in successfully controlling other epidemics

Understanding, measuring, and altering the “obesogenic” environment is critical to success

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BMJ 1997;315:477–80

than simple education about risk factors and needs a collaborative strategy with the multiple sectors which impact on the problem.⁹

Mediators

The ecological model uses total energy as mediator; for most conditions of human living it is interchangeable with fat energy. Fat intake is an important determinant of total energy intake, and for output, total energy expenditure is a major determinant of fat oxidation.

Energy intake—Dietary fat is very energy dense and has a limited effect on suppressing appetite and enhancing fat oxidation.¹⁰ This makes reducing dietary fat an obvious choice for reducing total energy to treat or prevent obesity. A reduction in dietary fat with an

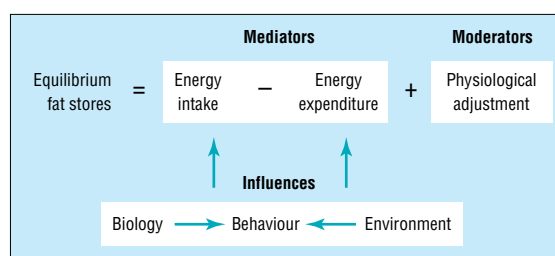
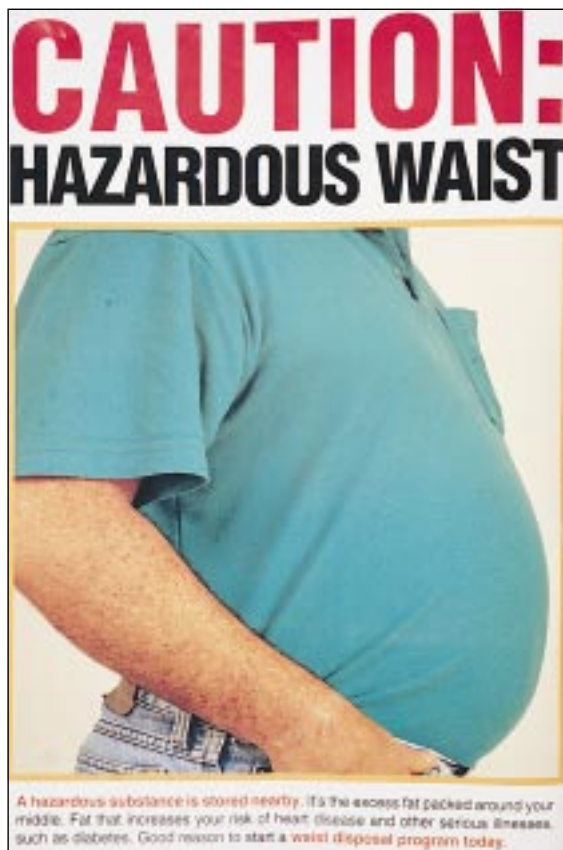


Fig 1 An ecological paradigm for understanding overfatness and obesity



otherwise free choice of food promotes a modest weight loss which is initially less than that from a conventional low energy diet.¹¹ However, the longer term results are similar,¹² and the reduced fat regimen seems easier to maintain.¹³ All weight loss programmes suffer from rebound weight gain, probably partly because of physiological defences against weight loss,¹⁴ but ultimately weight loss is limited by the high settling point of fat stores for people living in an environment that promotes obesity. To keep fat stores below this point often requires considerable effort, which is difficult to maintain in an unsupportive “obesogenic” environment.

At a population level, it seems that dietary fat and energy intake have not fallen as fast as energy output.¹⁵ The result is a large energy imbalance, leading to obesity. On the input side of the equation, the strategy of reducing dietary fat within the diet (that is, changing the foods eaten and the composition of meals) seems a more realistic approach than reducing total energy (decreasing the size and frequency of meals). Large reductions in the fat content of the modern diet seem unlikely, and they may not be necessary for a population based approach, as small changes made by a large percentage of the population often show up as greater improvements in a population’s disease index than do large shifts made by only a few people.¹⁶

Energy expenditure—The intensity of physical activity required for optimal oxidation of fat is controversial. Relative fat utilisation is higher during activity of moderate intensity such as walking, but absolute energy use is higher during vigorous exercise such as running. It has thus been suggested that vigorous exercise results in greater absolute fat oxidation.¹⁷ This may be true for aerobically fit people, but unfit people tend to oxidise less fat at all levels of intensity. Hence, vigorous

exercise—even if it could be carried out—is not likely to result in as much fat oxidation in unfit people as activity of more moderate intensity which can be comfortably sustained for longer periods. Obese people are usually unfit, and so moderately intense physical activity should be recommended for them.

As with fat intake, population benefits are more likely to come from modest increases in activity of low or moderate intensity in many people than from increases in high intensity exercise in a few. Indeed, part of the secular increase in obesity is probably attributable to modest, population-wide reductions in physical activity of low to moderate intensity or to reduction in “incidental movement” due to the introduction of labour saving technology.¹⁸

Moderators

Physiological adjustment refers to the metabolic and, in some cases, behavioural changes that follow a disequilibrium in energy balance and that minimise large fluctuations in body weight. For example, in response to a negative energy balance, initially appetite may increase or physical activity may decrease¹⁴; then, with weight loss, fat oxidation and resting metabolic rate may decline until a new energy balance is achieved.¹⁹ Physiological adjustment may be more vigorous in some people, as a result of biological factors such as sex, age, or genetic makeup.²⁰

One implication of this is that frequent plateaus, or slowing of weight losses over time, are a normal physiological response to energy disequilibrium.¹⁴ Adjustments seem to be more vigorous in response to weight loss than weight gain, especially in lean individuals,²¹ and they may also be more vigorous after rapid, rather than slow, changes. Hence the need to concentrate on long term loss of fat rather than short term, and usually temporary, loss of weight. This questions the ethics of programmes that advertise large weight losses in short periods.

Influences

Biological influences—Biological factors known to influence body fat levels include age, sex, hormonal factors, and genetics,²² all of which have been considered to be unalterable. The identification of the ob gene and its product leptin in 1994 caused widespread optimism about unlocking the cause of obesity and developing successful treatments.²³ A greater understanding of appetite control will undoubtedly come from research on leptin, but no major effect of single gene defects has yet been identified, and it is likely that the genetic influences on body fat levels are polygenic.

There are also important sex differences in fat storage.²⁴ The differences between the sexes are apparent early in life, become greatest with the onset of menses, then tend to decrease with the changes in hormone status in postmenopausal women.²⁵ Fat loss and maintenance of lower equilibrium fat stores also becomes more difficult with age.²⁶ Finally, there is increasing evidence of racial influences on energy balance.²⁷ These biological influences explain much of the variance in body fat in individuals within a given environment, but they do not explain the large population increases which represent the epidemic itself.

Behavioural influences—Behavioural factors typically thought to influence obesity are “sloth” and “gluttony,”

Table 1 Environmental influences on food intake and physical activity

Type of environment	Physical environment		Economic environment		Sociocultural environment	
	Food	Activity	Food	Activity	Food	Activity
Macro	Food laws and regulation Food technology Low fat foods Food industry policies	Labour saving devices Cycleways and walkways Fitness industry policies Transport system	Food taxes and subsidies Cost of food technology Marketing costs Food prices	Cost of labour versus automation Investment in parks and recreational facilities Costs of petrol and cars Costs of cycleways	Traditional cuisine Migrant cuisines Consumer demand Food status	Attitudes to recreation National sports Participating versus watching culture Gadget status
Micro	Food in house Choices at school or work cafeterias Food in local shops Proximity of fast food outlets	Local recreation facilities Second cars Safe streets Household rules for watching TV and video	Family income Other household expenses Subsidised canteens Home grown foods	Gym or club fees Owning equipment Subsidised local events Costs of school sport	Family eating patterns Peer attitudes Pressure from food advertising Festivities	Peers' activities Family recreation School attitude to sports Safety fears

which imply a potential for willful control over the forces affecting body weight. Behaviours are the result of complex psychological factors, including habits, emotions, attitudes, beliefs, and cognitions developed through a background of learning history. Biological and environmental influences also affect behaviour, and, in turn, energy balance. Cognitive factors (willpower based on knowledge, for example) may have only a minor effect on eventual behaviour, and this explains the limitations of education in the treatment and prevention of obesity. However, the causes and effects of behavioural factors do have to be considered,²⁸ and interventions to deal with these should be a part of any overall strategy.

Environmental influences—Environment can be broadly categorised into “macro” (of the wider population) and “micro” (with close proximity to the individual). In general, the macro-environment determines the prevalence of obesity in a population and the micro-environment, along with biological and behavioural influences, determines whether an individual is obese. The environmental influences on the amount and type of food eaten and the amount and type of physical activity taken are vast and underrated; table 1 shows some examples. A close examination of specific macro-environmental sectors (such as the fitness industry or the food service industry) or micro-environmental settings (such as the local gym or the workplace) will reveal many more interconnecting environmental influ-

ences than those listed. For example, food safety regulations, policies of food manufacturers, costs of cooking oils, and the availability of training programmes for food caterers can affect the choice, price, and quality of food at the work canteen.

Environmental influences represent the public health arm of the obesity problem. If the macro-environment is obesogenic, obesity will become more prevalent and programmes aimed at influencing individual behaviour can be expected to have only a limited effect. Historically, epidemics have been controlled only after environmental factors have been modified. Similarly, reductions in population levels of obesity seem unlikely until the environments which facilitate its development are modified. Yet this is often neglected in obesity management (as it was initially with tobacco control). Environmental change, such as regulation of the food industry or changes in building design, is likely to be unpopular. Although some changes may be overt, others—such as reductions of fat in the meat supply—may be more surreptitious.

Epidemiology of an ecological model

The model proposed in figure 1 bears a resemblance to the epidemiological triad (fig 2) which has proved to be a robust model with epidemics such as infectious diseases, smoking, coronary heart disease, and, more recently, injuries.²⁹ For obesity, “host” encompasses the biological and behavioural influences, plus physiological adjustment. “Environment” is similar in the two models, and “vehicle” is represented by energy intake (food) and energy expenditure (physical activity). Preventive interventions are superimposed on components of the triad in figure 2. These provide some options for a wider approach to obesity.

Recent advances in obesity research (especially in molecular biology) may have an impact on treatment at the individual level. It is clear, however, that there is a major deficiency in research into the “obesogenic” environment and potential interventions. Without a supportive environment, treatment programmes are likely to be ineffectual and preventive programs will be restricted to mass education strategies.

Conclusion

Obesity presents us with two challenges: to treat people who are currently obese and to prevent obesity in people who are still lean. Neither of these challenges is currently being met; hence it is important to re-examine the paradigms on which treatment and

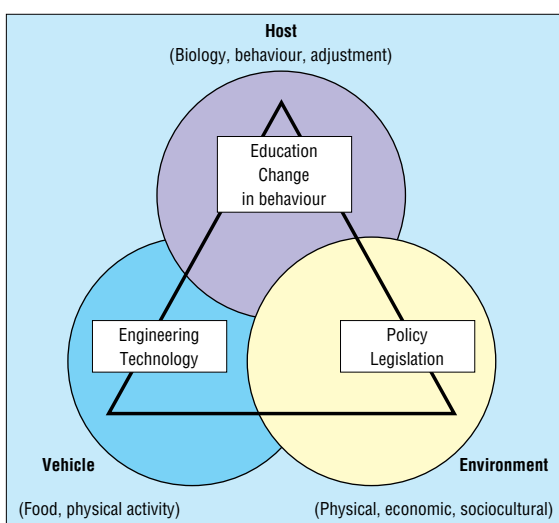


Fig 2 The epidemiological triad and potential intervention strategies for obesity

prevention programmes are based. The model presented here suggests that the driving force for the increasing prevalence of obesity in populations is the increasingly obesogenic environment rather than any "pathology" in metabolic defects or genetic mutations within individuals. A paradigm shift to understanding obesity as "normal physiology within a pathological environment" signposts the directions for a wider public health approach to the obesity pandemic.

- 1 James WPT. Epidemiology of obesity. *Int J Obesity* 1992;16(suppl 2):S23-6.
- 2 Magnus P, Bennett S. Trends in cardiovascular risk factors in Australia. *Med J Aust* 1994;161:519-27.
- 3 Hawks SR, Richins P. Toward a new paradigm for the management of obesity. *J Health Educ* 1994;25:147-53.
- 4 Ravussin E, Swinburn B. Energy metabolism in obesity. In: Stunkard AJ, Wadden TA, eds. *Obesity: theory and therapy*. 2nd ed. New York: Raven, 1992:97-124.
- 5 Swinburn B, Ravussin E. Energy balance or fat balance? *Am J Clin Nutr* 1993;57(suppl):766-71S.
- 6 Stubbs RJ. Macronutrient effects on appetite. *Int J Obesity* 1995;19(suppl 5):S11-9.
- 7 Flatt JP. Importance of nutrient balance in body weight regulation. *Diab Met Rev* 1988;4:571-81.
- 8 Schutz Y, Flatt JP, Jequier E. Failure of dietary fat intake to promote fat oxidation: a factor favouring the development of obesity. *Am J Clin Nutr* 1989;50:307-14.
- 9 Kickbush I. Approaches to an ecological base for public health. *Health Promotion* 1989;4:265-8.
- 10 Weststrate JA. Fat and obesity. *Int J Obesity* 1995;19(suppl 5):S38-43.
- 11 Lissner L, Heitman BL. Dietary fat and obesity: evidence from epidemiology. *Eur J Clin Nutr* 1995;49:79-90.
- 12 Prewitt TE, Schmeisser D, Bowen PE, Aye P, Dolecek TA, Langenberg P, et al. Changes in body weight, body composition, and energy intake in women fed high- and low-fat diets. *Am J Clin Nutr* 1991;54:304-10.
- 13 Lyon X-H, Di Vetta V, Milton H, Schutz Y. Compliance to dietary advice directed towards increasing the carbohydrate to fat ratio of the everyday diet. *Int J Obesity* 1995;19:260-9.

- 14 Prentice AM, Goldberg GR, Jebb SA, Black AE, Murgatroyd PR. Physiological responses to slimming. *Proc Nutr Soc* 1991;50:441-58.
- 15 Prentice AM, Jebb SA. Obesity in Britain: gluttony or sloth? *BMJ* 1995; 311:437-9.
- 16 Rose G. *The strategy of preventive medicine*. Oxford: Oxford University Press, 1992.
- 17 Glasser GA. Burning carbohydrate to lose fat. *Sports Med Digest* 1995;March:5.
- 18 James WPT. A public health approach to the problem of obesity. *Int J Obesity* 1995;19 (suppl 3):S37-46.
- 19 Liebel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. *N Engl J Med* 1995;332:621-8.
- 20 Heitmann BL, Lissner L, Sorensen TI, Bengtsson C. Dietary fat intake and weight gain in women genetically predisposed for obesity. *Am J Clin Nutr* 1995;61:1213-7.
- 21 Keys A, Brozek J, Kenschel A, Mickelsen O, Taylor HL. *The biology of human starvation*. Vol 1, Minneapolis: University of Minnesota Press, 1950.
- 22 Katahn M, McMinn MR. Obesity: a biobehavioral point of view. *Ann NY Acad Sci* 1990;602:189-204.
- 23 Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994;372:425-32.
- 24 Frisch RE. The right weight: body fat, menarche and fertility. *Proc Nutr Soc* 1994;53:113-29.
- 25 Rebuffe-Scrive M, Enk L, Crona N, Lonnroth P, Abrahamsson L, Smith U, et al. Fat cell metabolism in different regions in women: effect of menstrual cycle, pregnancy and lactation. *J Clin Invest* 1985;75:1973-6.
- 26 Bourdin M, Pastene J, Germain M, Lacour JR. Influence of training, sex, age and body mass on the energy costs of running. *Eur J Appl Physiol* 1993;66:439-44.
- 27 Tuten C, Petosa R, Sargent R, Weston A. Biracial differences in physical activity and body composition. *Obesity Res* 1995;3:313-8.
- 28 Brownell KD, Wadden TA. Etiology and treatment of obesity: understanding a serious, prevalent, and refractory disorder. *J Consult Clin Psychol* 1992;60:505-17.
- 29 Hadden W. Advances in the epidemiology of injuries as a basis for public policy. *Public Health Rep* 1980;95:411-21.

(Accepted 17 February 1997)

How to read a paper

Papers that report drug trials

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This is the sixth in a series of 10 articles introducing non-experts to finding medical articles and assessing their value

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BMJ 1997;315:480-3

"Evidence" and marketing

If you prescribe drugs, the pharmaceutical industry is interested in you and is investing a staggering sum of money trying to influence you. The most effective way of changing the prescribing habits of a clinician is through personal representatives (known in Britain as "drug reps" and in North America as "detailers"), who travel round with a briefcase full of "evidence" in support of their wares.¹

Pharmaceutical "reps" do not tell nearly as many lies as they used to (drug marketing has become an altogether more sophisticated science), but they have been known to cultivate a shocking ignorance of basic epidemiology and clinical trial design when it suits them.² It often helps their case, for example, to present the results of uncontrolled trials and express them in terms of before and after differences in a particular outcome measure.³ The recent correspondence in the *Lancet* and *BMJ* on placebo effects should remind you why uncontrolled before and after studies are the stuff of teenage magazines, not hard science.⁴⁻¹²

Making decisions about treatment

Sackett and colleagues have argued that before giving a drug to a patient the doctor should:

Summary points

Pharmaceutical "reps" are now much more informative than they used to be, but they may show ignorance of basic epidemiology and clinical trial design

The value of a drug should be expressed in terms of safety, tolerability, efficacy, and price

The efficacy of a drug should ideally be measured in terms of clinical end points that are relevant to patients; if surrogate end points are used they should be valid

Promotional literature of low scientific validity (such as uncontrolled before and after trials) should not be allowed to influence practice

- identify, for this patient, the ultimate objective of treatment (cure, prevention of recurrence, limitation of functional disability, prevention of later complications, reassurance, palliation, relief of symptoms, etc);

- select the most appropriate treatment, using all available evidence (this includes considering whether the patient needs to take any drug at all); and
- specify the treatment target (to know when to stop treatment, change its intensity, or switch to some other treatment).¹³

For example, in treating high blood pressure, the doctor might decide that:

- the ultimate objective of treatment is to prevent (further) target organ damage to brain, eye, heart, kidney, etc (and thereby prevent death);
- the choice of specific treatment is between the various classes of antihypertensive drug selected on the basis of randomised, placebo controlled and comparative trials—as well as non-drug treatments such as salt restriction; and
- the treatment target might be a phase V diastolic blood pressure (right arm, sitting) of less than 90 mm Hg, or as close to that as tolerable in the face of drug side effects.

If these three steps are not followed (as is often the case—for example in terminal care), therapeutic chaos can result.

Surrogate end points

A surrogate end point may be defined as a variable which is relatively easily measured and which predicts a rare or distant outcome of either a toxic stimulus (such as a pollutant) or a therapeutic intervention (a drug, surgical procedure, piece of advice, etc) but which is not itself a direct measure of either harm or clinical benefit. The growing interest in surrogate end points in medical research, and particularly by the pharmaceutical industry, reflects two important features of their use:

- they can considerably reduce the sample size, duration, and, therefore, cost, of clinical trials; and
- they can allow treatments to be assessed in situations where the use of primary outcomes would be excessively invasive or unethical.

In the evaluation of pharmaceutical products, commonly used surrogate end points include:

- pharmacokinetic measurements (for example, concentration-time curves of a drug or its active metabolite in the bloodstream);
- in vitro (laboratory) measures such as the mean inhibitory concentration of an antimicrobial against a bacterial culture on agar;
- macroscopic appearance of tissues (for example, gastric erosion seen at endoscopy);
- change in levels of (alleged) serum markers of disease (for example, prostate specific antigen¹⁴);
- radiological appearance (for example, shadowing on a chest x ray film).

But surrogate end points have some drawbacks. Firstly, a change in the surrogate end point does not itself answer the essential preliminary questions: “what is the objective of treatment in this patient?” and “what, according to valid and reliable research studies, is the best available treatment for this condition?” Secondly, the surrogate end point may not closely reflect the treatment target—in other words, it may not be valid or reliable. Thirdly, overreliance on a single surrogate end point as a measure of therapeutic success usually reflects a narrow clinical perspective. Finally, surrogate

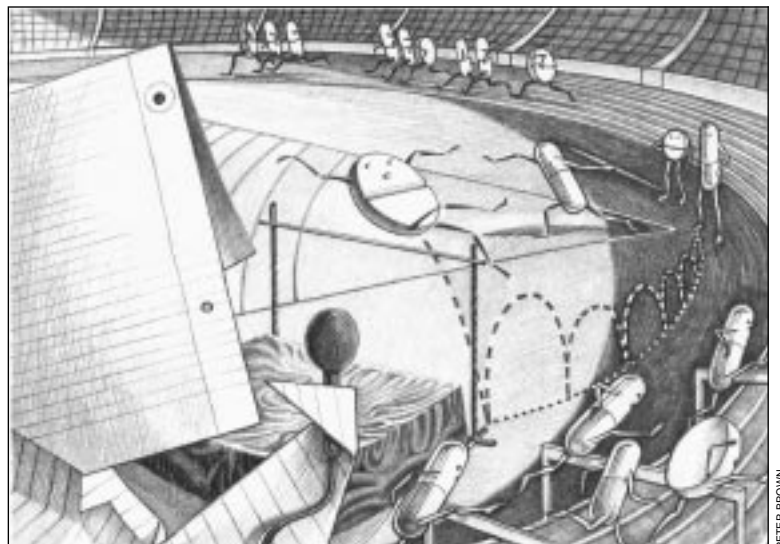
Features of the ideal surrogate end point

- The surrogate end point should be reliable, reproducible, clinically available, easily quantifiable, affordable, and show a “dose-response” effect (the higher the level of the surrogate end point, the greater the probability of disease)
- It should be a true predictor of disease (or risk of disease) and not merely express exposure to a covariable. The relation between the surrogate end point and the disease should have a biologically plausible explanation
- It should be sensitive—a “positive” result in the surrogate end point should pick up all or most patients at increased risk of adverse outcome
- It should be specific—a “negative” result should exclude all or most of those without increased risk of adverse outcome
- There should be a precise cut off between normal and abnormal values
- It should have an acceptable positive predictive value—a “positive” result should always or usually mean that the patient thus identified is at increased risk of adverse outcome
- It should have an acceptable negative predictive value—a “negative” result should always or usually mean that the patient thus identified is not at increased risk of adverse outcome
- It should be amenable to quality control monitoring
- Changes in the surrogate end point should rapidly and accurately reflect the response to treatment. In particular, levels should normalise in states of remission or cure

end points are often developed in animal models of disease, since changes in a specific variable can be measured under controlled conditions in a well defined population. However, extrapolation of these findings to human disease is likely to be invalid.¹⁵⁻¹⁷

The features of an ideal surrogate end point are shown in the box. If the “rep” who is trying to persuade you of the value of the drug cannot justify the end points used, you should challenge him or her to produce additional evidence.

One important example of the invalid use of a surrogate end point is the CD4 cell count in monitoring progression to AIDS in HIV positive subjects. The CONCORDE trial was a randomised controlled trial



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comparing early and late start of treatment with zidovudine in patients who were HIV positive but clinically asymptomatic.¹⁸ Previous studies had shown that starting treatment early led to a slower decline in the CD4 cell count (a variable which had been shown to fall with the progression of AIDS), and it was assumed that a higher CD4 cell count would reflect improved chances of survival.

However, the CONCORDE trial showed that, although CD4 cell counts fell more slowly in the treatment group, the three year survival rates were identical in the two groups. This experience confirmed a warning that was issued earlier by authors suspicious of the validity of this end point.¹⁹ Subsequent research in this field has attempted to identify a surrogate end point that correlates with real therapeutic benefit—that is, delayed progression of asymptomatic HIV infection to clinical AIDS, and longer survival time after the onset of AIDS.^{20–21} Using multiple regression analysis, investigators in the USA found that a combination of markers (percentage of CD4:C29 cells, degree of fatigue, age, and haemoglobin concentration) was the best predictor of progression.²⁰

Other examples of surrogate end points which have seriously misled researchers include ventricular premature beats as a predictor of death from serious cardiac arrhythmias,^{22–23} blood concentrations of antibiotics as a predictor of clinical cure of infection,²⁴ and plaques seen on magnetic resonance imaging in monitoring the progression of multiple sclerosis.²⁵

Before surrogate end points can be used in the marketing of pharmaceuticals, those in the industry must justify the utility of these measures by showing a plausible and consistent link between the end point and the development or progression of disease. It would be wrong to suggest that the pharmaceutical industry develops surrogate end points with the deliberate intention to mislead the licensing authorities and health professionals. However, the industry does, theoretically, have a vested interest in overstating its case on the significance of these end points. Given that much of the data relating to the validation of surrogate end points are not currently presented in published clinical papers, and that the development of such markers is often a lengthy and expensive process, one author has suggested setting up a data archive that would pool data across studies.²⁶

How to get evidence out of a drug rep

Any doctor who has ever given an audience to a “rep” who is selling a non-steroidal anti-inflammatory drug will recognise the argument that “this NSAID reduces the incidence of gastric erosion in comparison to its competitors.” The question to ask the rep is not “what is the incidence of endoscopic signs of gastric erosion in volunteers who take this drug?” but “what is the incidence in clinical practice of potentially life threatening gastric bleeding in patients who take this drug?” Other questions, collated from recommendations in *Drug and Therapeutics Bulletin*²⁷ and other sources,^{1–3} are listed below.

- See representatives only by appointment. Choose to see only those whose product interests you, and confine the interview to that product

Checklist for evaluating information provided by a drug company

- Does this material cover a subject which interests me and is clinically important in my practice?
- Has this material been published in independent peer reviewed journals? Has any significant evidence been omitted from this presentation or withheld from publication?
- Does the material include high-level evidence such as systematic reviews, meta-analyses, or double-blind randomised controlled trials against the drug’s closest competitor given at optimal dosage?
- Have the trials or reviews addressed a clearly focused, important and answerable clinical question which reflects a problem of relevance to patients? Do they provide evidence on safety, tolerability, efficacy and price?
- Has each trial or meta-analysis defined the condition to be treated, the patients to be included, the interventions to be compared and the outcomes to be examined?
- Does the material provide direct evidence that the drug will help my patients live a longer, healthier, more productive, and symptom-free life?
- If a surrogate outcome measure has been used, what is the evidence that it is reliable, reproducible, sensitive, specific, a true predictor of disease, and rapidly reflects the response to therapy?
- Do trial results indicate whether (and how) the effectiveness of the treatments differed and whether there was a difference in the type or frequency of adverse reactions? Are the results expressed in terms of numbers needed to treat, and are they clinically as well as statistically significant?
- If large amounts of material have been provided by the representative, which three papers provide the strongest evidence for the company’s claims?

- Take charge of the interview. Do not hear out a rehearsed sales routine but ask directly for the information below

- Request independent published evidence from reputable, peer reviewed journals
- Do not look at promotional brochures, which may contain unpublished material, misleading graphs, and selective quotations
- Ignore anecdotal “evidence,” such as the fact that a medical celebrity is prescribing the product
- Using the STEP acronym, ask for evidence in four specific areas:

Safety—the likelihood of long term or serious side effects caused by the drug (remember that rare but serious adverse reactions to new drugs may be poorly documented)

Tolerability—best measured by comparing the pooled withdrawal rates between the drug and its most significant competitor

Efficacy—the most relevant dimension is how the product compares with your current favourite

Price—should take into account indirect as well as direct costs

- Evaluate the evidence stringently, paying particular attention to the power (sample size) and methodological quality of clinical trials, and the use of surrogate end points. Do not accept theoretical arguments in the drug’s favour (“longer half life,” for example) without direct evidence that this translates into clinical benefit

- Do not accept the newness of a product as an argument for changing to it. Indeed, there are good scientific arguments for doing the opposite²⁸
- Decline to try the product via starter packs or by participating in small scale, uncontrolled “research” studies
- Record in writing the content of the interview and return to these notes if the “rep” requests another audience

In conclusion, it is often more difficult than you are being led to believe to weigh the potential benefits of a drug against its risks to the patient and cost to the taxpayer.²⁹ The difference between the science of critical appraisal and the pharmaceutical industry’s well rehearsed tactics of marketing and persuasion should be borne in mind when you are considering “evidence” presented by those with a commercial conflict of interest.

I am grateful to Dr Andrew Herxheimer for advice on this article.

The articles in this series are excerpts from *How to Read a Paper: the Basics of Evidence Based Medicine*. The book includes chapters on searching the literature and implementing evidence based findings. It can be ordered from the BMJ Publishing Group: tel 0171 383 6185/6245; fax 0171 383 6662. Price £13.95 for UK members, £14.95 for non-members.

- 1 Shaughnessy AF, Slawson DC. Pharmaceutical representatives. *BMJ* 1996;312:1494-5.
- 2 Bardelay D. Visits from medical representatives: fine principles, poor practice. *Prescribe International* 1995;4:120-2.
- 3 Bero LA, Rennie D. Influences on the quality of published drug studies. *Int J Health Technology Assessment* 1996;12:209-37.

- 4 Kleijnen J, de Craen AJ, van Everdingen J, Krol L. Placebo effect in double-blind clinical trials: a review of interactions with medications. *Lancet* 1994;344:1347-9.
- 5 Joyce CR. Placebo and complementary medicine. *Lancet* 1994;344:1279-81.
- 6 Laporte JR, Figueras A. Placebo effects in psychiatry. *Lancet* 1994;344:1206-9.
- 7 Johnson AG. Surgery as a placebo. *Lancet* 1994;344:1140-2.
- 8 Thomas KB. The placebo in general practice. *Lancet* 1994;344:1066-7.
- 9 Chaput de Saintonge DM, Herxheimer A. Harnessing placebo effects in health care. *Lancet* 1994;344:995-8.
- 10 Gotzsche PC. Is there logic in the placebo? *Lancet* 1994;344:925-6.
- 11 Rothman KJ. Placebo mania. *BMJ* 1996;313:3-4.
- 12 McQuay H, Moore A, Double DB, Georgiou A, Korkia P. Placebo mania. *BMJ* 1996;313:1008-9.
- 13 Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical epidemiology—a basic science for clinical medicine*. London, Little, Brown, 1991:187-248.
- 14 Bostwick DG, Burke HB, Wheeler TM, Chung LW, Bookstein R, Pretlow TG, et al. The most promising surrogate endpoint biomarkers for screening candidate chemopreventive compounds for prostatic adenocarcinoma in short-term Phase II clinical trials. *J Cell Biochem* 1994;56(suppl 19):283-9.
- 15 Gøtzsche P, Liberati A, Torri V, Rosetti L. Beware of surrogate outcome measures. *Int J Health Technology Assessment* 1996;12:238-46.
- 16 Lipkin M. Summary of recommendations for colonic biomarker studies of candidate chemopreventive compounds in Phase II clinical trials. *J Cell Biochem* 1994;56(suppl 19):94-8.
- 17 Kimbrough RD. Determining acceptable risks: experimental and epidemiological issues. *Clin Chem* 1994;40:1448-53.
- 18 CONCORDE Co-ordinating Committee. CONCORDE MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. *Lancet* 1994;343:871-81.
- 19 Jacobson MA, Bacchetti P, Kolokathis A et al. Surrogate markers for survival in patients with AIDS and AIDS related complex treated with zidovudine. *BMJ* 1991;302:73-8.
- 20 Blatt SP, McCarthy WF, Bucko-Krasnicka B, Melcher GP, Boswell RN, Dolan J, et al. Multivariate models for predicting progression to AIDS and survival in HIV-infected patients. *J Infect Dis* 1995;171:837-44.
- 21 Tsoukas CM, Bernard NF. Markers predicting progression of HIV-related disease. *Clin Microbiol Rev* 1994;7:14-28.
- 22 Epstein AE, Hallstrom AO, Rogers WJ, Liebson PR, Seals AA, Anderson JL, et al. Mortality following ventricular arrhythmia suppression by encainide, flecainide and moricizine after myocardial infarction. *JAMA* 1993, 270, 2451-55.
- 23 Lipicky RJ, Packer M. Role of surrogate endpoints in the evaluation of drugs for heart failure. *J Am Coll Cardiol* 1993;22(suppl A):179-84.
- 24 Hyatt JM, McKinnon PS, Zimmer GS, Schentag JJ. The importance of pharmacokinetic/pharmacodynamic surrogate markers to outcome. Focus on antibacterial agents. *Clin Pharmacokinetics* 1995;28:143-60.
- 25 Interferon beta-1b—hope or hype? *Drug Ther Bull* 1996;34:9-11.
- 26 Aickin M. If there is gold in the labelling index hills, are we digging in the right place? *J Cell Biochem* 1994;56(suppl 19):91-3.
- 27 Getting good value from drug reps. *Drug Ther Bull* 1983;21:13-5.
- 28 Ferner RE. Newly licensed drugs. *BMJ* 1996;313:1157-8.
- 29 Risk/benefit analysis of drugs in practice. *Drug Ther Bull* 1995;33:33-5.

When I use a word...

Buyers and sellers

These articles about words elicit an interesting postbag. I have recently been asked by F J Langfield of Frenchay in Bristol if I can remind him of the word for the inverse of a monopoly. A monopoly is defined in the *Oxford English Dictionary* as “the condition of having no competitor in the sale of some commodity or in the exercise of some trade or business.” What then do you call the condition in which you have no competitor in the purchase of some commodity?

Well monopoly comes from two Greek words, μόνος (monos) single and πωλέω (poleo) I sell—monopoly, one seller. So what we want is a word meaning one buyer. Attic Greek had more than one word meaning I buy, but the relevant one is ὀψωνέω (opsonéo), and the word we want is monopsony.

Monopsony was first coined in the 1930s, but in contrast to monopoly it is used almost exclusively by economists. For instance, in an article entitled “How to Pay for the National Health Service” (*Roy Soc Health J* 1971;91:217-21) Michael H Cooper, a social economist, defined a monopsony as “a consumer so large that it can exert pressure on price merely by the threat of withdrawing its custom.” One familiar instance is the government as a purchaser of healthcare. Other current or past examples of monopsonies, or at least oligopsonies, include the diamond trade, dominated by de Beers as both buyer and seller, the tobacco industry, and academic specialist book publication.

Oposonins are substances that combine with bacteria or other foreign cells, making them more susceptible to phagocytosis. To understand the genesis of the term opsonins (which we now call members of the complement group), we must explore the origins of ὀψωνέω more closely. It originally meant to buy ὄψων (opson), cooked meat or fish, non-staple food as opposed to bread, consequently anything eaten with bread to give it flavour, and hence seasoning or sauce. So, as Shaw put it in the preface to his play *The Doctor’s Dilemma* (1906), “the white corpuscles or phagocytes which attack and devour disease germs for us do their work only when we butter the disease germs appetisingly for them with a natural sauce which Sir Almroth [Wright] named opsonin [in *Proc Roy Soc* 1903;72:366].” According to Wright’s alter ego in the play, Sir Colenso Ridgeon, “To inject a vaccine into a patient without first testing his opsonin is as near murder as a respectable practitioner can get.” An opinion on which he seems to have had a monopoly.

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We welcome filler articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk.