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BMJ

Does the world need the *BMJ*?

Every institution needs to question its existence

To consider whether the world would be different if your institution disappeared is a sharper exercise than to compose its mission statement. Would the world miss the *BMJ*? The day that the *BMJ* is redesigned seems a good time for us to try to answer that question.

Nobody would start a new general medical journal today, and many that exist are beginning to disappear. Information scientists argue that there are too many journals, that much of what they publish is of poor quality, and that important material may be lost in a welter of the unimportant: the "signal to noise" ratio is horribly low.[1] Meanwhile, enthusiasts for the Internet curse the slowness and exclusivity of paper journals and predict their imminent demise.[2] They want a world where authors go directly to readers unimpeded by editors. The *BMJ*'s environment may not thus seem inviting, but that is nothing new—of the hundreds of journals started at the same time as the *BMJ* (1840) only a handful survive.

The first thing to get clear is what the *BMJ* is. For many readers it is that "blue mag" that pops up once a week, but the *BMJ* is more than that. It is also the *Student BMJ*, 20 local editions (in countries ranging from Brazil to Poland, many in local languages), a version on the worldwide web, and two different classified advertisement supplements. In the future readers might encounter *BMJ* material in other forms, and we are currently planning an electronic version that will be interactive and will use all the possibilities of the Internet. We might in the future send you material that we know will be specifically useful to you, or you might electronically access the *BMJ* to answer questions that arise as you consult with patients. We will respond to what you want. My bet is that many readers will continue to want the traditional journal, just as most people want to watch major sporting events at the same time as everybody else. You want to be part of something and to have the opportunity to stumble across the unexpected. And one of the attributes of good journalism is to fascinate people with subjects they never knew were interesting or relevant to them.

Whether journals in general survive will be determined by whether they "add value"—whether their contribution to the process of informing and educating doctors is sufficient for readers to continue to pay them for it. Some journals, it has to be said, add little value.[3] General journals like the *BMJ* tend to add more. We carry important scientific papers selected from the 5000 we receive each year and a great deal more. Our peer review system is well developed and is more concerned with improving the papers we publish than simply deciding which to publish. Through technical editing and design the material is presented in a way that can be understood by anybody, and we enhance the usefulness of the papers by publishing clusters on the same subject and adding editorials and commentaries. The aim is to deliver distilled material that helps doctors, who are always fighting time. And our audience stretches beyond clinical researchers. Indeed, our readers are probably our greatest asset.

But why does the world need the *BMJ* rather than any general medical journal? It may be because of its values, its flavour—something that is much more enduring than individual editors. The *BMJ* is the most general of the general medical journals, and it tries to provide readers with material from as wide a range of disciplines and methodologies as is necessary to practise medicine well. In particular, the *BMJ* has a long tradition of publishing research from primary care: at one time this may have seemed odd, but now the whole world is discovering the importance of primary care. One area where we have not paid enough attention is basic science, but we are starting today a new series of papers that will try to transmit to ordinary doctors the great excitement of basic science (p 43).

The heart of medicine is still the clinician consulting with the individual patient, and that is the lodestar of the *BMJ*. We are rooted in clinical medicine, and nothing gives us greater pleasure than to publish a scientifically sound paper with a message that will benefit patients directly. But medicine, like most important activities, is becoming increasingly complex. The modern doctor can benefit from the work of molecular biologists, philosophers, statisticians, physicists, sociologists, economists, and others. A broad range of methodologies—from clinical trials to anthropological observations and beyond—is needed to move medicine forward.[4] The *BMJ* explores that whole terrain and tries to present what it finds in a way that will be understandable and useful to doctors. We also aim to reach out to the many people other than doctors who are vital for improving health. Readability has always been one of our core values, but so is being rigorous. We want to make the journal both more rigorous and more readable, and we believe both can be achieved at once. One without the other is worthless.

Another longstanding value of the *BMJ* is being international. The future of successful medical journals is undoubtedly global. Yet, one of the *BMJ*'s greatest

strengths is that it is the one journal read by most doctors in Britain: based on the 110 000 members of the BMA, the *BMJ* is the forum where British medicine can decide what it thinks. Isn't this a paradox—being international and being British? We see it as a challenge. Britain at its best has values that the world appreciates: impartiality, fairness, honesty, rigour, clarity, an enthusiasm for debate, irony, and humour. The *BMJ* aims to bring those values to an international medical audience and to present British doctors with an international view of medicine—because every challenge faced by British medicine is being faced somewhere else as well. In pursuit of still greater international understanding we have appointed an editorial board that includes 28 members from outside Britain (p 52) and international networks of advisers on basic science, education, primary care, and information for health.

The *BMJ* is committed to education as defined by William Butler Yeats—"not the filling of a pail but the lighting of a fire." When we ask readers what they want more of (which we do regularly), they always answer, education. The *BMJ* offers education within a scientific context and encourages questioning rather than acceptance. One of our educational precepts is that information must be presented in many different forms, ranging from the highly successful ABCs (invented by my predecessor, Stephen Lock) through controversies to in depth systematic reviews. We continue to explore new educational methods, and the Internet opens up new possibilities.

Ernest Hart, the great 19th century editor of the *BMJ*, said that "a subject needing reform has to be kept before the public until the public demands reform." The *BMJ* led many important reforms in Victorian Britain, and, like the BMA, continues to campaign on many issues—including inequalities in health and the harmful effects of tobacco. Another closely related job for the *BMJ* is to put before doctors things that they don't necessarily want to hear. Hugh Clegg, editor from 1947 to 1965, wrote that "a medical editor has to be a keeper of the conscience of a profession, and if he tries to live up to this ideal he will always be getting into trouble." Increasingly editors are not "hes" and editing is a team activity, but the notion of pricking the profession to examine itself lives on.

Is all this enough? We are confident that readability and rigour, important and sometimes surprising material from all of medicine and beyond, an international scope, and an urge to campaign and amuse will mean that it is—even if the journal is beamed directly into your brain by satellite rather than pushed through your letterbox.

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Hangovers

Not the ethanol—perhaps the methanol

"Wine is only sweet to happy men," wrote an unhappy John Keats to his sweetheart.[1] His observation seems to have been vindicated. Harburg *et al* found that psychosocial factors such as guilt about drinking, a neurotic personality, becoming angry or depressed while drinking, and having suffered "negative life events" in the past 12 months are better predictors of symptoms of hangover than the amount of ethanol drunk.[2]

In fact, ethanol itself may play only a minor part in producing the thirst, headache, fatigue, nausea, sweating, tremor, remorse, and anxiety that hangover sufferers report. Hangover symptoms are worst at a time when almost all ethanol and its metabolite acetaldehyde have been cleared from the blood, and peak blood ethanol or acetaldehyde levels are not related to the severity of hangover.[3] Between a quarter and a half of drinkers claim not to experience hangover symptoms despite having been intoxicated.[2 4]

Congeners—complex organic molecules such as polyphenols, higher alcohols including methanol, and histamine, which occur in varying amounts in ethanolic drinks—are probably more to blame than ethanol. Chapman found that hangover symptoms were almost twice as common in volunteers who drank 1.5 ml/kg of bourbon whiskey—which has methanol concentrations of 260 mg/l—as in those drinking the same dose of vodka (0.039 mg of methanol per litre).[5] Pawan compared the hangover produced by different types of drink (but only one brand of each) in his study of 20 volunteers. The severity of hangover symptoms declined in the order of brandy, red wine, rum, whisky, white wine, gin, vodka, and pure ethanol.[6] Vodka and pure ethanol caused only mild headaches in two volunteers.

Jones has suggested that it is the metabolism of methanol to formaldehyde and formic acid that causes symptoms of hangover, with quicker methanol metabolisers suffering more.[7] The justification for this suggestion is threefold: the types of drink associated with more severe hangovers contain higher levels of methanol; the time course of methanol metabolism corresponds to the onset of symptoms; and a small dose of ethanol, which blocks the formation of formaldehyde and formic acid, provides an effective treatment for hangovers ("the hair of the dog").

The economic and social consequences of hangovers are probably considerable but difficult to quantify. Performance accuracy is impaired synergistically by

sleep deprivation and hangover.[8] Drivers perform less well in simulators when tested the morning after drinking ethanol.[9] Making driving with a hangover a criminal offence might be logical, but is probably impractical in the absence of a simple diagnostic test like breath alcohol.

Many pathophysiological disturbances occur during hangover, including dehydration; metabolic acidosis; hypoglycaemia; disturbed prostaglandin synthesis; abnormal secretion of vasopressin, cortisol, aldosterone, renin, and testosterone; increased cardiac output; tachycardia; and vasodilatation. Hypoglycaemia and acidosis can be treated with fructose or glucose,[9] and the cardiovascular abnormalities with β blockade,[10] but symptoms are not alleviated. However, rehydration and anti-inflammatory analgesics are helpful, particularly if treatment is started before bedtime.[11] A completely effective treatment is probably unattainable (since so many factors—such as lack of sleep, active or passive smoking, dietary indiscretions, unaccustomed physical activity, intermittent upper airway obstruction, and emotional disturbances—must play a part) and is arguably undesirable since the fear of hangover prompts most people to moderate their ethanol intake.[4] Even moderate amounts of ethanol can be damaging,[12] so a penalty for consumption is in our interests. Perhaps those who aspire to be one of Dr Johnson's "heroes" by drinking brandy[13] are sensible as well as brave.

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Monitoring blood glucose in gestational diabetes

Superiority of preprandial monitoring not proved

Gestational diabetes mellitus is defined as glucose intolerance first detected during pregnancy with reversion to normal after delivery. It is generally considered a consequence of the endocrine changes of pregnancy in women who are genetically predisposed to non-insulin dependent diabetes. Thus, it is associated with a subsequent cumulative incidence of diabetes as high as 60% after 16 years of follow up.[1] Since blood glucose concentrations do not have a bimodal distribution, the frequency of gestational diabetes will depend on the arbitrary blood glucose concentration chosen for diagnosis.

The impact of gestational diabetes is similar to that of established diabetes, although the complications are fewer and less severe. However, there is little consensus in the literature concerning the biochemical definition, perceived ill effects, or appropriate treatment. For initial treatment, dietary instruction is mandatory, and about a third of women will need insulin. In a recent study, De Veciana *et al* addressed the important question of how best to manage insulin treatment in such cases by comparing preprandial and postprandial blood glucose monitoring.[2]

In this study, timing of blood glucose measurement was compared in two groups of 33 patients with gestational diabetes requiring insulin. It was found that adjusting the insulin dose according to the results of postprandial rather than preprandial values improved diabetic control as reflected in concentrations of haemoglobin A_{1c}. Postprandial monitoring at one hour was associated with a lower frequency of neonatal hypoglycaemia and fetal macrosomia, and a lower rate of caesarean section. Pre-eclamptic toxaemia was not reduced.

The design of this study was satisfactory with regards to matching of groups for age, ethnic category, and physical characteristics. The study was not blinded—in practice this would have been difficult to achieve. Blood glucose values were obtained from the patients' own machines and therefore are potentially less accurate than via laboratory assay. Weekly home filter paper profiles[3 4] would have been preferable and complimentary to the use of data from home machines.

In both groups most women (86%) were Hispanic Americans, an ethnic group with a high prevalence of non-insulin dependent diabetes[5] and gestational diabetes and with an enhanced risk of large babies.[6] Furthermore, women in both groups of the study had unusually high blood glucose concentrations discovered at an atypically early stage of pregnancy. These features might not allow the findings to be readily

extrapolated to other ethnic groups or to women with less impaired glucose control. Fasting blood glucose concentrations were not measured in the postprandial group, and postprandial levels were not measured in those testing preprandially. This makes interpretation of the results difficult as preprandial and postprandial blood glucose concentrations are not independent variables.[7 8] The women in the postprandial group had lower haemoglobin A_{1c} concentrations with a higher insulin dose, but since no preprandial levels were measured it is uncertain if improvement in clinical outcome and blood glucose control is largely explicable on the basis of postprandial changes.

It is noteworthy that, in a previous treatment trial of gestational diabetes also including a high proportion of Hispanic Americans, fetal macrosomia was associated inversely with mean and fasting blood glucose concentrations but not with two hour postprandial concentrations.[9] If further studies confirm the importance of adjusting insulin on the basis of postprandial measurements, there might still be a difficulty in extending this principle to pregnant women with insulin dependent diabetes, who could suffer more from preprandial or nocturnal hypoglycaemia. In practice, most experienced diabetologists treating women during pregnancy measure blood glucose both before and two hours after meals. Both values are used in adjusting insulin dosages.

De Veciana *et al*'s study does support the purported benefits of achieving strict diabetic control, particularly in women with a greater gestational impairment of glucose homeostasis. Further controlled trials are still required, and in these the importance of preprandial versus postprandial monitoring could be examined. Investigations are also needed into the reported deleterious effects of maternal hypoglycaemia on intrauterine growth.[10 11]

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Controlling chickenpox in hospitals

Vaccination may be the way forward

Chickenpox seems to be affecting more older people.[1-3] More adult patients are being seen in hospital. The reasons for this are not clear, although Ross and Lantos have suggested that the explanation may simply be the increasing number of immigrants from tropical countries, where fewer adults have immunity to chickenpox.[4] Whatever the reasons for the trend, more adult patients with chickenpox are being seen in hospitals. Chickenpox is highly contagious from two or three days before the rash appears until the lesions crust. Fluid from the vesicles of shingles is also infectious. Chickenpox is potentially a very serious illness in adults, in pregnancy, and in patients who are immunosuppressed (including those taking corticosteroids[5]). Because the disease is transmissible before the rash appears it poses particular problems for the tracing and subsequent management of patients' contacts and also staff contacts.

The new edition of *Immunisation against Infectious Disease 1996*[6] recommends that people at increased risk of severe varicella zoster infection who are exposed to chickenpox or herpes zoster should be tested for antibodies to varicella zoster. If they have no detectable antibodies, human varicella zoster immunoglobulin should be issued. Given within 10 days of exposure, this can at least attenuate the illness in contacts. However, the immunoglobulin is scarce, and acyclovir may therefore have to be given on occasion. Neither alternative necessarily prevents the disease entirely.

Staff contacts who are not immune must be identified because they could transmit the disease to vulnerable patients while incubating the disease themselves. Current standard practice is that non-immune staff are excluded from work from the 10th to the 21st days after exposure to avoid transmission. Prophylactic acyclovir has been used to allow the member of staff to remain at work,[7] but this carries a risk of transmission if the rash breaks through despite the acyclovir.

These infection control measures may seem straightforward, but in practice tracing contacts and obtaining blood samples for antibody testing can be time consuming and expensive. Even the most rigorous efforts will inevitably miss some contacts, either because people are unaware of the risks or unaware that they have been in contact with the disease. Secondary cases may then occur with further risk of transmission. The

measures required to contain outbreaks may be costly: 166 person days of work were lost in a chickenpox outbreak in Brisbane, Australia,[8] and 82 incidents of nosocomial chickenpox in a 30 month period in Britain resulted in 12 secondary cases, £20 000 worth of VZIG being used, susceptible staff being moved from contact with patients, and elective admissions being restricted to those with a history of chickenpox.[2]

The rising incidence of chickenpox in our hospitals and the continued risk posed by inpatients with herpes zoster have led to calls for a targeted vaccination policy. A vaccine against chickenpox has been available for over 20 years. Developed and used extensively in Japan, it has also been licensed in some European countries, and in March 1995 the United States Food and Drug Administration approved its use in persons aged 12 months or over who have not had varicella.[9] Paradoxically, the guidelines for use of the vaccine endorsed by the American Academy of Pediatrics specifically state that it should not be given to children with immunosuppressive disorders. This contrasts with the targeted approach in European countries, where the vaccine is specifically given to such children. The United States authorities delayed approval of the vaccine because of two concerns: that the immunity might decline with age and so lead to a large increase in adult infections and that reactivation of vaccine virus could result in herpes zoster in later life. Similar concerns have also been expressed in Britain,[10] where doubts have also been voiced about universal immunisation on the grounds of a low perceived benefit for the individual child.

Britain has yet to license a varicella vaccine for any indication, though it is available on a compassionate, named patient, basis from Smith Kline Beecham and Pasteur Mérieux MSD. *Immunisation against Infectious Diseases 1996* now goes as far as suggesting that immunisation should be considered for immunosuppressed patients at long term risk of chickenpox. However, the data on the immunogenicity, safety, and efficacy of the vaccine collected for over 20 years have shown that its long term efficacy seems to be good.[11] Studies of use of the vaccine in children with renal transplants have also been favourable.[12] Almost certainly, therefore, lives could be saved by use of the vaccine in certain groups of children or adults for whom chickenpox could be a fatal illness.

Vaccination of non-immune hospital staff would protect both patients and staff as well as simplify infection control measures, but this suggestion is more controversial. More studies are needed since most of the data so far available are from experience with children. The safety and efficacy of the vaccine in adults needs to be confirmed, and information is also needed on the incidence of mild, but possibly infectious disease after vaccination. Nevertheless, the available data support the targeted vaccination of patients and health workers who are at risk. This would reduce the risk of the serious threat of severe varicella zoster infection in immunosuppressed patients. Such a policy would also reduce the costs of controlling outbreaks and days lost from work.

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Polymerase chain reaction

Identifies genes and infectious agents

The polymerase chain reaction (PCR) was devised just over a decade ago, yet it is already an integral part of much biological and medical research. A glance at current journal articles shows that it is also being used to develop new diagnostic tests, which are already having an impact on clinical practice. So it is important for doctors to know the principles on which new tests are based, some of the different versions of the method, and the uses to which they are put.

The polymerase chain reaction is a way of "amplifying" or making multiple copies of any desired piece of nucleic acid. It was first used to make copies of all or part of the DNA of genes. Figure 1 shows the principal steps in the procedure. Firstly, a double strand of DNA is separated into two single strands by heat. Secondly, two rows of nucleotides are marked or "primed" by the addition of two short strands—oligonucleotides—designed to bind specifically on either side of the section of interest in the gene. Thirdly, a polymerase enzyme synthesises a copy of the nucleotide sequence between the primers in the form of a new double strand. Fourthly, the process is repeated and at each stage the number of copies is doubled—from two to four to eight and so on. This can

be done quite simply because all the reagents can be added to one tube and the reactions controlled by changing the temperature (the first reaction at 94°C, the second at 55°C, and the third at 72°C using a special heat stable *Taq* polymerase). As a cycle takes only a few minutes it is possible to generate millions of copies of the DNA in a day.

RNA can also be studied by making a DNA copy of the RNA using the virus enzyme reverse transcriptase. This approach allows us to study messenger RNA (mRNA) in cells that are using the molecule to synthesise specific proteins or for detecting the genome of RNA viruses. Originally, unstable and toxic reagents had to be used, but this can now be avoided.

This technology has transformed the way many molecular studies are done. For example, if you want to determine whether a gene with a particular sequence is present, the polymerase chain reaction will amplify it and other tests can identify it.[1,2] If you want to determine whether a gene is directing a protein to be made in a particular tissue, you can detect the mRNA used to make it by taking the reverse transcriptase approach. You can even detect the particular cells in which it is being made by means of an in situ histochemical version of the test. There are limitations of course. You need to know at least some of the sequence of the gene, and detecting the mRNA does not prove that the protein is being made.

The polymerase chain reaction allows amplification from a convenient cell source of any desired gene sequence. The understanding of transmissible spongiform encephalopathies has been greatly assisted by studying the prion protein (PrP) gene, which seems to play a central role in the pathological process. The region of the gene particularly concerned with susceptibility to the disease has been identified, and this can be amplified and sequenced. For example, the result may show that a particular person has an amino acid substitution (deduced from the nucleotide sequence) that makes them susceptible to the iatrogenic form of Creutzfeldt-Jakob disease or to the familial type.[3]

In other contexts tissue typing may now be performed by probing the cell nucleic acid rather than using serological methods, and the tiny amounts of tissue obtained by chorionic biopsy can be probed for the presence of abnormal genes in the very early fetus. Foreign genetic material—of viruses or bacteria, for example—can be detected with great sensitivity and more rapidly than by conventional techniques. Furthermore, virus nucleic acid may be found when no virus can be recovered, perhaps because the virus has been neutralised or because it is present in a form that will not grow in the laboratory. For example, a recent paper suggested that coxsackievirus nucleic acid was present in the blood of patients suffering from insulin dependent diabetes.[4]

Such findings need to be studied critically from the technical point of view. For example, because the polymerase chain reaction is so sensitive it is possible to contaminate specimens in the laboratory and give rise to false positive results, so suitable control tests have to be run in parallel with the main assay. Of course, only if the whole organism can be grown in the laboratory can its biological properties be established with certainty. However, when the relation between a gene sequence and, say, drug sensitivity is understood—

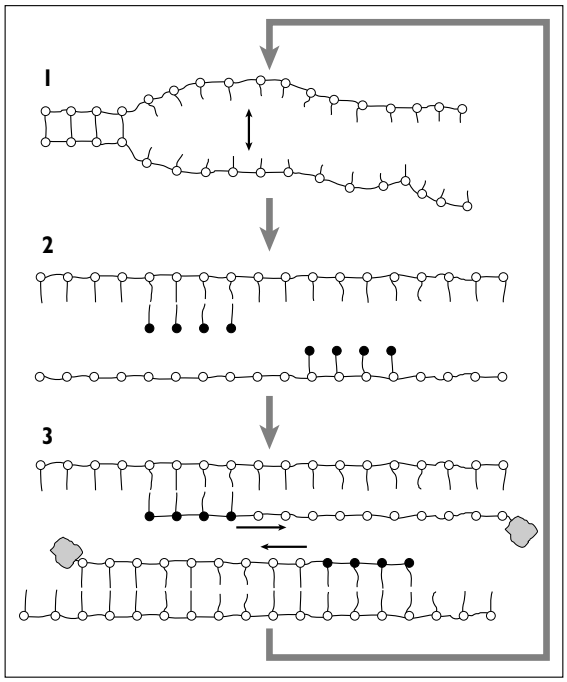

Fig 1 *Principal steps in the polymerase chain reaction (see text)*

as in the case of HIV[5]—or is being discovered—as in the case of the tubercle bacillus[6,7]—tests for the presence of changes in key sequences may give valuable information for assessing and managing cases. There are a few instances—such as Kaposi's sarcoma[8]—in which the apparent causative agent can be detected only by techniques based on the polymerase chain reaction, and others are likely to follow.

Not long ago immunoassays and enzyme linked immunosorbent assays (ELISAs) were regarded as tools for research and nothing more. After much development, often in commercial laboratories, kits are now available so that these powerful techniques are used routinely in hospital laboratories for the care of patients. The same will happen with the polymerase chain reaction. But it is important that we review carefully whether using one of these newly refined tests is the best way to obtain the information we need.

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