The results of Perucchini et al imply that if a fasting glucose threshold of 4.8 mmol/l is used as a screening test 70% of women do not need a diagnostic tolerance test and 19% of cases of gestational diabetes are undetected (1.9% of their population). For a challenge test threshold of 7.0 mmol/l 77% of women do not require a fasting tolerance test and 32% of cases are missed (3.3% of their population). Should a two step strategy be used then the fasting glucose value is preferable to the challenge test as the slight increase in the number of diagnostic tolerance tests needed overcomes the high number of undetected cases of gestational diabetes. In a one step procedure, performing a diagnostic tolerance test only in women with a fasting glucose value higher or equal to 4.8 mmol/l appears to consume fewer resources, human and financial, than submitting all subjects to a tolerance test. However, 19% of the women with gestational diabetes would be missed compared with none with the tolerance test. We do not know the clinical impact of not detecting these cases. Pre-existing but undiagnosed diabetes is unlikely to be missed with a fasting glucose value of 4.8 mmol/l cut off. Anyhow, data on pregnancy outcomes in the undetected cases of gestational diabetes are needed.

A fasting glucose value offers many advantages: it is easy to administer, well tolerated, inexpensive, reliable, and reproducible.[10] However, more studies are required before endorsing the fasting glucose value as the screening test for gestational diabetes. Its validity has to be established with the World Health Organisation and Sacks criteria. Its has to be compared with the 50 g selective screening strategy. The glucose fasting value has to be validated in different populations, especially those with a lower prevalence of gestational diabetes. The threshold of 4.8 mmol/l may need to be revised if screening is done in an office or surgery setting with glucose meters. Meters are generally accurate, but their precision varies. They may not be subject to the same quality control as laboratory assays.[11]

In conclusion, screening for gestational diabetes mellitus with a fasting glucose value is an attractive strategy. What we need now is an assessment of its effectiveness in decreasing the adverse perinatal outcomes associated with gestational diabetes as part of an intervention programme.

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1 Metzger BE, Coustan DR. Summary and recommendations of the fourth international workshop-conference on gestational diabetes mellitus. *Diabetes Care* 1998;21(suppl 2):B1617.
2 O'Sullivan JB, Mahan CM. Criteria for the oral glucose tolerance test in pregnancy. *Diabetes* 1964;13:278-85.
3 Meltzer S, Leiter L, Daneman D, Gerstein HC, Lau D, Ludwig S, et al. Clinical practice guidelines for the management of diabetes in Canada. Canadian Diabetes Association. *Can Med Assoc J* 1998;159(suppl 8):S1-29.
4 Persson B, Hanson U. Neonatal morbidities in gestational diabetes mellitus. *Diabetes Care* 1998;21(suppl 2):B79-84.
5 Canadian Task Force on the Periodic Health Examination: Periodic health examination, 1992 update 1: screening for gestational diabetes mellitus. *Can Med Assoc J* 1992;147:435-43.
6 Langer O, Rodrigues DA, Xenakis EMJ, McFarland MB, Berkus MD, Arredondo F. Intensified versus conventional management of gestational diabetes. *Am J Obstet Gynecol* 1994;170:1036-47.
7 Rey E. Usefulness of a breakfast test in the management of women with gestational diabetes. *Obstet Gynecol* 1997;89:981-8.
8 Perucchini D, Fischer U, Spinas GA, Huch R, Huch A, Lehmann R. Using fasting plasma glucose to screen for gestational diabetes mellitus: prospective population based study. *BMJ* 1999;319:812-5.
9 World Health Organisation. *Diabetes mellitus: report of a WHO study group.* Geneva: WHO, 1985.
10 McCance DR, Hanson RL, Pettitt DJ, Bennett PH, Hadden DR, Knowler WC. Diagnosing diabetes mellitus: Do we need new criteria? *Diabetologia* 1997;40:247-55.
11 Carr SR, Slocum J, Tefft L, Haydon B, Carpenter MW. Precision of office based blood glucose meters in screening for gestational diabetes. *Am J Obstet Gynecol* 1995;173:1267-72.

Treatment options for chronic hepatitis

Antivirals look promising

Over two billion people alive today have been infected with the hepatitis B virus and over 350 million of them are chronically infected carriers, of whom more than 75% are from South East Asia and the Western Pacific region. Although not all carriers are infectious, they represent an important reservoir of infection. Persistent carriers are at high risk of long term complications of infection, including chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Hepatitis B infection claims the lives of 1-2 million people every year and thus represents an important public health challenge. The recent licensing of a new class of drugs may offer much help to the infected populations of South East Asia, but it also poses a set of problems.

Hepatitis B vaccines, introduced in 1982 and incorporated into universal infant immunisation programmes, have proved successful in preventing infection and have reduced significantly the pool of carriers in several countries. Nevertheless, there remains a need for a treatment for persistent carriers to prevent them developing progressive liver disease. Cirrhosis and hepatocellular carcinoma are caused by active replication of hepatitis B virus in the hepatocytes. Hence, the primary goal of treatment is to eliminate the virus or stop its replication and suppress inflammatory processes in the liver.

Interferon alfa is currently licensed for treating chronic hepatitis B, but its use is limited because over half of all patients do not respond to treatment. Overall only 30-40% of white adults have a sustained response to interferon therapy.[1] Similar response rates can be achieved in Asian patients, but only if the patients are carefully selected on evidence of continuing viral replication and liver damage.[2-4] Antiviral agents are therefore being investigated as possible alternative treatment options. To date, the most promising results have been seen with second generation nucleoside analogues,[5] such as lamivudine and famciclovir. Other antiviral agents under evaluation include BMS200, 475, ganciclovir, and adefovir dipivoxil. Combination therapy will probably be required in the longer term.

Though clinical trial results are promising, there is a long way to travel to reach practical regimens that will be useful in routine clinical settings in the countries of

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the Asian-Pacific region. While clinical guidelines can define which patients should be treated and what tests should be used to determine a treatment response, in most developing countries the cost of treatment will be the major limiting factor; and the costs and logistics of screening for asymptomatic hepatitis B infection and assessment of active replicative HBV infection are also substantial. It is therefore important to obtain cost effectiveness data to convince health authorities of the benefits of treatment; establish procurement programmes to ensure the continued availability of good quality drugs; and adapt strategies currently being used to reduce vaccine costs.

From a public health point of view, the overall goal is to ensure that effective treatments for chronic hepatitis B infection are made accessible to those patients who most need them. A product that can be used outside the specialist setting, which affords easier patient management, and which is cheaper than the current standard would take us closer to achieving this goal. Lamivudine is the first of the new antiviral treatment options to be licensed for chronic hepatitis B in the Asian-Pacific region. It is available for treating HIV and AIDS in many countries, and is now being approved for treating chronic hepatitis B. A one year, randomised, double blind clinical trial of over 350 Chinese patients with chronic hepatitis B showed that lamivudine (25 or 100 mg once daily) was associated with significant histological improvement in chronic hepatitis infection compared with placebo.[6] Most patients in this study (334) entered a continuation study, in which those who had received lamivudine were randomised either to continue on lamivudine or to switch to placebo and those who had received placebo switched to lamivudine. In the lamivudine group, DNA reduction, hepatitis B e antigen seroconversion, and normalisation of alanine transaminase values were all sustained after one year, representing a continued response to treatment over the two year treatment period.

Clinical trials have also shown not only that lamivudine is suitable for adults with compensated liver disease but also that it may have a role in treating decompensated liver disease and as a prophylactic against reinfection in patients with liver transplants[7 8] and in paediatric patients.[9] These factors, combined with its good safety profile, oral formulation, and lower cost make it a promising treatment option for a much wider group of patients than can currently be treated with interferon.

In clinical trials some patients treated with lamivudine have developed YMDD variants of hepatitis B. For example, in the large Asian multicentre trial[6] this had occurred in 14% of patients after one year and 42% after two years of treatment. In vitro studies and clinical observations during follow up suggest that these YMDD variants may be less likely to replicate efficiently than wild type hepatitis B virus.[10] Furthermore, in the Asian clinical trials partial virological and clinical responses were maintained in patients with YMDD variants; hepatitis B virus DNA and alanine transaminase levels were reduced and remained lower than baseline values.[11 12] Nevertheless, the long-term clinical importance of the YMDD variants has yet to be defined.

The development of specific antiviral therapies offers a new opportunity to treat chronic carriers of hepatitis B virus. Used in concert with hepatitis B vaccines, these drugs will probably assume an important role in managing chronic hepatitis B, but there is a need to define more precisely the indications for treatment. The consensus among several experts in the Asian-Pacific region is that all patients with chronic hepatitis B infection and evidence of associated liver disease should be considered as candidates for lamivudine therapy.

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1 Dusheiko GM. Lamivudine treatment of chronic hepatitis B. *Rev Med Virol* 1998;8:153-9.
2 Lok AS, Wu PC, Lai CL, Johnson YN, Lau YN, Leung EKY, et al. A controlled trial of interferon with or without prednisone priming for chronic hepatitis B. *Gastroenterology* 1992;102:2091-7.
3 Martin P, Hann HW, Westerberg S, Munoz SJ, Rubin R, Maddrey WC. Interferon-alpha2b therapy is efficacious in Asian-Americans with chronic hepatitis B infection: a prospective controlled trial. *Dig Dis Sci* 1998;43:875-9.
4 Sarin SK, Guptan RC, Thakur V, Malhotra S, Malhotra V, Banerjee K, et al. Efficacy of low-dose alpha interferon therapy in HBV-related chronic liver disease in Asian Indians: a randomized controlled trial. *J Hepatol* 1996;24:391-6.
5 Dusheiko GM. A pill a day, or two, for hepatitis B? *Lancet* 1999; 353:1032-3.
6 Lai CL, Chien RN, Leung NW, Chang T-T, Guan R, Tai D-I, et al. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *N Engl J Med* 1998;339:61-8.
7 Grellier L, Mutimer D, Ahmend M, Brown D, Burroughs AK, Rolles K, et al. Lamivudine prophylaxis against reinfection in liver transplantation for hepatitis B cirrhosis. *Lancet* 1996;348:1212-5.
8 Perrillo R, Rakela J, Dienstage J, Levy L, Martin P, Wright, et al. Multicenter study of lamivudine therapy for hepatitis B after liver transplantation. *Hepatology* 1999;29:1581-6.
9 Sokal E, Roberts EA, Mieli-Vergani G, McPhillips P, Johnson M, Boxall E, et al. Dose finding and safety of lamivudine in children and adolescents with chronic hepatitis B. *Hepatology* 1998;28:489A.
10 Melegari M, Scaglioni PP, Wands JR. Hepatitis B mutants associated with 3 TC and famciclovir administration are replication defective. *Hepatology* 1998;27:628-33.
11 Atkins M, Hunt CM, Brown N, Gray F, Sanathanan L, Woessner M, et al. Clinincal significance of YMDD mutant hepatitis B virus (HBV) in a large cohort of lamivudine-treated hepatitis B patients. *Hepatology* 1998;28:319A and in press.
12 Schiff E. Lamivudine for hepatitis B in clinical practice. *J Med Virol* (in press).

Correction

Nutritional hyperhomocysteinaemia

This editorial by Mohan and Stansby (12 June, pp 1569-70) contained an error in the dose given for folic acid supplementation. The third sentence of the fifth paragraph should have read: "The effective dose of supplementation has not yet been determined, but maximal therapeutic effect is seen with doses over 400 µg [not 400 mg] and after four to six weeks."

We ask all editorial writers to sign a declaration of competing interests (www.bmj.com/guides/confli.shtml#aut). We print the interests only when there are some. When none are shown, the authors have ticked the "None declared" box.