Screening asymptomatic people at high risk for hepatitis C:

The case against

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The hepatitis C virus is usually transmitted parenterally through blood products or shared needles. Most infected people develop mild chronic hepatitis, which tends to pursue an asymptomatic course over years or decades.¹ It is not known how many of those affected will eventually develop clinical sequelae from liver disease.

Risk groups

Screening blood donations for antibodies to the hepatitis C virus has led to a considerable reduction in the incidence of transfusion associated hepatitis.² The United Kingdom's National Blood Transfusion Service has introduced a hepatitis C "lookback" programme to identify and screen those known to have received infected blood before testing of donations began in 1991. Other individuals at risk include injecting drug users, people with haemophilia, and health care workers. According to one estimate there may be 200 000 people with chronic hepatitis C in the United Kingdom.³ Should asymptomatic individuals belonging to these groups be offered screening for hepatitis C? This question raises both medical and ethical issues which share an analogy with screening for infection with HIV.

A positive test result for hepatitis C comes as a devastating blow to a healthy person. Concerns are raised about the mode of viral acquisition, risk of transmission to close contacts, marriage, employment and life insurance prospects, and the future risk of cirrhosis and hepatoma. Recent media coverage has heightened the anxieties of those infected and their families. It is difficult for the doctor to allay these concerns because so many questions about this virus remain unanswered.

The largest group of high risk individuals to consider is current and previous injecting drug users. Studies from around the world have indicated that 60-80% of injecting drug users are infected with hepatitis C.¹ Despite the increasing use of needle exchanges, active injecting drug users will remain at risk of future infection or reinfection with a variety of bloodborne viruses. Many departments offer screening for hepatitis C to these people, even though the risk-benefit of this strategy remains to be evaluated.

Uncertain clinical course

The clinical course of chronic hepatitis C in individual patients cannot be forecast. The widely quoted prediction that 20% of patients with chronic hepatitis C develop cirrhosis within 16 years of infection comes from long term follow up of patients with a history of transfusion associated hepatitis.⁴⁻⁵ There is some evidence that chronic hepatitis C pursues a less aggressive course in cases resulting from injecting drug use.⁶ In many patients the disease may run a prolonged, indolent course with no clinical consequences. Death from liver disease occurred in only 3.3% of 568 patients followed for an average of 18 years after an episode of transfusion associated hepatitis, compared with 1.5% of a control group of 984 patients who had transfusions and did not develop hepatitis.⁷ The possible impact of coinfection with the recently discovered hepatitis G virus, another common cause of post-transfusion hepatitis, also remains to be determined.

Do asymptomatic people benefit from early treatment?

The principles of mass screening require the clinical course of the disease to be understood and for accepted and effective treatment to be available.⁸ The inconsistent results of treatment add to the uncertainty of managing chronic hepatitis C. Interferon alfa is the only licensed treatment and requires thrice weekly subcutaneous injections for between 6 and 18 months.⁹⁻¹⁰ Current recommendations are that, to warrant treatment, patients should have hepatitis C virus RNA detectable in serum, abnormal serum transaminase activity, and histological evidence of moderate or severe inflammatory activity on liver biopsy. With these criteria a sustained response, defined as a normal serum alanine transaminase activity persisting six months after treatment is stopped, is achieved in only 25% of patients. Unfortunately these biochemical end points may underestimate the risk of virological relapse, a factor that becomes increasingly common on long term follow up.¹¹ Furthermore it will take many years to determine whether interferon reduces the risk of progression to cirrhosis and hepatoma.

It is recognised that hepatitis C patients with genotype 1, cirrhosis, pronounced obesity, immunosuppression, and iron overload all have reduced probability of response to interferon.³ Also, patients with mild infection and normal serum transaminase activity do not seem to respond.¹² It may therefore be possible to select a subgroup of patients who are more likely to benefit from treatment, but further data is required to confirm this.

It has been recommended that all asymptomatic carriers of hepatitis C should undergo liver biopsy irrespective of their serum transaminase activities, because up to a third will show histological features of chronic active hepatitis or cirrhosis.¹³ Asymptomatic patients recruited into treatment programmes have appreciable morbidity related to repeated liver biopsies and the side effects of interferon alfa. Regular clinic visits and blood tests are required to monitor treatment. It is not clear that the current benefits of treatment warrant these undesirable intrusions. The cost of assessment, investigation, and treatment of chronic hepatitis C is very high. One evaluation of cost effectiveness showed that 1% of lives might be saved at a cost per life saved of \$616 000 or a cost of \$72 000 per life year gained.¹⁴ These costs compare unfavourably with the cost of other health care interventions.

Will mass screening prevent transmission?

It could be argued that the anxieties engendered by screening might be acceptable if there were evidence that people testing positive for hepatitis C could reduce the risks to themselves and to others by preventive measures. It is becoming increasingly clear, however, that the hepatitis C virus is of low infectivity unless transmitted by contaminated needles or blood products. Mother to infant transmission can occur, but the risk is low unless the mother is coinfecting with HIV.¹⁵ Heterosexual transmission has been identified,¹⁶ but large cohorts of partners of infected individuals have been tested for antibodies to the hepatitis C virus, with negative results. Homosexual transmission seems to be

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BMJ 1996;312:1349-50

uncommon also. Those found by screening to have hepatitis C should be advised to avoid sharing needles, minimise alcohol intake, and use barrier methods of contraception in new relationships. Wider introduction of needle exchange schemes and health education programmes might prove to be more practical and cost effective than mass screening for reducing the spread of hepatitis C.

Conclusions

People who request hepatitis C screening should be offered careful counselling before testing. There should be specialist follow up for those found to be infected. More widespread screening of asymptomatic individuals cannot be justified until the course of the disease is better understood, treatment with clear clinical benefit becomes available, or a vaccine is produced.

- 1 Alter MJ. Epidemiology of hepatitis C in the West. *Semin Liver Dis* 1995;15:5-14.
- 2 Donahue JG, Munoz A, Ness PM, Brown DE Jr, Yawn DH, McAllister HA Jr, et al. The declining risk of post-transfusion hepatitis C virus infection. *N Engl J Med* 1992;327:369-73.
- 3 Booth JCL, Brown JL, Thomas HC. The management of chronic hepatitis C virus infection. *Gut* 1995;37:449-54.
- 4 DiBisceglie AM, Goodman ZD, Ishak KG, Hoofnagle JH, Melpolder JJ, Alter HJ. Long-term clinical and histopathological follow-up of chronic post-transfusion hepatitis. *Hepatology* 1991;14:969-74.

- 5 Tremolada F, Casarin C, Alberti A, Drago C, Tagger A, Ribero M, et al. Long-term follow-up of non-A, non-B (type C) post-transfusion hepatitis. *J Hepatol* 1992;16:273-81.
- 6 Gordon SC, Elloway RS, Long JC, Dmuchowski CF. The pathology of hepatitis C as a function of mode of transmission: blood transfusion vs. intravenous drug use. *Hepatology* 1993;18:1338-43.
- 7 Seeff LB, Buskell-Bales Z, Wright EC, Durako SJ, Alter HJ, Iber FL, et al. Long-term mortality after transfusion-associated non-A, non-B hepatitis. *N Engl J Med* 1992;327:1906-11.
- 8 Neugut AI, Pita S. Role of sigmoidoscopy in screening for colorectal cancer: a critical review. *Gastroenterology* 1988;95:492-9.
- 9 Dusheiko G.M. Rolling review—the pathogenesis, diagnosis and management of viral hepatitis. *Aliment Pharmacol Ther* 1994;8:229-53.
- 10 Poyndar T, Bedossa P, Chevallier M, Mathurin P, Lemonnier C, Trepo C, et al. A comparison of three interferon alpha-2b regimens for the long-term treatment of chronic non-A, non-B hepatitis. *N Engl J Med* 1995;332:1457-62.
- 11 Lau JYN, Mizokami M, Ohno T, Diamond DA, Kniffen J, Davis GL. Discrepancy between biochemical and virological responses to interferon-alpha in chronic hepatitis C. *Lancet* 1993;342:208-9.
- 12 Sangiovanni A, Spinzi GC, Sciarada R, Prada A, Bissoli F, Morales R, et al. Randomized controlled trial of HCV healthy carriers treatment with interferon. *Hepatology* 1995;22:290A.
- 13 McMahon RF, Yates AJ, McLindon J, Babbs C, Love EM, Warnes TW. The histopathological features of asymptomatic hepatitis C virus-antibody positive blood donors. *Histopathology* 1994;24:517-24.
- 14 Shiell A, Briggs A, Farrell GC. The cost effectiveness of alpha interferon in the treatment of chronic active hepatitis C. *Med J Aust* 1994;160:268-72.
- 15 Zanetti AR, Tanzi E, Paccagnini S, Principi N, Pizzocolo G, Caccamo ML, et al. Mother-to-infant transmission of hepatitis C virus. *Lancet* 1995;345:289-91.
- 16 Thomas DL, Zenilman JM, Alter HJ, Shih JW, Galai N, Carella AV, et al. Sexual transmission of hepatitis C virus among patients attending sexually transmitted disease clinics in Baltimore - an analysis of 309 sex partnerships in Baltimore. *J Infect Dis* 1995;171:768-75.

Lesson of the Week

Paradoxical embolism in a young woman

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Paradoxical embolus should be considered in all patients with acute arterial occlusion but no obvious arterial embolic source

Acute arterial ischaemia of the lower limb is common and mainly affects elderly people. It is usually due to thrombosis or embolism from a source in the left side of the heart. We describe the case of a young woman who presented with evidence of acute arterial embolism and venous thrombosis. This highlights a diagnosis that should be considered in all patients with an unusual presentation of leg ischaemia.

Case report

After an alcoholic binge a 31 year old woman fell asleep in an uncomfortable position curled up on a sofa. She woke the next morning with blue swollen feet that were tingling. She ignored this, but over the next seven days her condition deteriorated and her feet became more painful and blistered. When admitted to the local hospital, she was dishevelled and dehydrated with a fever of 39.5°C. Her heart rate on admission was 70 beats/min in sinus rhythm, and she was hypotensive at 90/60 mm Hg. There were no heart murmurs. Her foot pulses were impalpable, which was thought to be due to oedema; her pulse status was not investigated further at this stage. She was thought to have bilateral leg cellulitis and was treated with intravenous antibiotics. When her right leg failed to improve after three days she was reviewed by the local surgeons, who correctly diagnosed arterial ischaemia, started anticoagulation treatment with heparin, and arranged for transfer to this hospital.

On admission her general condition had improved, but the right foot was clearly unsalvageable and there was a large ulcer over the dorsum of the left foot (fig 1). Examination of the leg pulses showed the absence of a right femoral arterial pulse, while in the left leg pulses were palpable as far as the popliteal fossa. Occlusions of the right common femoral and left distal popliteal arteries were confirmed by duplex Doppler ultrasonography, which also unexpectedly showed an extensive left iliofemoral deep vein thrombosis. Angiography con-

firmed the ultrasonographic findings and showed poor flow in only one vessel in both calves. Arterial embolism, in particular paradoxical embolus, was suspected. Transoesophageal echocardiography showed no obvious embolic source, but a patent foramen ovale with a reversible shunt was demonstrated during Valsalva's manoeuvre. The right ventricle was dilated, and pulmonary embolism was subsequently confirmed by a ventilation-perfusion scan. Interestingly, the electrocardiogram recorded on admission to our hospital had shown a typical S1, Q3, T3 pattern consistent with pulmonary embolism despite the absence of respiratory symptoms and signs. A diagnosis of paradoxical arterial embolus was made.

Anticoagulation was continued, but long term compliance with warfarin was thought to be unlikely because of the patient's poor social circumstances, and a Venatech inferior vena caval filter was therefore inserted. Above knee amputation of the right leg was performed, and this has healed well. The patient has had no further embolic episodes, the caval filter is working without obvious complication, and she has been advised to continue warfarin treatment.

Comment

Paradoxical embolism describes the passage of a venous embolus across an intracardiac defect or a right to left shunt across the great vessels to lodge in the systemic arterial circulation. The shunt may be a consequence of congenital heart disease but can also occur across a patent foramen ovale if right atrial pressure exceeds that in the left atrium. Such a pressure reversal is a transient occurrence during the normal cardiac cycle, but it may also occur when right atrial pressure is raised physiologically during Valsalva's manoeuvre or pathologically in right heart failure or acute pulmonary embolus.¹

Paradoxical embolus is a rarely diagnosed cause of arterial ischaemia, but it would be recognised more often if

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BMJ 1996;312:1350-1