home that sensible drinking is pleasurable, but that children know that excessive drinking can be highly problematic. Allowing children in their early teens to drink small quantities of alcohol in the home may well be the best way to give them the skills to drink sensibly once they start to drink elsewhere.

PHILIP GRAHAM

Developmental Psychiatry Section,
Department of Psychiatry,
University of Cambridge,
Douglas House,
18b Trumpington Road,
Cambridge CB2 2AH

1 Royal College of Physicians. *Alcohol and the young.* Report of a Joint Working Party of the Royal College of Physicians and British Paediatric Association. London: Royal College of Physicians, 1995.
2 Day NL. Research on the effects of prenatal alcohol exposure—a new direction. *Am J Public Health* 1995;85:1614-5.
3 Larroque B, Kaminski M, Dehaene P, *et al.* Moderate prenatal alcohol exposure and psychomotor development at preschool age. *Am J Public Health* 1995;85:1654-61.
4 Abel EL. An update on incidence of FAS: FAS is not an equal opportunity defect. *Neurotoxicol Teratol* 1995;17:437-43.
5 Kelleher K, Chaffin M, Hollenberg J, *et al.* Alcohol and drug disorders among physically abusive and neglectful parents in a community based sample. *Am J Public Health* 1994;84: 158690.
6 Mayhew P, Maughan NA, Mirrlees-Black C. *The British crime survey.* London: HMSO, 1992.
7 Wolfe DA. Children of battered women: the relation of child behavior to family violence and maternal stress. *J Consult Clin Psychol* 1985;53:657-65.
8 Sher K. *Children of alcoholics: a critical appraisal of theory and research.* Chicago, Chicago University Press, 1991.
9 Office of Population Censuses and Surveys. *Teenage drinking in 1994.* London: OPCS, 1994.
10 Green G, Macintyre S, West P, *et al.* Like parent like child? Associations between drinking and smoking behaviour of parents and their children. *British Journal of Addiction* 1991;86:745-58.
11 King AJC, Coles B. *Views and behaviors of 11,13 and 15 year olds from 11 countries.* Ottawa: Ministry of National Health and Welfare, 1992.
12 Lynskey MT, Fergusson DM. Childhood conduct problems, attention deficit, and adolescent alcohol, tobacco and illicit drug use. *J Abnorm Child Psychol* 1995;23:281-302.
13 Rossow I, Wichstrom L. Parasuicide and use of intoxicants among Norwegian adolescents. *Suicide Life Threat Behav* 1994;24:174-83.
14 Edwards G, Anderson P, Babor T, *et al. Alcohol policy and the public good.* Oxford: Oxford University Press,1994
15 Sutton M, Godfrey C. *The health of the nation targets for alcohol: a study of the economic and social determinants of high alcohol consumption in different population groups.* York: University of York, Centre for Health Economics, 1994.
16 Department of Health. *Sensible drinking.* Report of an Interdepartmental Working Group. London: Department of Health, 1995.
17 Royal College of Physicians, Royal College of Psychiatrists, Royal College of General Practitioners. *Alcohol and the heart in perspective: sensible limits reaffirmed.* London: Royal College of Physicians, 1995.
18 Alcohol Concern. *Pop fiction? The truth about alcopops.* London: Alcohol Concern, 1996.
19 Hansen WB, Johnson CA, Flay BR, *et al.* Affective and social approaches to prevention of multiple substance abuse among seventh grade students: results from Project SMART. *Prev Med* 1988;18:135-54.
20 Health Advisory Service. *Review of services for children and adolescents who misuse alcohol and other substances.* Sutton, Surrey: HAS Advisory Service, 1995.

Hepatitis C infection after blood product transfusion

The cloning of the hepatitis C virus (HCV) [1] and the subsequent development of sophisticated serological assays [2] has lead to the identification of HCV as the major cause of hepatitis after transfusion in adults and children. Many questions remain with regard to methods of transmission, natural history, and outcome of infected children, and the indications and efficacy of potential treatment.

Transmission of infection

The risk of infection is mainly confined to children who received blood products or transplanted organs before 1990 when universal screening for HCV was established. HCV transmission has been reported with all blood products including factor VIII,[3] immunoglobulin D,[4] and immunoglobulin infusions.[5] Although passive transfer of HCV antibodies from blood products has been reported and may lead to confusion,[6] the risk of active infection is highest in children who received multiple transfusions or pooled blood products for their underlying disease.[7]

The current Blood Transfusion Service 'Look Back' study (in which all blood donors before 1991 are screened for HCV and both donors and any previous recipients traced) has confirmed reports from many centres worldwide that the children most at risk include those with haemolytic anaemia,[8] previous leukaemia,[9] solid organ tumours,[10] haemophiliacs,[7] renal dialysis patients,[11] and bone marrow,[12] kidney,[13] and liver transplant recipients.[14 15]

Currently, the prevalence of HCV infection in British blood donors is low (<1%) compared with other parts of the world such as Egypt,[16] Italy,[17] and Japan.[18] The high prevalence in these countries may be related to sporadic infection as well as to intrafamilial and sexual transmission, which may be as high as 15% in Italy [17] and 24% in Japan,[18] although uncommon in other populations.[4]

It is clear that while sexual transmission does occur over time and may be the main route of intrafamilial spread,[19] the risk is less with HCV than with hepatitis B or HIV. In contrast to hepatitis B, vertical transmission is less likely (1-10%).[20] Although passive transfer of maternal HCV antibodies to their babies has been recorded,[20] active infection is unlikely unless associated with high levels of maternal HCV RNA [21] or co-infection with HIV.[22] Breast feeding does not transmit HCV.[23]

Diagnostic tests

The initial diagnosis of HCV depended on first generation assays which demonstrated antibody to a recombinant HCV structural protein c-100.[2] Subsequent assays which incorporated other structural and non-structural antigens have increased sensitivity, particularly the third generation recombinant immunoblast assay (RIBA-II).[2] Nevertheless these assays do not differentiate previous exposure from ongoing infection or passive antibody transfer.[6]

The development of methodology to detect and quantify HCV RNA by reverse transcription polymerase chain reaction (RT-PCR) is more specific [24] and may be a sensitive marker of both infection and of underlying liver disease.[25] Diagnostic confusion arose with the early ELISA assays in which there was false positivity in patients with autoimmune hepatitis [26] or syphilis.[27] Such patients with non-specific positivity are likely to be both RIBA negative and HCV- RNA negative. Identification of HCV genotype (I to VI) does not improve diagnostic yield but may predict natural history or response to treatment as patients with genotype I appear to be less responsive to interferon.[28 29]

Natural history of HCV infection

There is little current information about the natural history of HCV infection in childhood. The available information is based on small studies over the last five years or extrapolated from adult studies in patients with post-transfusion hepatitis. It is likely that the natural history and risk of progression to liver disease will vary depending on the underlying disease for which the blood products were required.

Anti-HCV antibodies may persist in patients with resolved infection or may disappear at some time after a self limiting hepatitis.[30] A study in kidney transplant recipi-

ents reported that up to 90% of children remained infected and at least 80% had biochemical evidence of hepatitis.[13] A similar study identified that 45% of children infected after open heart surgery had persistent HCV infection with biochemical hepatitis. The remaining 55% of patients who became HCV seropositive had absent HCV RNA, and normal hepatic transaminase values indicating resolved HCV infection.[31]

It may be difficult to define the extent of liver disease as there is no correlation between HCV seropositivity and the development of chronic liver disease, although the likelihood of coexisting liver disease is increased if hepatic transaminase values are raised.[25] A number of studies have indicated that there is no good correlation between transaminase values and histological evidence of hepatic inflammation and thus it may be necessary to perform a liver biopsy to assess the extent of histological damage.[32]

Adult studies have indicated that HCV infection is associated with significant chronic liver disease, progression to cirrhosis in 20–30% and the development of hepatocellular carcinoma in some patients. It is likely that the rate of progression from infection to liver disease and cancer may extend over 30 years.[33 34]

A recent review of 33 children with cryptogenic chronic liver disease in Italy indicated that HCV infection was responsible in 48% of the patients of whom 88% had previous parenteral exposure. Only 11% of children developed normal liver function but none developed liver failure, suggesting that HCV caused a low grade hepatitis in this group of children.[35] Two similar studies supported this finding as approximately 42% of children with parenterally acquired HCV infection developed a mild to moderate hepatitis over three years without cirrhosis.[36 37]

In 17 children who had survived malignant disease an aggressive hepatitis was identified in 30%, although there was no progression of the liver disease within a year.[38] In addition, an Italian study found no evidence of cirrhosis in 13 HCV positive children followed up over four years.[37] It seems that approximately 40% of infected children will develop hepatitis but the rate of progression to cirrhosis has not yet been determined.

The risk of developing liver disease may be higher in children who have been previously treated for malignancy[38] or in haemophiliacs with co-infection with HIV[39] and in patients with thalassaemia who have underlying hepatic haemosiderosis.[40]

Although non-specific autoantibodies may be associated with HCV infection, there is some evidence that the virus stimulates an autoimmune reaction, with the production of liver/kidney microsomal antibodies[41] creating difficulties with both diagnosis and treatment.

Treatment of HCV

The long term studies in adults indicating the significance of HCV in the development of chronic liver disease and cancer,[33 34] and the recent publication of effective treatment with interferon, have lead to pressure for treatment of HCV in childhood. In two large studies, 50% of adults demonstrated histological and biochemical response to interferon alfa within 4–12 months of starting treatment.[42 43] Relapse followed cessation of treatment in half the patients within three months. Those patients who had a shorter disease duration, were younger, had less active liver disease with low hepatic alanine transaminase and low HCV RNA values or genotype 2 had a more favourable outcome.[29]

To date there are few published studies documenting the response of interferon alfa treatment in children with chronic HCV infection. Twenty one of 51 treated patients with thalassaemia had disappearance of HCV RNA

without significant relapse when interferon was discontinued.[44] A similar adult study in thalassaemic patients reported that although 73% of patients initially responded only 53% had a complete response,[45] suggesting that children may respond better. An uncontrolled Spanish study that treated 12 children with interferon alfa (3 MU/m² three times a week for six months) reported that 90% of children had normalisation of liver biochemistry and improved histology at 15 months but only 60% cleared HCV RNA.[46]

A controlled study in 21 Italian children using lymphoblastoid interferon alfa (3 MU/m² three times a week for 12 months) reported that 45% of children responded with loss of HCV RNA and associated histological improvement. There was no relapse up to 30 months follow up.[47] A second study using a higher dose of recombinant interferon alfa (5 MU/m² three weekly for four months) had similar findings.[48]

In contrast, a pilot study of six patients who had previously been cured of malignancy showed no response to interferon alfa (4 MU/ m² for 12 months) and no patient cleared HCV RNA,[49] suggesting that this group of children may be more resistant to treatment.

The addition of oral ribavirin to interferon treatment has some encouraging results in adults[50] but is not yet available for use in children. Liver transplantation for end stage HCV liver disease is only effective in the short term as recurrence of HCV is almost 100% and may cause severe graft damage.[51 52]

Selection for treatment

Selection for treatment is controversial and is based on the results from adult studies and the few studies in childhood. The aim of treatment should be to eradicate the HCV by achieving complete loss of HCV RNA from both liver and serum and thus prevent the progression to chronic liver disease, cirrhosis, and the development of liver cancer.

There is general agreement that children who have evidence of ongoing infection (that is, who remain HCV RNA positive) and in whom there is evidence of biochemical or histological liver disease should be considered for treatment as discussed below. It is not yet clear whether treatment is indicated for active HCV infection without liver disease. Adult studies have indicated that the response to treatment is improved in those who have a shorter duration of disease[29] and thus response may be improved in HCV infected children before the development of liver disease.

Treatment schedule

Any child selected for treatment should have a full evaluation of liver function. This should include abdominal ultrasound and α fetoprotein to detect hepatic carcinoma, HCV genotype to determine response to interferon, liver biopsies before and after treatment, serial liver function tests, HCV serology, and HCV RNA estimation.

Treatment should consist of subcutaneous interferon alfa in dosages ranging from 3–6 MU/m² three times a week for at least six months with subsequent maintenance treatment considered for those children who respond with a reduction or complete loss of HCV RNA. As our understanding of the natural history and response to treatment for hepatitis C is limited it is essential that these children should be managed and treated only as part of scientific multicentre based studies.

Summary

HCV infection has been demonstrated in multiply transfused children who received blood products or transplanted organs before universal screening in 1990. The risk

of active infection is related to the number of transfusions or pooled blood products. Accurate diagnosis of infection is dependant on utilisation of third generation RIBA and identification of HCV RNA by RT-PCR.

The natural history of HCV in childhood is undetermined and prospective long term studies should be undertaken. It is likely that about 40% of infected children will develop chronic hepatitis with progression at some time to cirrhosis and have an increased risk of developing liver cancer. Treatment with interferon alfa may be effective in up to 50% of children and only those children with documented infection with HCV RNA should be selected for treatment. In order to answer important questions about natural history, outcome, and the necessity and efficacy of treatment response, treatment for these children should only be as part of scientifically conducted studies on a multicentre basis.

D A KELLY

Birmingham Children's Hospital NHS Trust,
Ladywood Middleway, Ladywood,
Birmingham B16 8ET.

1 Choo Q-L, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A non-B viral hepatitis genome. Science 1989;244:359-62.
2 McHutchinson J, Person JL, Govindarajan S, et al. Improved detection of hepatitis C virus antibodies in high-risk populations. Hepatology 1992;15:19-25.
3 Shopnick RI, Brettler DB, Bolivar E. Hepatitis C virus transmission by monoclonal purified viral-attenuated factor VIII concentrate. Lancet 1995;346:645.
4 Meisel H, Reip A, Faltus B, et al. Transmission of hepatitis C virus to children and husbands by women infected with contaminated anti-D immunoglobulin. Lancet 1995;345:1209-11.
5 Taliani G, Guerra E, Rosso R, et al. Hepatitis C virus infection in hypogammaglobulinemic patients receiving long-term replacement therapy with intravenous immunoglobulin. Transfusion 1995;35:103-7.
6 Kuderia G, Price C, Chewley J. Passively transfused hepatitis C antibody. Lancet 1992;340:1291.
7 Eyster ME, Fried MW, Di Bisceglie AM, Goedert JJ. Increasing hepatitis C virus RNA levels in hemophiliacs: relationship to human immunodeficiency virus infection and liver disease. Multicenter Hemophilia Cohort Study. Blood 1994;84:1020-3.
8 Devault KR, Friedman LS, Westerberg S, Martin P, Hosein B, Ballas SK. Hepatitis C in sickle cell anaemia. J Clin Gastroenterol 1994;18:206-9.
9 Arico M, Maggiore G, Silini E, et al. Hepatitis C infection in children treated for acute lymphoblastic leukemia. Blood 1994;84:2919-22.
10 Monteleone PM, Andrzejewski C, Kelleher JF. Prevalence of antibodies to hepatitis C virus in transfused children with cancer. Am J Pediatr Hematol Oncol 1994;16:309-13.
11 Schlipkoter U, Gladziwa U, Cholmakov K, et al. Prevalence of hepatitis C virus infections in dialysis patients and their contacts using a second generation enzymed-linked immunosorbent assay. Med Microbiol Immunol-(Berl) 1992;181:173-80.
12 Fujii Y, Kaku K, Tanaka M, Kaneko T, Matumoto N, Shinohara K. Hepatitis C virus infection and liver disease after allogeneic bone marrow transplantation. Bone Marrow Transplant 1994;13:523-6.
13 Orloff SL, Stempel CA, Wright TL, et al. Long-term outcome in kidney transplant patients with hepatitis C (HCV) infection. Clin Transplant 1995;9:119-24.
14 Pastore M, Willems M, Cornu C, et al. Role of hepatitis C virus in chronic liver disease occuring after orthotopic liver transplantation. Arch Dis Child 1995;72:403-7.
15 Nowicki MJ, Ahmad N, Heubi JE, Kuramoto IK, Baroudy BM, Balistreri WF. The prevalence of hepatitis C virus (HCV) in infants and children after liver transplantation. Dig Dis Sci 1994;39:2250-4.
16 el Gohary A, Hassan A, Nooman Z, et al. High prevalence of hepatitis C among urban and rural population groups in Egypt. Acta Tropica 1995;59:155-61.
17 Napoli N, Fiore G, Vella F, Fera G, Schiraldi O. Prevalence of antibodies to hepatitis C among family members of patients with chronic hepatitis C. Eur J Epidemiol 1993;9:629-32.
18 Oshita M, Hayashi N, Kasahar A, et al. Prevalence of hepatitis C virus in family members of patients with hepatitis C. J Med Virol 1993;41:251-5.
19 Marino N, Di Pietro M, Moschitto P, et al. Intrafamily spread of hepatitis C virus infection. Microbiologica 1994;17:147-50.
20 Roudot-Thoraval F, Powlotsky JM, Thiers V, et al. Lack of mother-to-infant transmission of hepatitis C virus in human immunodeficiency virus-

21 Resti M, Azzari C, Lega L, et al. Mother-to-infant transmission of hepatitis C virus. Acta Paediatr 1995;84:251-5.
22 Weinrub PS, Veereman-Wauters G, Cowan MJ, Thaler MM. Hepatitis C virus infection in infants whose mothers took street drugs intravenously. J Pediatr 1991;119:92931.
23 Lin HH, Kao JH, Hsu HY, et al. Absence of infection in breast-fed infants born to hepatitis C virus infected mothers. J Pediatr 1995;126:589-91.
24 Parvaz P, Guichard E, Chevallier P, Ritter J, Trepo C, Sepetjan M. Hepatitis C: description of a highly sensitive method for clinical detection of viral RNA. J Virol Methods 1994;47:83-94.
25 Read AE, Donegan E, Lake J, et al. Hepatitis C in liver transplant recipients. Transplant Proc 1991;23:1504-5.
26 Abuaf N, Lunel F, Giral P, et al. Non organ specific autoantibodies associated with chronic hepatitis C virus. J Hepatol 1993;18:359-64.
27 Thomas DL, Rompalo AM, Zenilman J, Hoover D, Hook EW, Quinn TC. Assocation of hepatitis C virus infection with false-positve tests for syphilis. J Infect Dis 1994;170:157981.
28 van der Poel CL, Cuypers HT, Reesink HW. Hepatitis C virus six years on. Lancet 1994;344:1475-9.
29 Tsubiota A, Chayama K, Ikeda K, et al. Factors predictive of response tointerferon-alpha therapy in hepatitis C virus infection. Hepatology 1994;19:1088-94.
30 Al-Mahroos FT, Ebrahim A. Prevalence of hepatitis B, hepatitis C and human immune deficiency virus markers amoung patients with hereditary haemolytic anaemias. Ann Trop Paediatr 1995;15:121-8.
31 Matsuoka S, Tatara K, Hayabuchi Y, Nii M, Mori K, Kuroda Y. Post-transfusion chronic hepatitis C in children. J Paediatr Child Health 1994;30:544-6.
32 Naito M, Hayashi N, Hagiwara H, et al. Serum hepatitis C virus RNA quantity and histological features of hepatitis C virus carriers with persistently normal ALT levels. Hepatology 1994;19:871-5.
33 Bruix J, Calvet X, Costa J, et al. Prevalence of antibodies to hepatitis C virus in Spanish patients with hepatocellular carcinoma and hepatic cirrhosis. Lancet 1989;i:1004-6.
34 Jeffers LJ, Hasan F, De Medina M, et al. Prevalence of antibodies to hepatitis C virus among patients with cryptogenic chronic hepatitis and cirrhosis. Hepatology 1992;15:187-90.
35 Bortolotti F, Vajro P, Cadrobbi P, et al. Cryptogenic chronic liver disease and hepatitis C virus infection in children. J Hepatol 1992;15:73-6.
36 Bortoletti F, Vajro P, Barbera C, et al. Hepatitis C in childhood epidemiological and clinical aspects. Bone Marrow Transplant 1993; 12: suppl 21-3.
37 Iorio R, Guida S, Porzio S, Fariello I, Vegnente A. Chronic non-A non-B hepatitis: role of hepatitis C virus. Arch Dis Child 1993;68:219-22.
38 Inui A, Fujisawa T, Miyagawa Y, et al. Histological activity of the liver in children with transfusion-associated chronic hepatitis C. J Hepatol 1994;21:748-53.
39 Eyster ME, Diamondstone LS, Lien JM, Ehmann WC, Quan S, Goedert JJ. Natural history of hepatitis C virus infection in multi-transfused haemophiliacs: effect of co-infection with human immunodeficiency virus. Journal of Acquired Immune Deficiency Syndromes 1993;6:602-10.
40 Zurlo MG, De Stefano P, Borgna-Pignatti, et al. Survival and causes of death in thalassaemia major. Br J Haematol 1993;15:202-6.
41 Ma Y, Peakman M, Lobo-Yeo A, et al. Differences in immune recognition of cytochrome P4502D6 by liver kidney microsomal (LKM) antibody in autoimmune hepatitis and chronic hepatitis C virus infection. Clin Exp Immunol 1994;97:94-9.
42 Davies GL, Balart LA, Schiff ER, et al. Treatment of chronic hepatitis C with recombinant interferon alpha; a multicentre randomized, controlled trial. N Engl J Med 1989;321:1501-6.
43 Di Bisceglie AM, Martin P, Kassianides C, et al. Recombinant interferon alpha therapy for chronic hepatitis C. A randomized double-blind, placebo-controlled trial. N Engl J Med 1989;321:1506-10.
44 Clemente MG, Congia M, Lai ME, et al. Effect of iron overload on the response to recombinant interferon-alfa treatment in transfusion-dependent patients with thalassemia major and chronic hepatitis C. J Pediatr 1994;125:123-8.
45 Wonke B, Donohue SM, Hoffbrand AV, Scheuer PJ, Brown D, Dusheiko G. Recombinant alpha 2B interferon (IFN) in the treatment of chronic hepatitis C disease in thalassaemia major (TM). Bone Marrow Transplant 1993; 12 (suppl 1): 24-5.
46 Ruiz-Moreno M, Rua MJ, Castillo I, et al. Treatment of children with chronic hepatitis C with recombinant interferon-alpha: a pilot study. Hepatology 1992;16:882-5.
47 Iorio R, Pensati P, Porzio S, Sariello I, Guida S, Vegnente A. Lymphoblastoid interferon alpha treatment in chronic hepatitis C. Arch Dis Child 1996; 74:152-6.
48 Bortolotti F, Giacchino R, Vajro P, et al. Recombinant interferon alpha therapy in children with chronic hepatitis C. Hepatology 1995;22:1623-7.
49 Cesaro S, Rosetti F, De Moliner L, Crivellaro C, Zanesco L, Bortolotti F. Interferon for chronic hepatitis C in patients cured of malignancy. Eur J Pediatr 1994;153:659-62.
50 Sakamoto N, Enomoto N, Marumo F, Sato C. Prevalence of hepatitis C virus infection among long-term haemodialysis patients: detection of hepatitis C virus RNA in plasma. J Med Virol 1993;39:11-5.
51 Wright TL, Donegan E, Hsu HH, et al. Recurrent and acquired hepatitis C viral infection in liver transplant recipients. Gastroenterology 1992;103:317-22.
52 Gane E, Portmann B, Naoumov N, et al. Long-term outcome of hepatitis C infection after liver transplantation. N Engl J Med 1996;334:815-20.