Epidemiology of the hepatitis C virus

Nick Crofts

Sandy Thompson

John Kaldor

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Consultants

Dr Nick Crofts and Dr Sandy Thompson

Epidemiology and Social Research

The Macfarlane Burnet Centre for Medical Research

Professor John Kaldor

Epidemiology

The National Centre in HIV Epidemiology and Clinical Research

Contact

Epidemiology and Social Research Unit

The Macfarlane Burnet Centre for Medical Research

PO Box 254, Fairfield, Victoria 3078

Phone: (03) 9282 2169

Fax: (03) 9482 3123

Email: crofts@burnet.edu.au

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Contents

Project team

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Executive summary

The availability since 1990 of commercial assays to test for infection with the hepatitis C virus (HCV) enabled investigation of its epidemiology to begin in earnest. Current serological assays do not distinguish between incident and old infections, or whether infections acquired have resolved or remain to cause ongoing liver damage. Measurement of markers in the serum does not necessarily reflect what is occurring in the liver. Moreover, the costs associated with tests such as quantitative polymerase chain reaction (PCR), genotyping and serotyping, in addition to the need to avoid repeated invasive liver biopsies, means that our knowledge at this early stage of investigation of the epidemic is imperfect. This report of the epidemiology of HCV summarises the state of knowledge to the end of 1998. The report is based upon extensive literature reviews of the world medical literature and the compilation of a research register that identifies Australian studies completed or in progress and the ideas which researchers and practitioners involved in HCV have identified as areas where information is deficient.

The hepatitis C virus in Australia

Although there are Australian data on the prevalence and incidence of HCV in some specific populations, including those at high risk of infection, there are no reliable data on its prevalence in the general population. It has been estimated that there are already about 143,000 Australian residents currently chronically infected with HCV, and that around 11,000 new infections are acquired each year among injecting drug users (IDUs). These figures are based upon extrapolations of small surveys and make several assumptions. We have poor data about participation in particular activities associated with transmission or about the average risk of transmission per event.

Transmission of hepatitis C virus

Injecting drug use

The major group in which transmission of HCV is ongoing is IDUs. The strongest predictor of risk among IDUs is duration of injecting: opiate as opposed to stimulant use has also been associated consistently with a higher prevalence of infection. Other predictors such as association with prison history or with methadone maintenance may reflect the extent (frequency, degree of control) of drug usage. Further efforts to increase the availability and use of sterile injecting equipment and to promote basic hygiene among IDUs are necessary, especially in situations of extreme risk such as prisons and IDUs among marginalised groups such as Aboriginal and Vietnamese-speaking people.

Blood or blood products

A history of receiving blood products before the beginning of blood-donor screening is likely to account for a substantial proportion of HCV-infected individuals who are not IDUs. This is particularly likely to have affected regular recipients of fractionated plasma derivatives such as people with haemophilia who received Factor VIII before heat treatment procedures were implemented. Transmission of HCV in blood products received in Australia is now, and will continue to be, rare.

Tattooing and skin penetration

Tattooing and skin penetration procedures such as ear piercing and acupuncture could potentially transmit HCV, in the same way as has been well documented to occur with the hepatitis B virus (HBV). Tattooing occurs with greater frequency among those who inject drugs, and the disclosure of illicit injecting may be incomplete. However, there are studies that demonstrate an increase in the prevalence of HCV among tattooed individuals who deny ever having injected drugs. There is evidence from surveys of skin penetration premises in some States in Australia that infection control in skin penetration and tattooing premises is substandard. Relevant education in infection control of tattooists and skin penetration operators and those who oversee the registration of premises is an identified need. National guidelines and standardised information would help reduce the confusion and conflicting advice that skin penetration operators receive.

Health care settings

Transmission of HCV in health care settings has been identified as an important mode of transmission in some countries other than Australia, including Japan. Well-documented outbreaks of nosocomial transmission have occurred among patients with immunosuppressive conditions who have frequent venepuncture or access to veins. The need for proper cleaning and sterilisation of all instruments entering sterile body sites is obvious and the exhortation to health care workers (HCWs) to regularly and thoroughly wash their hands needs constant re-emphasis.

The risk of occupational transmission of HCV to HCWs has been investigated through cross-sectional prevalence studies, surveillance of HCWs following needlestick injury from positive source patients and in cohorts of hospital staff negative for HCV antibody on enrolment. Such data suggest that the risk of transmission of HCV through percutaneous injury is higher than for human immunodeficiency virus (HIV) but lower than for HBV. Predictably, risk of acquiring HCV occupationally is related to frequency of blood contact, volume of blood involved, prevalence of HCV in the patient population and probably the level of viraemia.

Sexual, household and vertical transmission

Increasingly, evidence suggests that the risk of HCV transmission through sexual contact or through ordinary household contact is very low. Mother-to-child transmission is known to occur, risk increasing with level of viraemia as measured by quantitative HCV-RNA PCR or with maternal coinfection with HIV. Unanswered questions in relation to mother-to-child transmission include whether Caesarean section lowers the risk of transmission, and the role of breast feeding in transmission, although in both cases any influence is likely to be small.

Coinfection with HIV, stage of chronic liver disease (CLD) and level of viraemia may be important determinants of the efficiency of transmission in all circumstances.

Natural history of hepatitis C virus infection

A major gap in our knowledge about HCV concerns the natural history of infection. Such knowledge is critical to resource allocation and development of cost-effective strategies for prevention and treatment.

Acute HCV infection is generally anicteric and relatively asymptomatic, making it difficult to determine when infection occurred. Surrogate markers of potential for exposure (eg year of first injection or blood transfusion) may be used, but are inevitably subject to error: personal risk factors may be unknown or denied. Of people infected with HCV, most will fail to eliminate it, and estimates of those who develop chronic HCV infection vary between 50 and 90 per cent. We lack information on the extent to which those who clear the virus can extinguish their antibody response, and what proportion progressively clear the virus over time.

Follow-up of transfusion-associated cases of HCV infection indicate that the average time taken to develop cirrhosis is about 20 years, but the time range over which liver disease develops is wide. Some reports describe carriers of HCV RNA who have developed minimal liver damage or chronic persistent hepatitis (CPH) that has not progressed over decades, prompting speculation about whether a healthy carrier state exists. More rapid progression is also common, and histological assessment of liver biopsies suggests that among those with persistent viraemia, few have livers that are histologically normal, even when serum alanine aminotransferase (ALT) levels are normal. HCV disease is often slowly progressive and potentially results in severe liver disease, but the features of the virus or host which mediate the effect are unknown. Much better information is needed about which patients are prone to develop cirrhosis and which are likely to have an indolent course. Among the factors that may influence or reflect the severity of disease are: the route by which infection was acquired, patient age, viral genotype (including multiple infections, viral load, coinfections (HIV, HBV), environmental cofactors (alcohol, nutrition), duration of infection, and host immune factors.

Although there is some evidence that certain genotypes may be associated with a worse prognosis, clinical trials suggest that those patients who are most likely to respond to interferon (IFN) are those who are less likely to progress to advanced disease. Pooled information from randomised trials of IFN therapy demonstrate a complete response rate (in terms of normalised ALT levels) to standard regimes (3 MU for 6 months) of about 50 per cent, with a sustained response rate of 20 per cent. Preliminary evidence suggests that treatment with higher doses of IFN or for longer duration may provide greater and more sustained response rates. Many patients experience side effects from IFN treatment and are unable to tolerate treatment. Whether current therapies favourably alter the natural history of chronic HCV infection to reduce morbidity and mortality is a critical and yet to be answered question.

Our current understanding of the rate at which people can and do progress through the stages of HCV disease is poor. HCV infection can progress through CLD and ultimately result in hepatocellular carcinoma (HCC). Given that disease progression may be multifactorial, the extent to which viral hepatitis viruses contribute to the development of CLD and HCC in Australia is unknown. In order to assess the importance of these chronic hepatotrophic viruses, we need to obtain good baseline data on the prevalence of HCV in the cases of HCC and ensure that such information continues to be collected. The incidence of HCC probably will increase in coming decades as the effect of chronic infection in those infected as a result of IDU becomes evident.

Preface

It was not until 1988 that the HCV was first identified, although its existence had been suspected for some time. Even before this identification, the role of a virus other than hepatitis A (HAV) or HBV in the causation of post transfusion hepatitis and of long-term liver disease was clear. With the availability of assays for the presence of viral genetic material and for antibody to the virus, investigation of the epidemiology of HCV could begin in earnest.

Early studies confirmed that HCV was blood borne, showing high prevalences among recipients of blood and blood products and among IDUs. Screening of blood donors for antibody to HCV decreased the rate of posttransfusion viral hepatitis to negligible levels. However, increasing evidence of continuing transmission of HCV among IDUs at high rates poses challenges for control of the epidemic, as IDUs make up the major core group for HCV in western communities. As well, the natural history of chronic HCV infection remains ill-defined, posing problems for development of sensible approaches to treatment and evaluation of the efficacy of treatment approaches.

In this context it is difficult to formulate policy decisions about resource allocation or program development. There is, therefore, a need to review both the current understanding of HCV epidemiology and current directions of research into that epidemiology so that informed decisions can be made about the need and directions for further research, and to enable appropriate and necessary policy and program decisions to be made. To this end, this review was commissioned by the Commonwealth Department of Health and Family Services in November 1995. We present a review of the epidemiology of HCV.

Methods

Literature reviews were carried out to identify published articles relating to HCV and the particular topic of interest through MEDLINE searches for the period from January 1990 through August 1996. Further reports were identified from bibliographies of published articles, from reports of conference proceedings, and from abstracts, reports and articles submitted by researchers as part of the review of current research into the epidemiology of HCV in Australia. A further update was carried out in March 1999 to bring the literature review up to the end of 1998.

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Abbreviations

αFP	alpha-foetoprotein
ALT	alanine aminotransferase
BcAg	hepatitis B core antigen
CAH	chronic active hepatitic
CAPD	constant ambulatory peritoneal dialysis
CC	cholangio-carcinoma
CDI	Communicable Diseases Intelligence
CI	confidence interval
CLD	chronic liver disease
CPH	chronic persistent hepatitis
DNA	deoxyribonucleic acid
EHO	environmental health officer
EIA	enzyme immunoassay
EV	oesophageal varices
FHF	fulminant hepatic failure
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HCW	health care worker
HD	haemodialysis
HDV	hepatitis D virus
HIV	human immunodeficiency virus
HLA	human lymphocyte antigen
HVR	hypervariable region
IDU	injecting drug use(r)
IFN	interferon
LCD	large cell dysplasia
LOH	loss of heterozygosity
MBCMR	Macfarlane Burnet Centre for Medical Research
M-H	Mantel-Haenszel
MHC	major histocompatibility complex
MLC	metastatic liver cancer
MU	million units
NANBH	non-A, non-B hepatitis
NCHECR	National Centre for HIV Epidemiology and Clinical Research
NIH	National Institutes of Health, Bethesda, MD, USA
OR	odds ratio
ORF	open reading frame
PCR	polymerase chain reaction
PHA	Public Health Association
RFLP	restriction fragment length polymorphism
RIBA	recombinant immunoblot assay
RNA	ribonucleic acid
RR	relative risk, rate ratio
RT	reverse transcriptase
RT-PCR	reverse transcriptase polymerase chain reaction
SSCP	single strand conformational polymorphism
STD	sexually transmissible disease
TA	transfusion associated

1 Virology - consequences of infection

The hepatitis C virus (HCV) is a single-stranded positive-sense RNA virus closely related to the Flaviviruses. Its entire genome has been mapped and the structural proteins are derived from the 5′ end of the genome, and non-structural proteins from the 3′ end.

1.1 Virus replication and interaction with host cellular processes

The HCV replication cycle begins with entry into cells, such as hepatocytes and leucocytes, possibly through interaction with cells possessing Fc receptors (Branch 1996). With HCV, the rate of viral protein synthesis seems to be partly regulated by positive and negative translational control elements in the 5' untranslated region of the mRNA. Cellular and viral proteins may switch these RNA control elements on and off. Since HCV is a positive sense RNA virus, encapsulated viral RNA has the correct anatomy to serve in three ways: as a messenger RNA which is translated into viral proteins; as a replication intermediate that is copied into a negative strand; and as a genomic RNA packaged into a virion. RNA signals may be used by HCV to apportion the positive strand population, balancing the need for replication intermediates with the need for RNAs to be packaged into virions, and therefore helping to regulate the rate of replication.

Anti-viral activities of the systemic immune system and anti-viral factors produced within the virus-infected cell also strongly influence the rate of viral multiplication. The HCV replication complex has the potential to form double-stranded RNA, a potent activator of intracellular anti-viral defence pathways and interferon (IFN). Branch (1996) thus argues that through a combination of regulatory pathways built into the virus, intracellular anti-viral responses and the actions of the immune system, HCV is suppressed following acute infection. Chronic HCV infection results from the battle between anti-viral responses and HCV replication and mutation. Because of the immune response, during chronic infection the levels of HCV RNAs and proteins in the liver are very low, almost undetectable, although the liver is constantly bathed in blood containing HCV. However, HCV generally persists despite the immune response, presumably despite a low rate of replication and perhaps reflecting the ability to infect and perhaps disarm the immune system.

1.2 Immune response to hepatitis C virus infection

There is evidence from *in vivo* studies that at least some neutralising antibody responses occur, and that they are highly strain specific, allowing other strains to emerge and perpetuate infection in the face of measurable neutralisation. Thus, host responses are generally unable to contain the emergence of neutralisation-resistant variants (Farci et al 1994). There is also evidence from chimpanzee models and multiply-transfused thalassaemia patients that there is no protective response against either heterologous or homologous rechallenge (Farci et al 1992; Lai et al 1994).

1.3 Effects of genetic diversity of the hepatitis C virus

Considerable genetic variation exists in different isolates of HCV. This appears to be the result of frequent mutation during the somewhat imprecise replication process typical of RNA viruses. The genetic variation is classified as being of two main types: quasispecies and genotypes.

1.3.1 Quasispecies

'Quasispecies' refers to the genetic heterogeneity of the HCV population within an infected individual, that is, the population of HCV genomes is present as a group of closely related, yet heterogenous, sequences. Homologous viral populations have been observed at the start of infection, with sequence heterogeneity developing some years later.

It is uncertain whether the observed genetic drift reflects inherent viral evolution or whether immune selection drives the sequence variability and antigenic variation of the amino terminus of E2/NS1.This ability to change sequence may be a mechanism by which HCV escapes immune surveillance and establishes persistent infection in the host. Thus, under immune pressure the virus might mutate rapidly and exist simultaneously as a series of related but immunologically distinct variants (Alter 1995a). Although mutations occur throughout the HCV genome, most occur in a relatively short, hypervariable segment of the E2/NS1 domain (Weiner et al 1991).

Naito et al (1995) examined the relationship between nucleotide complexity and diversity of hypervariable region 1 and various stages of the carrier states using polymerase chain reaction (PCR)-SSCP (single strand conformational polymorphism). There were no significant differences in the number of SSCP bands among the stages of HCV infection: normal alanine aminotransferase (ALT) (20); chronic hepatitis with elevated ALT (50); cirrhosis (22); hepatocellular carcinoma (HCC) (24). The authors' findings suggest that the quasispecies complexity of the hypervariable region is independent of the stage of chronic HCV infection. Koizumi et al (1995) examined the same question in a smaller number of patients (42 total) and reported contradictory findings: the percentage of patients with a single band was 41 in chronic active hepatitis (CAH), 22 in cirrhosis, and 0 in HCC. If these findings are correct, then they support the diversity of HCV quasispecies becoming more complex as the disease stage progresses. Honda et al (1993) examined 28 patients with liver disease of varying severity for nucleotide diversity spanning the region from the core to envelope. Intrapatient variation in nucleotides increased significantly with severity of liver disease, except in cirrhosis complicated by HCC. Histological findings correlated most with quasispecies diversity, not time from infection. The authors conjecture that replication of HCV is more active in patients with severe liver disease, and an error-prone RNA polymerase causes mutation during replication. Kurosaki et al (1995a) examined four patients for SSCP patterns and reported that the population of quasispecies changed during the course of chronic infection, more so where transaminase levels were high. They argue that the population of quasispecies changes during the course of infection.

Sakamoto et al (1995) examined nucleotide sequences of the hypervariable region of HCV genomes obtained from plasma and liver tissue of eight patients with chronic HCV infection. Comparison of the SSCP patterns revealed that the number, mobility, and density of bands were the same between the plasma and the liver. The authors concluded that the population and the diversity of HCV quasispecies as detected by the hypervariable region sequence are the same between the plasma and the liver despite rapid mutations, indicating that rapid changes in the population of HCV quasispecies also occur in the liver.

1.3.2 Genotypes

Heterogeneity of genomes is observed among different HCV isolates - a result of the accumulation of mutations during evolution of the viruses. This diversity has led to its classification into 'genotypes', based upon genetic relatedness. Although each genotype was initially thought to have a distinct geographical location [HCV type I being

the major genotype in the United States of America (USA) and Europe, and types II, III and IV being reported initially only from Japan], it is now clear that different genotypes are distributed worldwide (Takada et al 1993). No well-defined culture system or classification based upon clinical manifestations has yet been identified for these variants.

These genetic variations are important as they may have an effect on clinical outcome, on response to treatment, on diagnostic testing and on vaccine development.

1.3.3 Nomenclature for designation of genotypes

There are various nomenclatures for designating genotypes (table 1).

Table 1 Correspondence among the major published classification systems for hepatitis C virus genotypes

From Pawlotsky et al (1995a). HCV types are designated by Arabic numerals in order of discovery (1, 2, 3 etc). Subtypes are designated using these numerals and lower case letters.

Consensus proposed by Simmonds et al (1994)	Okamoto et al (1993)	Cha et al (1992)	Nakao et al (1991)
1a	I	1a	PT
1b	II	1b	K1
1c	NC[A]	NC	NC
2a	III	2a	K2a
2b	IV	2b	K2b
2c	NC	NC	NC
3a	V	3	NC
3b	NC	NC	NC
4a	NC	4	NC
5a	NC	NC	NC
6a	NC	NC	NC

[A] NC=not classified.

The degree of correspondence of the full-length nucleotide sequences among types, subtypes and isolates within a given subtype are 65.7 to 68.9 per cent, 76.9 to 80.1 per cent and 90.8 to 99 per cent, respectively. There are other characteristic differences specific for a given genotype, such as the length of the open reading frame (ORF). The C gene is the most highly conserved gene of HCV, and nucleotide sequence within this region accurately predicts genotype. The 5′ NC region is the most highly conserved region of the HCV genome, but cannot accurately predict genotype. Characteristic genotype changes occur throughout the E1 gene, so that analyses of fragments of 100 nucleotides have proved sufficient to accurately predict genotype. Cha et al (1992) reported that several short nucleotide motifs throughout the HCV genome are predictive of genotype.

Current methods of genotype determination that do not include sequence analysis are not definitive. Although methods that detect genotype-specific antibodies would be advantageous for epidemiological studies, antibody markers are, at best, indirect markers of genotype and have limited specificity. There are problems because of lack of

complete sequence data, and minor inconsistencies between typing systems. Genotyping should be based ultimately on sequence identity.

1.3.4 Distribution of hepatitis C virus genotypes

Distribution of HCV genotypes can vary by geographical area, positivity in first-generation or second-generation tests, liver disease (presence, absence), or mode of transmission (IDU compared to other modes) (Davidson et al 1995; Simmonds 1996) (table 2).

Table 2 Geographical distribution of genotypes

Type 1 isolates - widely distributed:	**Isolate**
Predominant genotype in North and South America and Europe	I/1a II/1b
Predominant genotype in Asia	11/1b
Within Japan, Taiwan and probably China	1a, 2a, 2b
Thailand, Singapore, Bangladesh, East India	3
The African continent - a very different distribution:	
North and Central Africa, Egypt, Middle East	4
Southern Africa	5
Hong Kong - significant proportion of isolates	6
Vietnam, Thailand	7, 8, 9

1.3.5 Clinical implications of genotypic diversity

Most studies have found that genotype 1b is associated with more severe liver disease, although there is some concern that the type of genotype may be confounded by length of infection. In many European countries, genotype distributions vary with the age of patients, possibly reflecting the introduction of different genotypes through practices such as IDU (Craxi et al 1991; SW Chan et al 1992; McOmish et al 1994; Anonymous 1995a). Mahaney et al (1994) found that types 2b, 3, and 4 were found almost as frequently in IDU as type 1b (ratio 11:12) whereas in patients who had acquired HCV as a consequence of blood transfusion, type 1b predominated over other types in a ratio of 20:3 (P=0.015). Cirrhosis has been observed in infections of all known genotypes, and there is little evidence of completely non-pathogenic variants (Dusheiko et al 1994). Kobayashi et al (1996) compared 100 patients with genotype 1 (1b) and 36 with genotype 2 for deterioration of liver histology with a mean of over eight years of follow-up. Patients with genotype 1 were more likely to have higher HCV-RNA titres, and those with genotype 1 had greater deterioration of liver histology and were more likely to develop HCC. Pozzato et al (1994a) compared genotypes from Italian and Japanese patients and found that NS4-positive patients were significantly older, had significantly lower ALT levels and had significantly more cirrhosis than NS4-negative patients. Although the 1b genotype was more commonly associated with cirrhosis, most (74%) patients were type 1b, making comparison with any other genotype difficult. There are also suggestions that HCV genotype 3 is associated with a more aggressive form of CLD than the liver disease associated with types 1 and 2 (Preston et al 1995).

Preston et al (1995) examined HCV serotype and genotype in a cohort of 96 people with haemophilia infected with HCV and the relationship between genotype and severity of CLD as determined by liver biopsy. HCV serotype was determined by specific enzyme-linked immunosorbent assays (EIAs) and genotype by restriction fragment length

polymorphism (RFLP) and HCV viral sequencing. The pattern of genotype distribution was unlike that of HCV-infected United Kingdom blood donors in that five of the six known HCV genotypes were represented (50% were type 1; 13%, type 2; and 18%, type 3). An unexpected observation was the presence of HCV genotype 4 in four patients and type 5 in two patients. An additional feature was the presence of mixed infection, detected in 14 and 7 per cent by serotype and genotype analysis, respectively. Liver biopsies were available from 51 patients. Cirrhosis was present in five of 27 (19%) individuals with type 1, in two of nine (22%) with type 2, and five of eight (63%) of those with type 3. The heterogeneous pattern of HCV genotype distribution in this cohort of patients and the observed relationship between the severity of the liver disease and specific HCV genotype may relate to their reinfection with different HCV types, which could differ in their replication rates and in their capacity to induce HCV antibody formation.

McGuiness et al (1996) found that HCV genotype 1b had a significantly higher mean intrahepatic HCV-RNA load compared with the other genotypes (McGuiness et al 1996). They also reported the effect of IFN on reducing intrahepatic HCV-RNA levels, but did not find an association of HCV viral load with more severe liver disease assessed either histologically or by serum transaminase levels.

However, the influence of HCV genotype on the severity of subsequent disease is very difficult to establish in cross-sectional clinic-based studies, and there is a need for more epidemiologically sound longitudinal studies of community-based cohorts to define the effect with any degree of certainty (Sallie 1995).

1.3.6 Studies examining genotypes in liver and serum

Infection with multiple genotypes is not commonly reported when this is measured by HCV-RNA genotyping of random serum samples, even in patients whose mode of HCV acquisition is attributed to IDU. Sallie (1995) suggests that these findings might be an artefact of the selective and exponential amplification power of PCR, which dictates that if one of a pair of competing molecular species is even slightly dominant during the early rounds of the PCR, it will rapidly become increasingly more dominant during later cycles (Sallie 1995). However, there are type-specific priming techniques used to try to minimise this effect. Sallie (1995) suggests that the infrequent finding of multiple genotypes is important for two reasons: firstly, it supports the concept of ‘molecular Darwinism’; and secondly, it suggests that some genotypes of HCV have mechanism(s) by which replication (and/or packaging and/or export into the serum) of other genotypes may be attenuated or even abrogated completely (Sallie 1995).

Doubts have been raised about the interpretation of the relationship of genotypes to liver damage. Castillo et al (1995) performed a paired serum/liver biopsy study of genotypes, and reported that a mixed HCV genotype infection was detected in a significantly higher proportion of liver specimens than serum specimens. The authors suggested two possible explanations: that the HCV-RNA load may be higher in liver cells than in serum, permitting detection of the HCV subtype in the hepatocytes when the total body load of virus is lower; or that HCV genotyping in serum may reflect only those HCV genotypes that are actively replicating in hepatocytes and being released into the circulation, whereas in liver cells, those other HCV genotypes may be synthesising viral proteins but are not actively replicating (or in a latent infection state). Thus, serum HCV genotyping may not reflect the viral population infecting the liver of a given patient. Types might also be detected in an inactive replication phase. Based upon these results the authors raise the possibility that serum HCV genotyping may, therefore, not reflect the viral population infecting the liver of a given patient.

This is reinforced by Kao et al (1994) who examined 20 patients in Taiwan with chronic HCV infection experiencing acute hepatitis exacerbations. They used PCR with genotype-specific primers, comparing the group with exacerbations with 26 patients who did not appear to experience acute exacerbations. Eleven (55%) of the group with exacerbations had mixed genotype infections, and those with heterologous infection were significantly

younger than the nine without (55 v. 67 y, $P<0.05$). By contrast, only two of the non-exacerbation group had mixed genotype HCV infections detected, and these two patients had higher mean ALT levels. The emergence of the new genotype coincided with the abrupt elevation of serum ALT levels. There was no consistent virus genotype emerging during these exacerbations, and often the newly introduced virus disappeared although the original virus was also seen to disappear. The authors conclude that their work suggests the importance of preventing superinfection in patients with chronic HCV infection to diminish the progression of chronic hepatitis. An alternative explanation of these data is that co-existent infection with more than one genotype can commonly occur, but that usually only one genotype is replicating, with occasional episodes of multiple genotype replication coinciding with increased hepatitic activity. Either multiple genotype replication causes increased hepatocyte damage, or less likely, increased hepatocyte damage causes multiple genotype replication when multiple genotypes are present.

Castillo et al (1995) and Kao et al (1994) raise doubts about the design of many of the published studies on the effect of HCV genotypes. Measurement of HCV-RNA genotype in serum at random times may not identify all of the genotypes present that are capable of causing disease and further transmission. Much more attention needs to be paid to the virology of acute exacerbations, and how these acute exacerbations relate to long-term progress of liver and extrahepatic manifestations of HCV infection.

2 Diagnostic tests for hepatitis C virus infection

2.1 Antibody tests

The initial clone of HCV was from the NS4 region and the derived protein was designated 5-1-1 (Cerino and Mondelli 1991). This was expanded to form the c100-3 antigen that served as the basis of the first-generation anti-HCV assay. The antibody tests contain antigens derived from the conserved parts of the HCV genome, but the serological response to the prototype strain is not uniform in carriers infected with different genotypes. Second-generation assays added the c22 core antigen and the c33c antigen from the NS3 region. The third-generation assay adds an NS5 protein and reconfigures some of the earlier antigens. The third-generation assay provides only incremental benefits in terms of disease prevention because of a very small increase in sensitivity but does not provide improved specificity. Nonspecificity remains generally unexplained but has been associated with aged sera, hyperglobulinaemia, rheumatoid-factor positive sera, sera from persons recently vaccinated for influenza and persons with past or current syphilis (Sonmez et al 1997).

The sensitivity of detection of anti-HCV is influenced by the degree of conservation in different regions of the genome among different HCV strains. Most patients with chronic HCV infection are anti-C22 positive, indicating a strong anti-capsid response. Improvements in test sensitivity have been achieved by identifying antigenic sites and immunodominant epitopes (Dusheiko et al 1994).

Table 3 Relationship between serological markers of hepatitis C virus and phases of hepatitis C virus infection

From Brunetto et al (1994).

	Prodromic	Acute	Chronic	Recovery
Viraemia				
HCV-RNA	++	++	++	+/-
Antibodies against structural proteins				
Anti-C22	-	-/+	++	+
Anti-E1	-	-	+/-	-
Anti-E2	-	-/+	+/-	-
Antibodies against nonstructural proteins				
Anti-C33	-	-/+	+	-
Anti-C100	-	-/+	+/-	-

Using a recombinant immunoblot (RIBA), HCV-reactive sera fall into two groups: strongly positive, with at least 3+ anti-capsid and anti-NS3 profiles; and weakly positive, with absent or weakly reactive (1+ or 2+) profiles. Over 90

per cent of the former group are viraemic, compared with less than 10 per cent of the latter. Such weak profiles are also seen early in seroconversion and late in the course of extinction of viral replication (Dubois et al 1998).

2.2 Other tests

The only direct marker of HCV infection is the detection of HCV RNA, typically by reverse transcriptase (RT) PCR. Other methods are *in situ* hybridisation and branched DNA amplification assays.

The 5' NC region of the HCV genome contains sequence domains that are conserved among all known genotypes. Because of the relative conservation of this region, primers and probes from these domains can be utilised in assays for universal detection of HCV RNA in HCV-infected individuals and are superior to those from NS3 and core in sensitivity and specificity.

The branched-chain DNA amplification assay is easy to perform and reproducible, but it is significantly less sensitive than RT-PCR assays (Gretch et al 1995). Difficulties with consistency of PCR results are known to occur. Branched-chain DNA amplification is widely used for measuring the level of HCV viraemia, although the sensitivity may vary with the genotype being analysed.

The presence of HCV RNA in the absence of anti-HCV antibodies may reflect lack of immune reactivity, particularly in immunosuppressed and haemodialysed patients. There are presently no antibody patterns that distinguish between persistent viraemia and episodes of resolved viraemia, as the antibody patterns are frequently similar. A proportion of people who clear HCV RNA may lose antibody reactivity, so that all identifiable traces of HCV infection may disappear.

Dow et al (1993) reported on the results of 3,832 samples referred for confirmatory testing after being positive in a screening test at blood donation. All were tested by recombinant immunoblot assay (RIBA3) with 2,710 negative, 945 indeterminate and 177 positive results. HCV RNA was detected by PCR in an average of 69.5 per cent of RIBA3 positives but only 0.53 per cent of the RIBA3 indeterminates. HCV viraemia was greatest among samples reactive with all four RIBA3 bands (84.1%) and lowest in those reactive with only two bands (34.1%). Of RIBA3- positive samples containing three bands, all samples containing NS5 band were PCR positive. Type 1 genotype was the commonest genotype (53%) among RIBA-positive samples with all four bands, type 3 was the commonest genotype among RIBA-positive samples with three (45%) and two (54%) bands. NS5 indeterminates were the most common (40.2%) single-band pattern but yielded no PCR-positive samples, followed by c33 (23.3%) with one PCR positive and c100 (20.2%) with one PCR positive, whereas c22 indeterminates were least common but included three PCR-positive donors. All five RIBA3 indeterminate PCR-positive donors were type 3 genotype.

The absence of antibody response to the 5-1-1 protein is frequent in genotype III/2a HCV carriers and may help predict the response to IFN therapy (Yuki et al 1992).

Quantitative determination of viral load using PCR-based techniques is useful in predicting and measuring response to therapy, but its place in assessment of overall prognosis is yet to be ascertained (Berger et al 1998).

3 Methodological issues in hepatitis C virus epidemiology

Even before HCV infection was identified as a leading cause of non-A, non-B hepatitis (NANBH), particularly in industrialised countries, there had been work on determining the epidemiological features of the condition. Particular questions were related to routes of transmission, long-term outcome and patterns of occurrence within populations. Investigations led to a recognition of the considerable methodological challenges that face epidemiological research in HCV, even before the virus itself had been identified. Although the ongoing development of immunological and molecular methods for detecting HCV infection has removed some major obstacles, many of the challenges remain.

Primary among the challenges is probably the difficulty in detecting newly acquired HCV infection. Recognition of such cases is an essential requirement in several areas of HCV epidemiology. These cases provide the best means of investigating routes of transmission, but the greater the time passed since infection was acquired, the more difficult it becomes to elicit accurate information on the circumstances of exposure. Cases for which the time of acquisition is known represent the best opportunity to study HCV natural history because it is possible to relate disease progression to time elapsed since the infection was acquired.

Detection of newly acquired infection is difficult primarily because only a very small proportion of cases appear to manifest a clinical illness - hence, people who have recently become infected are not likely to seek medical care for acute hepatitis. If they do happen to undergo testing, the only way that the timing of infection can be established is through a known history of exposure, or a documented negative test in the recent past. Unlike some other viral infections, it is not yet possible to identify acute HCV infection by detection of an IgM antibody response.

The second major issue in HCV epidemiology has been the difficulty in gaining access to populations at high risk of infection. The major route of transmission, IDU, is an activity that is illegal, socially marginalised and often undertaken by people who are not in close contact with the health system. In addition, people who have injected drugs but no longer do so may not be keen to acknowledge this aspect of their past. For these reasons, people with, or at risk of, HCV infection may be difficult to recruit into studies and follow-up for any length of time. It is also an ongoing challenge to enumerate these subpopulations.

Investigation of the natural history of HCV infection needs to take into account the long and variable course of disease progression. It appears that four or five decades of follow-up will be required to fully characterise the long-term outcome of chronic HCV infection. Study of outcomes is further complicated by their multifactorial aetiology. For example, cirrhosis and cancer of the liver occurring in a person with HCV infection may also be linked to HBV infection and alcohol consumption.

Finally, HCV epidemiology needs to take account the complex and evolving diagnostic methodology for HCV infection. Since the virus was identified, there has been a rapid development of both immunological and molecular techniques for detecting HCV antibodies and genetic material. Researchers of the epidemiology of HCV have difficulty in gaining access to adequate diagnostic testing, much of which is expensive and requires specialised laboratory skills to carry out.

4 Populations at risk and transmission pathways

4.1 Injecting drug users

People who inject themselves or are injected by someone else with illicit drugs (IDUs) are at risk of many infectious diseases because of unsterile injecting techniques, usually related to the illicit nature of the activity. HCV is the most common of these infections among IDUs, with very high proportions of most IDU populations studied having been exposed and being chronically infected. Conversely, among populations at risk of blood-borne or sexually transmissible diseases (STDs) (eg STD clinic patients), or indeed often among general populations (eg blood donors), a history of IDU is found to be the commonest risk factor. Such histories are often hidden, however, and difficult to ascertain. For instance, in a study of attenders at a drug treatment centre in Baltimore, USA, in 1990-91, 21 per cent of patients gave no history of IDU and yet had similar prevalences of HCV to those who gave such a history, raising the possibility that they did not fully disclose HCV-risk behaviour in this setting (Fingerhood et al 1993). As well, where this has been studied, HCV continues to spread among IDUs often despite the introduction of seemingly effective HIV prevention strategies in the same populations.

4.1.1 Prevalence and associations of prevalence of hepatitis C virus among injecting drug users

Prevalence of HCV among IDUs is almost uniformly very high, across a wide range of studies in varied populations and many countries. Table 4 (see *Tables* section) shows the prevalence from 77 studies in 28 countries. Some variation in prevalence is caused by the sensitivity and specificity of the assay used, but most variation is related to the length of time the HCV-infected person had been injecting (see next paragraph). In general, prevalence of antibodies to HCV is higher than of antibodies to HBV and HIV, but there are exceptions to this (eg Switzerland - Chamot et al 1990, Rohrig and Grob 1990; Poland - Halota et al 1991).

Multiple studies have found that the strongest association of HCV seropositivity among IDUs is duration of injecting (Bell et al 1990; Girardi et al 1990; Rohrig and Grob 1990; Donahue et al 1991; Smiatacz et al 1991; Zeldis et al 1992; Crofts et al 1993; Scheitlin et al 1992; Patti et al 1993; Crofts et al 1994; Lucidarme et al 1994; van Beek et al 1994; Chetwynd et al 1995; Crofts et al 1995; Galeazzi et al 1995; Robinson et al 1995; Smyth et al 1995; Thomas et al 1995a; Bolumar et al 1996; Garfein et al 1996; Kemp et al 1998; Lamden et al 1998; Smyth et al 1998). In almost all cases, age is also associated but only because of relationship to duration of injecting. Some studies have found extremely high prevalences within very short periods after beginning to inject, and prevalences up to 100 per cent after eight years of injecting; these rates vary to some degree with the specificity of the assay and the population studied (table 5). However, there is increasing evidence that at least at some times and in some places new initiates into injecting are at the highest risk of exposure to HCV. For example, in a study of IDUs in Baltimore, USA, recruited between 1988 and 1991, prevalences approaching 50 and 75 per cent were found in IDUs who had only been injecting for less than four months and five to eight months, respectively (Garfein et al 1996).

Among the group of IDUs in this study who had been injecting for less than one year, the associations of HCV seropositivity were: injecting daily, not always using new equipment, and injecting cocaine. HIV seropositivity in the same group, however, was associated with sexual, but not injecting, risk variables. The authors' conclusion was that

in Baltimore, USA, in these years most HCV infections among IDUs occurred 'very soon after initiation of injection drug use'. One difficulty with this as with many United States studies was that the investigators were limited to enrolling IDUs aged 18 years and over, posing a potential sampling bias. However, several studies have replicated these results, finding high rates of exposure among IDUs within very short periods after beginning to inject (table 5).

Table 5 Prevalence of antibody to hepatitis C virus among injecting drug users by duration of injecting

Reference	Lower duration (years[A])	Prevalence (%)	Upper duration (years)	Prevalence (%)	Assay (generation)
Bell et al (1990)	<2	67	8+	100	1
Galeazzi et al (1995)	<4	40	>8	91	2
Smyth et al (1995)	<2	70	>2	95	2
Thomas et al (1995)			2+	78	1
Garfein et al (1996)	0-4 m	47	1-2	80	1
Garfein et al (1996)	5-8 m	72	5-6	82	1-2
Garfein et al (1996)	<1	64.7			1-2
Robinson et al (1995)	<4	53			1
van Beek et al (1994)	<3	26	>10	94	2
Lucidarme et al (1994)	<6 m	33	2+	90	2
Bolumar et al (1996)	<1	69	4-8	87.0	2
Bolumar et al (1996)	<4	78.9	8+	90.0	2
Chetwynd et al (1995)	<5	73.5	>10	92.5	2
Kemp et al (1998)	<5	35.6	>10	86.7	2

[A]Duration is in years unless stated otherwise; m, months.

A study in Hong Kong found that type 6a was associated with a history of IDU among blood donors to a far greater extent than was type 1b, suggesting a more recent introduction of type 6a into the IDU population (Prescott et al 1996).

A second major association of HCV seropositivity among IDUs is exposure to HBV (ie those IDUs with antibody to HCV are more likely to have antibody to HBV and *vice versa*) (Bell et al 1990; Gloria et al 1991; Trubner et al 1991; Rodriguez et al 1992a 1992b; Zeldis et al 1992; Cheng 1993; Fingerhood et al 1993; Patti et al 1993; van Beek et al 1994; Coppola et al 1994; Crofts et al 1994; de Miguel et al 1994; Quaranta et al 1994; Galeazzi et al 1995; Bolumar et al 1996) although two studies have reported not finding such association (Payeras Cifre et al 1992; Westh et al 1993). There are indications that IDUs who are exposed to both HCV and HBV are commonly exposed to HCV some months or years in advance of their exposure to HBV (Rodriguez et al 1992a, 1992b; Abdel Rahman et al 1993; Crofts et al 1995) and that where an IDU has been exposed to only one of these two viruses, it is much more likely to have been HCV (Gloria et al 1991; Pont et al 1991; Trubner et al 1991; Li et al 1993; Coppola et al 1994; Crofts et al 1995; Hedberg and Gaub 1995; Ichimura et al 1995; Tennant and Moll 1995). This most probably is a result of the much higher proportions of IDUs in any injecting network who are infectious for HCV than for HBV.

Several studies have found associations between HCV seropositivity and particular drugs, with HCV exposure more common among those most commonly injecting heroin or other opiates than amphetamines or other stimulants (Zeldis et al 1992; Crofts et al 1993, 1994; van Beek et al 1994; Selvey et al 1996). However, where cocaine is more commonly injected, it has also been found to be more associated with HCV (Fingerhood et al 1993; Thomas et al 1995a; Garfein et al 1996). One possible explanation of these findings is the relationship of HCV risk to frequency of injecting, with opiates *on average* injected more frequently than stimulants in many settings (although the variance of frequency is greater with stimulants); increased risk where cocaine is commonly injected - mostly in parts of the USA - could then be a result of the very high frequency of injecting among injectors of cocaine. A second, not exclusive, explanation may be that different injecting networks have different degrees of risk behaviour for HCV. In either case, it would be the behaviour rather than the particular drug which raises the risk of HCV transmission; the drug simply standing as a marker for the other factor(s). There is no evidence currently in the literature to explain this association or test either of these hypotheses.

However, HCV seropositivity is clearly associated with injecting, and in several studies with the frequency of injecting (Girardi et al 1990; Rohrig and Grob 1990; Van den Hoek et al 1990; Thomas et al 1995a; Garfein et al 1996). The inverse of this is the negative association in one study of HCV seropositivity with smoking, as opposed to injecting, heroin (Van den Hoek et al 1990). The Baltimore cohort study found injecting daily or more often to be strongly associated with HCV exposure, especially among young and new IDUs (Garfein et al 1996). A study of homosexual men in San Francisco in 1983-84 found a relatively low rate of HCV seropositivity among those who gave a history of IDU, and suggested this was because frequency of injecting was low in this group - only 9 per cent injected daily or more often (Osmond et al 1993a). The sharing of needles and syringes has also been shown in several studies to be associated with HCV seropositivity (Girardi et al 1990; Rohrig and Grob 1990; Scheitlin et al 1992; Chetwynd et al 1995; Galeazzi et al 1995; Garfein et al 1996), although one study has found no such association (Cacopardo et al 1992) and one found the association to be weak (P=0.062) (Bolumar et al 1996). One study found an increase in the numbers of other IDUs with whom equipment had been shared among HCV- seropositive people compared with people who were seronegative (Robinson et al 1995). One study found that daily drug expenditure of over 65 Irish pounds was associated with HCV seropositivity (Smyth et al 1998).

Although there is a definite association between a history of sharing of needles and syringes and exposure to HCV, there are some indications of HCV exposure among some IDUs who present no history of sharing. For instance, in a study of 110 IDUs presenting between 1992 and 1994 at a treatment centre in New Zealand, 27 claimed never to have shared injecting equipment; 14 (76%) of 19 tested were anti-HCV positive, a rate similar to those who gave a history of sharing (Robinson et al 1995). In a cohort study of IDUs in Victoria, the incidence of HCV seroconversion among those who frequently reported sharing needles and syringes was 16.9 cases per 100 person-years, compared with an incidence of 4.3 per 100 person-years among those who denied sharing needles and syringes (Crofts and Aitken 1997). A study of a cohort of IDUs in Sydney found an incidence of 11.9 per cent per year among IDUs who reported never sharing needles and syringes, compared with about 30.2 per cent per year among those who reported sharing (van Beek et al 1998). These and other, anecdotal, data raise the possibility of blood transfer between IDUs in ways other than reuse of contaminated needles and syringes. This possibility is strengthened by the observation on video of possible routes of blood-borne transmission among IDUs other than overt sharing of needles and syringes (Crofts 1994), and by analogy from studies of transmission in dialysis units (*vide infra*).

4.1.2 Alcohol and injecting drug use

An increased prevalence of HCV over the general population has been observed in people with histories of excessive alcohol consumption [eg 1.33% (cf 0.46% in blood donors) (Santos et al 1994); 14.5% (Verbaan et al 1993); 18.4% (Mendenhall et al 1993b)]. This has been shown to be because of a history of IDU in many people with alcoholism, although it has been commented that eliciting this history may be a difficult process (Jiang et al 1995), and that the history may reside in the distant past (Mendenhall et al 1993b). In one study 58 per cent of HCV-positive patients

with alcoholism gave a history of IDU compared with 2 per cent of HCV-negative patients (Befrits et al 1995); conversely, in another, 77 per cent of people with alcoholism with a history of IDU were HCV positive compared with 16.7 per cent of those with no history of IDU (Jiang et al 1995). It has been said that IDU is 'the predominant route of HCV transmission among alcoholics' (Jiang et al 1995).

This association is found also from investigation of current HCV patients, in whom excessive alcohol consumption, especially among those with a previous history of IDU, may be more common than among the general population (Verbaan et al 1993; MacLennan et al 1994). One study reported that 60 per cent of the IDUs studied had a history of excessive alcohol consumption (Strasser et al 1995).

The combination of excessive alcohol consumption and increased prevalences of HCV infection as a result of IDU lead to higher prevalences of, and more severe, CLD. For example, one study found among patients with alcoholism that 21 per cent of HCV-positive patients were classified as having severe liver disease compared with 7 per cent of HCV-negative patients ($P<0.05$) (Befrits et al 1995). A second similar study concluded that 'HCV is responsible, at least in part, for the portal and/or lobular hepatitis associated with alcoholic liver disease' (Rosman et al 1993). In this latter study, anti-HCV was strongly associated in these patients with alcoholism with a history of IDU: 67 per cent of people were HCV seropositive compared with 4 per cent of people who were HCV seronegative ($P<0.001$).

4.1.3 Genotypes and injecting drug use

There are at least six major genotypes of HCV with many subtypes, and there is a variable geographical distribution of the different genotypes (see section 1.3). The activity and prognosis of HCV-related liver disease may depend upon the particular genotype(s) involved, with HCV type 1b the most aggressive in terms of pathogenesis. The response to IFN therapy also may be genotype dependent, with HCV type 1b having a poorer response than other genotypes.

Studies of HCV genotypes among IDUs have found a varying predominance of different genotypes depending on location; most of these studies are European. Among IDUs in France, for instance, one study found a marked predominance of HCV type 1a (13/15, 87%) with occasional type 1b and 2a, and also found that the only coinfections with different HCV genotypes occurred in IDUs (Gournay et al 1995). Another French study found a high rate of HCV type 1a (33% of cases), but that the predominant type was 3a (63% of cases) (Pawlotsky et al 1995b); in one-third, 78 per cent of HCV-positive IDUs had genotypes 1a or 3 (Dubois et al 1997). In Austria, a national study found the most prevalent genotype to be type 1b, but this type was less common among IDUs than among other populations (Hofmann 1995). In Italy the commonest genotypes were found to be types 1, but type 3 was much more common among IDUs than among other groups [52% of those with genotype 3 infection had a history of IDU compared with 9% of those with types 1, and 2% of those with types 2 (Pontisso et al 1995)]. Another Italian study also found that types 1a and 3a were commoner among IDUs than among other groups (48.8 and 21.1%, respectively, of IDU infections compared with 17.6 and 11.2% of others) (Silini et al 1995). In East Anglia in England genotype 1 predominated among IDUs with small proportions made up of genotypes 2 and 3 (Majid et al 1995). In a study in Iceland, of 40-PCR positive IDUs, 57.5% had genotype 1, 37.5% had type 3a and 2.5% had type 1b (Love et al 1996). Similarly, in an Amsterdam IDU cohort, serotype 1 was predominant (57.2%), followed by 3 (26.8%) (Beld et al 1998b). It was noted in a Swedish study of genotypes among blood donors, that while genotype 1a was commonest (40%) (with 29% having type 3a; 20%, type 2b; 10%, type 1b), a history of IDU was commoner in donors with genotype 3a than in those with type 1a (Shev et al 1995b). In a study carried out in Chiang Mai, Thailand, in 1994, type 3a was commonest among IDUs (30% of infections), followed by 1a (21%), 1b (13%), 3b (13%) and 6a (2%) (Apichartpiyakul et al 1994). An Australian study found that 60% of serotypes from

IDUs stored in 1971 were type 1, and less than 10% were type 3; almost 30% were type 2. In 1994, the use of genotyping found a similar proportion with type 1, but less than 5% were type 2, and almost 30% were type 3, suggesting a more recent date of introduction of type 3 (Moaven et al 1996).

These differing distributions of genotype according to risk classification and some other evidence have led several groups to suggest that different genotypes have been introduced into different populations at different times. The study of French blood donors referred to above (Gournay et al 1995) found that the risk factors for HCV infection may differ for different genotypes, and that the mean time elapsed since HCV infection was much higher for genotype 1b than for 1a (15.2 y cf 9.1 y). On the basis of this finding, the authors postulate that there have been two distinct epidemics of HCV in France: the first with genotype 1b which began more than 10 years ago and infected patients who received blood transfusions, and the second which occurred more recently with genotype 1a and infected mainly IDUs (table 6).

Table 6 Genotypes of hepatitis C virus by route of acquisition (France 1995)

From Gournay et al (1995).

Genotype	Sporadic *(%)*	IDU *(%)*	Blood transfusion *(%)*	Total *(%)*
1a	4 *(36)*	13 *(87)*	2 *(20)*	19 *(53)*
1b	6 *(55)*	1 *(7)*	7 *(70)*	14 *(39)*
2a	1 *(9)*	1 *(7)*	1 *(10)*	3 *(8)*
2b	0	0	0	0
Total	11	15	10	36
Coinfection	0	3	0	3

Pawlotsky et al (1995b), in the second French study referred to above, found that IDUs with HCV infection were younger and had a different genotype distribution from blood transfusion recipients and sporadic cases, with much higher proportions infected with genotype 3a. The authors concluded that transmission of HCV genotype 3a has only been observed over the last 20 years in France, whereas other genotypes were being transmitted up to 40 years ago. These results suggested to Pawlotsky et al (1995b) that for the past 20 years there have been two ongoing independent epidemics of HCV in France. An Italian study with similar findings that patients with genotype 3 were significantly younger and more likely to have a history of IDU came to the same conclusion (table 7) (Pontisso et al 1995).

Table 7 Genotypes of hepatitis C virus by route of acquisition (Italy, 1995a)

From Pontisso et al (1995).

Exposure	Genotype (%)			PCR -ve (%)
	HCV-1	HCV-2	HCV-3	
Blood transfusion	23	32	5	27
Surgery	24	28	21	25
Injecting drug use	9	9	52	30
Unknown	44	38	22	18

Another Italian study (Silini et al 1995) with similar findings concluded that genotypes 1a and 3a were recently introduced in Italy, presumably via needle-sharing among IDUs, and from this reservoir to other groups, 'particularly among younger subjects' (table 8).

Table 8 Genotypes of hepatitis C virus by route of acquisition (Italy, 1995b)

From Silini et al (1995).

Patient category	HCV genotype *(%)*					Total
	1a	1b	2a	3a	Other	
IDU	44 *(49)*	13 *(14)*	1 *(1)*	19 *(21)*	13 *(14)*	90 *(100)*
Non-IDU	22 *(18)*	46 *(37)*	38 *(30)*	14 *(11)*	5 *(4)*	125 *(100)*

χ^2 analysis $P<0.001$.

A study in Hong Kong found that type 6a was associated with a history of IDU among blood donors to a far greater extent than was type 1b, suggesting a more recent introduction of type 6a into the IDU population (Prescott et al 1996).

In summary, there is variation in the distribution of HCV genotypes both geographically and between different risk categories. In particular, it would seem from these mainly European data that genotype 3a is a more recent arrival, at least in Europe, and that the route by which it arrived was through IDU contacts with Asia. Some data indicate that the situation is similar in Australia. The importance of these very tentative conclusions is still unclear, but given firstly that there is evidence that some genotypes may be more pathogenic, these data may provide an alternative explanation: that the 'less pathogenic' genotypes may simply have been present in the populations a shorter time, and have, therefore, had less time to cause disease. Secondly, given evidence that there is a differential response to IFN with different genotypes, there is a need to understand which genotypes are present in which populations when determining policy about the availability of IFN.

4.1.4 Contribution of injecting drug use to hepatitis C virus prevalence in other populations studied

Many populations have been studied for prevalence and associations of HCV exposure. Two factors stand out as the major associations: a history of blood transfusion prior to the introduction of screening, and a history of IDU. In the following sections the evidence relating to the contribution of IDU to exposure in other populations is reviewed.

4.1.5 Blood donors

A history of IDU is very common among blood donors found to be HCV antibody positive (table 9). For instance, in an important study at the Sydney Blood Bank, the authors conclude that: 'A history of injecting drug use was elicited as the most important risk factor in ... blood donors with antibodies to hepatitis C' [relative risk (RR) 63, 95% confidence interval (CI) 19, 260] (Kaldor et al 1992).

Table 9 Percentage of blood donors seropositive for hepatitis C virus, and percentages of HCV-seropositive blood donors with histories of injecting drug use

Percentages (pct); with a history of injecting drug use (c h/o IDU).

Site	Reference	Pct HCV +ve *(n)*	Pct HCV+ves c h/o IDU *(n)*	Odds ratio	95% CI	Comments
Cairo	Bassily et al (1995)		26.6 *(188)*	2.5		
Copenhagen	Winston et al (1995)		76 *(21)*			Includes tattooing
Denmark	Gronboek et al (1996)		76 *(21)*			Includes tattooing
France	Jullien (1995)	0.38% *(19,632)*				Risk factors: IDU (*P*=0.0000006) and history of transfusion (*P*=0.0071)
France	Maisonneuve et al (1991)		6.8 *(117)*			
France	Saura et al (1997)		25			
France	Tullen et al (1993)	0.25%				French BB screening: risk factors in donors: IDU and previous transfusion
Goteborg	Shev et al (1995a)		51[A]			Independently associated with anti-HCV and HCV-RNA positivity: IDU (*P*<0.001), blood transfusion (*P*<0.01), tattoos (*P*<0.001)
Iceland	Love et al (1995)	0.07% *(12,000)*	100 *(8)*			
Norway	Nordoy et al (1994)	0.10% *(16,756)*	56 *(16)*			
Sicily	Soresi et al (1998)			5.74		Case control
Switzerland	Zufferey et al (1992)	0.27% *(20,373)*	9 *(55)*			
Sydney	Kaldor et al (1992)	0.31% *(217,020)*		63	19-260	
Sydney	McCaughan et al (1992)		56 *(50)*			
Thailand	Sawanpanyalert et al (1996)	2.2% *(1,756)*				h/o IDU in some +ve donors
Trent Region	Neal et al (1994)	53%			Lower limit 20	
USA	Conry-Cantilena et al (1996)		42			

[A]Proportion of those +ve for HCV with IDU history.

4.1.6 Men who have sex with men

Although some studies have found higher than expected prevalences of HCV seropositivity among men with a history of homosexual contact, here as elsewhere the strongest association with HCV infection is a history of IDU. For example, in a study of 735 homosexual or bisexual men 34 (4.6%) were confirmed HCV positive (Osmond et al 1993a). The study concludes that a 'history of intravenous drug use and blood transfusion were significantly

associated with HCV positivity (OR)=14.3 and 4.4, respectively)', and that 'IVDU was by far the strongest risk factor for HCV positivity but was not a significant risk factor for HBV infection' (OR, odds ratio; IVDU, intravenous drug use; Osmond et al 1993a). Further, in this cohort, once IDU history was taken into account, the number of sex partners had no relationship with HCV seropositivity. In a cohort of homosexually active men, 7.6 per cent were seropositive for HCV; only HIV-1 infection (OR=3.18, $P<0.0001$) and IDU in the previous six months (OR=7.24, $P<0.0001$) remained significantly associated with the presence of HCV antibody in multivariate analysis (Bodsworth et al 1996). Among 435 homosexual men recruited from a municipal STD clinic from 1983 to 1984, 25 per cent reporting IDU and 5 per cent of men with no IDU were anti-HCV positive; on multivariate analysis, only IDU was significantly associated with anti-HCV positivity (OR 6.4, 95% CI 3.2, 12.5) (Buchbinder et al 1994). Among 926 homosexual or bisexual men 15 (1.6%) were HCV seropositive, and only IDU and a history of HAV were marginally associated with HCV (Donahue et al 1991).

4.1.7 Prisoners and prison entrants

See also section 4.7

High proportions of prisoners and prison entrants are HCV seropositive, in general because such high proportions have histories of IDU. In Hamburg, Germany, of 539 prisoners in one study about 80 per cent of those with a history of IDU were HCV positive and 50 per cent of the total HCV infections were due to IDU (Gaube et al 1993). In Valencia, Spain, 45 per cent of prisoners in 1991 were HCV seropositive, but of IDUs, 90 per cent were seropositive whereas only 14 per cent of non-IDUs were (Anon et al 1995). Similarly in Victoria, Australia, in 1991-92 of 3,627 prison entrants (>99% of all prison entrants) 46 per cent gave a history of IDU; 39 per cent were anti-HCV positive including 914 (64%) of the male IDUs (Crofts et al 1995). Thirty seven per cent of 408 people voluntarily tested for HCV antibody at entry into the main reception centre in New South Wales between June and December 1994 were found to have antibody to HCV (Butler et al 1997). A history of IDU, previous imprisonment, sharing of injecting equipment and having had a tattoo were all significantly associated with the diagnosis of HCV antibody. Of 70 new prisoners admitted to a Norwegian national prison, 46 per cent were anti-HCV positive, and IDU was the predominant risk factor for HCV infection (Holsen et al 1993).

4.1.8 Pregnant women

Of 5,672 pregnant women living in North Italy, anti-HCV prevalence was 0.7 per cent (40/5,672), higher than that observed among blood donors in the same geographical area (0.2%). IDU was by far the main risk factor for HCV infection, resulting in a significantly higher risk than in the control group [50 v. 5.9% (OR 15.8, CI 5.4-45.5)] (Marranconi et al 1994). Of 4,551 pregnant women in Catalonia, 1 per cent were HCV seropositive; again, IDU was the only risk factor associated with HCV infection (Salleras et al 1994). One United States study found 75 of 1,700 consecutive pregnant women seropositive for HCV, and they were found significantly more likely to have a history of IDU (Leikin et al 1994). A second study, which found 4.3 per cent of 599 inner-city prenatal patients anti-HCV positive, also found IDU to be the most commonly identified risk factor for anti-HCV-positive status: 'although risk factor-targeted screening would have failed to detect half of the anti-HCV-positive women in this study' (Silverman et al 1993).

4.1.9 Hepatitis C virus clinic patients

Of all people referred to clinics because of their HCV diagnosis, varying but high proportions give a history of IDU as the most likely cause of their exposure to HCV. The proportions of consecutive patients with diagnoses of HCV infection who gave histories of IDU were 34 per cent of 50 admitted to a Norwegian medical department (Bell et al 1992), 64 per cent of 160 in Finland (Pohjanpelto 1992), 51 per cent of 342 referred to the liver clinic of a major Melbourne general hospital (Strasser et al 1995), 24 per cent of 59 at a United States community teaching hospital (Woodall et al 1994), and 43 per cent of 63 patients at a gastroenterology/hepatology practice in Ottawa (Scully et al

1993). In most of these studies, the male to female ratio was high (2.4:1 to 5:1), but the proportions of males and females with HCV who gave a history of IDU was comparable. Generally, too, in these studies those HCV-infected patients who gave a history of IDU were younger than those who gave a history of receipt of transfusions.

4.1.10 Sexually transmissible disease clinic patients

Studies of people at STD clinics have generally been carried out with the aim of assessing the contribution of sexual transmission to spread of HCV. A familiar picture emerges from review of these data, especially with regard to important transmission factors - IDU is the most important association with HCV in this group. For instance, of 1,292 patients attending an STD clinic during a one-month period and having syphilis serology performed, 99 (7.7%) were positive for anti-HCV, of whom 45 per cent reported IDU, the most important association on multivariate analysis (Weinstock et al 1993). There was a similar finding at three STD clinics in North Carolina, USA, in 1988, where 75 per cent of HCV seropositive patients admitted a history of IDU (Fiscus et al 1994). Furthermore, of 526 persons who attended an STD clinic in Oslo, Norway, during four months in early 1990, the overall prevalence of anti-HCV was 7 per cent; three-quarters of those positive gave histories of IDU (Rollag et al 1993).

4.1.11 Other clinic patients

Of 425 consecutive patients in one orthopaedic surgeon's operative practice for one year, 19 (4.5%) were positive for HCV infection using a second-generation screening assay. The highest correlation with a positive test was the presence of tattoos and the second highest was IDU, but only after a second interview, since most patients did not report this risk on the initial questionnaire (Simonian et al 1995). Of 50 anti-HCV-positive patients attending an Accident and Emergency Department in a suburban Detroit community hospital (USA), a history of blood transfusions (58%) or of IDU (22%) were the most common factors elicited on first interview, but a remote history of IDU or tattoo application was elicited in 55 per cent of individuals less than 40 years old (Meyer and Gordon 1991).

4.1.12 Incidence of hepatitis C virus and associations of incidence among injecting drug users

Incidence of HCV infection is difficult to measure except in situations in which there are serial measurements of serological status because of the low clinical attack rate (ie the small proportion of people acutely infected with HCV who present with a recognisable hepatitic syndrome). There are, therefore, few useful data on the incidence of HCV to be found in most notifiable diseases surveillance systems (ie passive reporting); few active surveillance systems for acute viral hepatitis exist. As well, opportunities for serial serological measurements among IDUs are also few. As a result, compared with the plethora of studies examining prevalence of HCV and its associations among IDUs, there are very few studies of incidence of HCV and its associations in the same populations (table 10). These are, however, extremely important because of the light they shed on the detailed circumstances of transmission - knowledge necessary to devise effective prevention strategies - and on identifying areas of need and assessing the effectiveness of preventive interventions.

Table 10 Incidence of hepatitis C virus infection among injecting drug users

Site and population	Reference	No. of sero-converters	Year(s) of study	Rate per 100 person-years	95% CI	Associations
Veneto - clinic cohort	Galeazzi et al (1995)	2	92	6.2	1.6, 24.8	Needle sharing
Amsterdam - clinic cohort	Van den Hoek et al (1990)	17	86	14.2	0, 30.3	
			87	5.3	0, 11.2	
			88	11.4	3.5, 19.3	
			89	10.2	0, 21.8	
Baltimore	Garfein et al (1998)	13		16.0		Young IDUs, injecting < 2y, continuing to inject during follow-up
Baltimore	Villano et al (1997)	43	88-96	6.4		Frequent injecting, sharing of injecting equipment
Naples - treatment centres	Rezza et al (1996)	21		28.6	17.8, 43.4	Age >28 y, injecting cocaine; MMT[A] protective
Seattle	Hagan et al (1999)	18	94-96	26.9	17.0-39.0	Fewer years injecting, indirect exchange use or pharmacy purchases
Sydney	van Beek et al (1998)	31	92-95	20.9	13.5-28.3	Age <20y, imprisonment
Vancouver	Strathdee et al (1997)	24		18.6	11.1-26.0	
Victoria prison entrants - all	Crofts et al (1995)			18.3		Young age, shorter stay in prison
				41		
Victoria - cohort study	Crofts et al (1993)	5		19.6	2.4, 36.8	Older, male injecting longer, more opiate use, based in the country
Victoria - cohort study	Crofts & Aitken (1997)	19	90-91	16.610.9	6.9, 40.0	
			92-93	8.1	5.5, 21.8	
			94-95		3.6, 18.0	
Queensland - MMT clinic	Selvey et al (1997)	5	94-95	11	2, 20	
Victoria - MMT clinic	Crofts et al (1997b)	19	91-95	22.2	14.2, 34.8	

[A]MMT, Methadone maintenance treatment.

A key question involves the relative efficiencies of transmission of HCV and HIV among IDUs, and the effect of HIV prevention measures on the transmission of HCV. It might be expected that the introduction of measures designed to decrease the spread of HIV among IDUs (eg provision of sterile needles and syringes, increased access to methadone maintenance programs, peer and other education) through the 1980s might be expected to have an

effect on the transmission of HCV in the same populations. Data on this point are scarce, because investigations of the epidemiology of HCV generally did not begin until after these programs started and began to have an effect. One indication of the effect of these measures to prevent spread of HIV transmission of HCV among IDUs comes from surveillance data for acute viral hepatitis, where the incidence of NANBH has been documented over the relevant period. A second comes from longitudinal studies (clinic-based or field-based) where transmission of both viruses is studied directly in the same populations.

4.1.13 Surveillance data

Few countries have published analyses of surveillance data for acute NANBH over the relevant period. A review of Italian surveillance data on acute hepatitis found that the national rate of acute NANBH decreased significantly during the last decades (Zanetti et al 1995b). However, while the incidence of transmission-associated (TA)-NANBH decreased markedly, the percentage of patients with acute NANBH who give a history of IDU has risen from 18 to 33 per cent, suggesting that if there has been a decline in incidence among IDUs, it has been smaller than that among transfusion recipients.

Arising from United States surveillance data is a case-control study that compared people acutely infected with HBV or with HCV with controls who remained seronegative for the respective virus (Hagan et al 1995). This study, carried out in a United States county, was unusual in two ways: it has one of the few and one of the oldest needle and syringe exchange programs in the USA, and it is one of four sentinel counties for acute viral hepatitis. The study found that, after adjusting for demographic characteristics and duration of injecting drugs, non-use of the exchange during 1991-93 was associated with a six-fold greater risk of HBV (OR 5.5; 95% CI 1.5, 20.4) and a seven-fold greater risk of HCV (OR 7.3; 95% CI 1.6, 32.8). The authors estimate that use of the syringe exchange would have led to a 65 per cent reduction in incidence of HCV among IDUs in this county.

4.1.14 Cohort and clinical studies

Studies of IDUs followed over time with regular (or more often irregular, but at least repeated) measurements of both serological status and behavioural characteristics provide the most direct and useful measures of incidence rates and associations of behaviours and incidence. These studies potentially suffer from many biases, however, and generalising from such studies requires care: this caveat relates more to measured incidence rates than to the associations between behaviours and viral transmission.

A prospective follow-up study of 268 IDUs in Amsterdam, the Netherlands, recruited from methadone maintenance clinics and an STD clinic for IDU sex workers in Amsterdam, found that despite a diminution in incidence of HIV from 1986 through 1989, incidence of HCV was ‘high and stable’ through the same period (table 11) (Van den Hoek et al 1990). Prevalence of HCV among the IDUs on entry was 73 per cent and of HIV was 35 per cent. Seroconversion to HCV in this study was associated only with ‘recent injecting’.

Table 11 Incidence of human immunodeficiency virus and hepatitis C virus among injecting drug users in Amsterdam

From Van den Hoek et al (1990).

	Year:	1986	1987	1988	1989	Total
HCV	Total no.	3	2	8	3	16
	Person-years	17.8	50.3	64.1	26.9	159.0
	Incidence rate[A]	16.9	4.0	12.5	11.2	10.1
HIV	Total no.	5	4	6	1	16
	Person-years	42.6	97.2	131.9	54.2	326.0
	Incidence rate[A]	11.7	4.1	4.6	1.8	4.9

[A]Per 100 person-years.

A similar study among 106 initially HCV-seronegative IDUs attending drug treatment centres in Naples in 1991 through 1993 found that 21 had seroconverted, an incidence rate for HCV of 28.6 per 100 person-years (95% CI 17.8, 43.4) (Rezza et al 1996). The HIV incidence in the same period was zero (out of 281 initially HIV-seronegative IDUs who were followed) (95% CI 0.0, 1.7). Seroconversion to HCV was associated with older age (>28 y), to some degree with duration of injecting, and with the injecting of cocaine. The authors point out that risks for HIV infection (then at low prevalence in this region) were different from this. As well, they associate cocaine as a risk factor for HCV infection with the frequency of injecting and, therefore, of sharing, not as a result of any pharmacological or behavioural factor associated with the drug itself. 'Participants who had not been having methadone treatment in the previous six months were approximately 3 times more likely than the others to be HCV-infected' (lower 95% CI 0.9), suggesting some protective effect of participation in methadone maintenance. However, small numbers may have obscured real associations, as duration and frequency of injecting were found to be associated with HCV seroconversion but not significantly.

A study of 227 IDUs attending treatment centres in Veneto, Italy, found two seroconverters to HCV of 34 initially HCV-seronegative followed for at least six months, an incidence rate of 6.2 per 100 person-years (95% CI 1.6, 24.8) (Galeazzi et al 1995). Only one of the seroconverters reported sharing needles and syringes before seroconversion. A study in Sweden found that of 106 IDUs initially seronegative for HCV, 21 per cent seroconverted over unstated periods of time (so that incidence rates are not available from this study) (Widell et al 1991). However, 3 per cent are also reported to have lost antibody in the same period. These figures may be misleading, however, because of the use of the first-generation assay in this study.

In a field-based prospective study of IDUs in Victoria, Australia, five seroconverters were found among 32 initially HCV-seronegative IDUs in 1991-92, an incidence rate of 19.6 per 100 person-years (95% CI 14.1, 27.2) (Crofts et al 1993). Those who seroconverted were older, more likely to be male, had been injecting longer, more often reported opiate use, and were more likely to be based in rural areas. A further report from this same study after five years found 19 seroconverters and an overall incidence of 10.7 per 100 person-years (Crofts and Aitken 1997). A study of prison entrants in Victoria, Australia, in 1991-92 found, among those who entered prison more than once in the 12 months, incidences of 12.6 and 18.3 per 100 person-years for HBV and HCV, respectively (Crofts et al 1995). In men who injected drugs and were aged less than 30 years (29% of all prison entrants), these were 21 and 41 per 100 person years. Seroconversion to HBV or HCV was associated with young age and a shorter stay in prison.

4.1.15 Discussion

The generally very high prevalences of HCV among IDUs would seem to indicate that the virus has been present among most of these populations for some decades, long enough to reach endemicity. This is perhaps also indicated by the much greater variability of HIV prevalence in these populations. (Perhaps where there has been wider spread of HIV among an IDU population there is an apparent decrease in prevalence of HCV exposure because of decreased antibody response). The data on genotypes in these populations suggest, however, that this has been a dynamic situation, with the introduction of genotypes new to a particular population over time.

The extremely rapid rises in prevalence in the first few years of injecting seen in some studies may be explicable, to some extent, by sampling bias, with those more at risk of exposure also more readily accessible for study, but they also indicate the rapidity with which a blood-borne virus can spread in these populations in the absence of preventive measures. The increased infectiousness of HCV over HBV in most of these populations, as indicated by the earlier infection with HCV, probably relates more to higher prevalences of infectious people than any inherent property of the virus or the viral carrier.

The contribution of IDU is underestimated because of difficulties of ascertainment (which may vary from country to country, time to time, researcher to researcher or group to group), an ignorance of, or a reluctance to, acknowledge the widespread nature of IDU in these societies, and the length of time since the event(s) which may have been very few in number.

The evidence of continuing high rates of transmission of HCV among IDUs in situations in which HIV and HBV spread seem to be controlled demands explanation. Firstly, the prevalence of HCV carriage is generally much higher than that of HIV or HBV in most populations of IDUs (in Australia, on average, of the order of 50% of current IDUs will be infectious for HCV compared with less than 2% for HIV and HBV), then much smaller frequencies of behaviours allowing transmission of these viruses are sufficient to maintain a high rate of transmission of HCV than would be the case with low prevalence viruses such as HIV or HBV. Secondly, because of relatively higher concentrations of infectious particles in the blood of an HCV carrier than in that of an HIV carrier, for most of the course of the infection, much smaller amounts of blood would be necessary to carry an infectious dose. Both these factors can explain continued high rates of HCV transmission simply because of continued sharing of needles and syringes, albeit at a much reduced rate and one sufficient to substantially decrease the transmission of HIV and HBV in the same populations.

The findings of relatively high incidences of HCV transmission among IDUs who report never sharing needles and syringes with the video observation of unsafe practices other than needle and syringe sharing, and the findings from dialysis units of environmental contamination resulting in HCV transmission, raise doubts about the ability of eradication of needle and syringe sharing (if this is possible) to completely control the spread of HCV among IDUs. However, it has been argued that the relative contribution of sharing of needles and syringes to the transmission of HCV among IDUs is much greater than that of sharing of other injecting equipment or environmental contamination. On this basis, further diminution in the sharing of needles and syringes is both a necessary and perhaps a sufficient condition for control of the epidemic among IDUs (Crofts et al 1999).

Further, the observations that, at least in some populations of IDUs, substantial proportions are exposed to HCV within the first year or two of beginning to inject provide further challenges. In general, these young IDUs are not in touch with treatment programs, and are less in touch with needle exchange than their older counterparts. They constitute a group especially difficult to contact and among whom to promote behavioural change.

And lastly, high prevalences among IDUs entering methadone maintenance programs, and continued high incidences among those attending such programs, cast doubt on the usefulness of these programs in slowing HCV transmission among IDUs.

The epidemiology of HCV infection among IDUs, therefore, currently poses great challenges for control of the epidemic. Facing these challenges is urgently and vitally necessary. As can be seen from this report, IDUs are the only substantial core group for continued transmission of HCV, and if the overall epidemic is to be contained, it is among IDUs that control of the HCV epidemic must be the first priority.

4.2 Nosocomial transmission: transmission of hepatitis C virus by medical procedures and in the health care setting

4.2.1 Introduction

HCWs and their clients are exposed to HCV through contact with blood and other body fluids. In addition to being detected in blood, HCV RNA has been detected in ascitic fluid, seminal fluid and in urine from HCV-positive patients with CLD (Liou et al 1992). HCV transmission in the health care setting can occur from client to staff, from staff to client or between patients. The transmission may be direct or via contaminated instruments and other surfaces.

4.2.2 Background

Hepatitis viruses were among the first viruses found to be transmitted by blood or blood products. The recognition of hepatitis B surface antigen (HBsAg) in 1965 provided a mechanism for screening blood donors to reduce the transmission of hepatitis by blood transfusion (Boscan et al 1995). However, testing for HBsAg did not prevent all cases of TA-hepatitis even though it substantially reduced the transmission of HBV. After the development of a serological test to detect HAV, it became apparent that 95 per cent of all posttransfusion hepatitis were associated with neither HAV nor HBV (Feinstone et al 1975; Aledort 1993). This type of hepatitis became known as NANBH and early studies reported the incidence of NANBH to be as high as 21 per cent after transfusion (Gocke 1972; Alter et al 1975). The introduction of measures such as the use of nonpaid donors instead of paid donors and the exclusion of institutionalised donors in the late 1970s reduced the incidence of posttransfusion NANBH to around 10 per cent (Barbara and Contreras 1991).

Retrospective studies showed that donors with elevated levels of ALT appeared more likely to transmit hepatitis to recipients than those with normal ALT levels. A similar relationship was seen between the presence of hepatitis B core antibody (HBcAb) and donor infectivity. These findings led to the use of ALT levels and HBcAb as surrogate tests for NANBH in many countries between 1986 and 1988. However, surrogate screening for NANBH using anti-HBcAg screening was not effective in areas where HBV infection was endemic and most of the adult population tested positive to serum antibody to HBcAg. To overcome this problem, donor populations in these regions were often tested for HBsAg instead of HBcAb (Wang et al 1994).

In late 1989, HCV was isolated and serological tests that detected antibody to HCV became available (Choo et al 1989). First-generation EIAs were based on the detection of antibodies to a part of the HCV genome called the C100 antigen. False positives were common with these first-generation EIAs and the sensitivity of these assays was reported to range from 59 to 85 per cent (McFarlane et al 1990). The sensitivity and specificity of HCV EIAs improved with the introduction of second-generation EIAs which incorporated structural antigens of HCV in addition to the C100 antigen. Around the time the second-generation assays were developed, RIBA2 also became available. The RIBA2 system utilised four different recombinant HCV antigens to increase test sensitivity. When used together with the second-generation EIA, false positives are uncommon (Laurian et al 1992; Watson et al 1992).

Techniques to detect HCV nucleic acid sequences using PCR technology have also been developed. However, limited access, prohibitive cost and interlaboratory variability has resulted in variable findings from studies using

PCR techniques. The recent availability of commercial PCR kits has improved the standardisation of seroprevalence studies and improved reliability (Tilston et al 1994).

4.2.3 Blood transfusion recipients

Investigations carried out after cloning HCV and development of a serological assay for the detection of antibody to HCV have shown that 80 to 95 per cent of hepatitis infections that have occurred in recipients of blood transfusions in the last two decades were associated with HCV infection (Aach et al 1991; Tremolada et al 1991).

Studies performed in the 1970s and early 1980s estimated that the posttransfusion risk of NANBH infection was between 5 and 18 per cent (Alter et al 1981; Stevens et al 1984). The risk was reduced by 30 to 56 per cent after the introduction of screening for the surrogate markers of NANBH; elevated levels of serum ALT and HBcAb (Koziol et al 1986; Donahue et al 1992). After the introduction of first-generation screening assays for antibodies to HCV this risk was further reduced by 60 to 84 per cent and the subsequent introduction of second-generation testing has been estimated to reduce the risk by 88 to 93 per cent (table 12).

Table 12 Posttransfusion risk of hepatitis C virus infection by country

Country	Rate of HCV infection in recipients	Reference
***After the introduction of screening for surrogate markers* (%)**		
Australia	1.0	Ismay et al (1995)
Japan	4.9-16.3	Japanese Red Cross Non-A hepatitis Research Group (1991)
Spain	10.7	Gonzalez Quintela et al (1995)
Taiwan	11-12.4	Lee et al (1991b), Wang et al (1994)
USA	1.54	Donahue et al (1992)
***After the introduction of first-generation screening*[A] (%)**		
Canada	1.1	Preiksaitis and Rivet (1995)
Finland	0.3	Ebeling et al (1991)
Japan	1.9-3.3	Japanese Red Cross Non-A Hepatitis Research Group (1991)
Spain	1.5	Gonzalez Quintela et al (1995)
Sweden	<0.06	Norda et al (1995)
USA	0.57	Donahue et al (1992)
***After the introduction of second-generation or third-generation screening*[A] (%)**		
Spain	0.86	Gonzalez Quintela et al (1995)
Taiwan	0	Wang et al (1994)
USA	0-0.06 per unit	Alter (1995b), Nelson et al (1992)

[A]Studies that used both HCV antibody screening and supplemental testing.

The risk of acquiring HCV through blood transfusion has steadily declined with the introduction of screening tests for HCV-specific antibody. In addition to these screening tests, other mechanisms have been introduced to improve the safety of blood and blood products. These include donor interviewing and deferral to preclude donors with risk factors associated with chronic or acute hepatitis or HIV infection.

Further prospective studies are required to estimate the incidence of posttransfusion hepatitis in different geographical areas with high or low prevalence of HCV in donor populations. The prevalence of HCV antibodies in different populations varies from about 1 per cent in most developed countries to <10 per cent in developing countries (Purcell 1994). However, in Egypt, the prevalence of HCV antibody is estimated to be between 10 and 20 per cent (Hibbs et al 1993).

4.2.4 People with haemophilia

Studies have shown that the prevalence of HCV in people with haemophilia who received nonheat-treated concentrates after 1970 ranges from 60 to 96 per cent (Brettler et al 1990; Eyster et al 1993; Lee et al 1995). These differences are probably because of different patient selection criteria and the use of different detection systems.

Studies using second-generation assays have demonstrated that before effective procedures to inactivate virus in clotting factor concentrates were introduced, the rate of HCV transmission in people with haemophilia who were previously untreated was as high as 100 per cent (Laurian et al 1992; Watson et al 1992; Lee et al 1995).

The introduction of viral inactivation processes, such as pasteurisation, steam treatment and solvent-detergent treatment used in the preparation of clotting factor concentrates, has substantially decreased the risk of HCV transmission in people with haemophilia (Mannucci et al 1990a, 1992; Suomela 1993; Bertorp 1994). However, isolated reports of new transmissions continue.

4.2.5 Dialysis

Prevalences and associations of hepatitis C virus exposure among dialysis patients

Raised prevalences of antibody to HCV among patients receiving dialysis have been noted in multiple studies from many parts of the world (table 13, see *Tables* section). However, there is much more variation in prevalence according to location and other factors than there is, for instance, among IDUs. This remains the case even when discrepancies in prevalence rates as a result of the use of first-generation or second-generation HCV antibody assays are accounted for (Rosen et al 1996a, 1996b). This, and the various associations of HCV seropositivity among dialysis patients, suggests that factors other than simply dialysis are responsible for exposure to HCV among these patients.

In general, the prevalence of anti-HCV among patients who have received dialysis is about 30 per cent, but it ranges from 0 per cent in some South American centres (Ibarra et al 1995; Fernandez et al 1996), to 75 per cent or more in Romania (Boscan et al 1995), at an Italian centre (Fabrizi et al 1994), and in Indonesia (Hadiwondowo et al 1994). A study in the USA of 2,304 dialysis centres found an overall prevalence of less than 10 per cent (Tokars et al 1996). There are no published data on the prevalence of anti-HCV among dialysis patients in Australia.

Several studies have compared prevalences among patients who have received haemodialysis (HD) and patients who have received constant ambulatory peritoneal dialysis (CAPD) at the same dialysis centre (Castelnovo et al 1995; Cendoroglo Neto et al 1995b; Dussol et al 1995; Golan et al 1996; McIntyre et al 1994; Vanderborght et al 1995). Three have found the prevalence to be 3.7, 3.8 and 4.6 times higher among HD patients than among CAPD patients (Castelnovo et al 1995; Vanderborght et al 1995; Golan et al 1996); the fourth, from Brazil covering 1987-90, found equal prevalences (Cendoroglo Neto et al 1995b).

Among HD patients, many studies have found two major associations: number of transfusions received and duration of dialysis; most find these to be inextricably associated. Several investigators have found that HCV seropositivity in HD patients is most strongly associated with a history of blood transfusion; for instance, in two Japanese studies, prevalence among HD patients with a history of transfusions was 3.9 and 1.4 times higher than among HD patients with no such history (Fujiyama et al 1995; Nakayama et al 1996).

The evidence supports the hypothesis that a major part of the transmission of HCV to dialysis patients has in the past come from the receipt of contaminated blood transfusions. However, even among dialysis patients who have never received a transfusion, the rate of HCV seropositivity is increased over the general population, raising the possibility of nosocomial transmission in these settings. Several investigators have also reported on prevalence of anti-HCV among dialysis staff, finding rates between 0 and 7.9 per cent (Jankovic et al 1994; Tokars et al 1994, 1996; Ambrozaitis et al 1995; Anonymous 1995c; Cassidy et al 1995; Fujiyama et al 1995). There may be some association between the degree of nosocomial transmission in a dialysis centre (reflected in higher prevalences among CAPD or nontransfused HD patients) and staff exposure, but this is not clear from current studies. For instance, in two studies where prevalence among HD patients overall was high, and prevalence among nontransfused HD patients or CAPD patients was also substantially elevated (25.7 and 17%, respectively), prevalence among dialysis staff was 2.3 and 2.9 per cent (Fujiyama et al 1995; Vanderborght et al 1995) compared with 0 to 1.6 per cent in other centres with lower prevalences among patients.

Other associations of HCV seropositivity among dialysis patients reported by some studies include ethnicity (Huraib et al 1995; Golan et al 1996); exposure to HBV (Boscan et al 1995; Cendoroglo Neto et al 1995b; Dussol et al 1995; Incandela et al 1994; Slizien et al 1995); and gender (male - Huraib et al 1995; female - Kumar et al 1994; Dussol et al 1995).

Many of these studies have investigated the proportions of patients who have detectable serum HCV RNA by serostatus. Most find very high proportions of anti-HCV positives viraemic, from 41 (Fabrizi et al 1994) and 56 per cent (Tsuyuguchi 1994) to 96 (Bukh et al 1993b) and 98 per cent (Courouce et al 1995), depending partly on the date of the study and therefore the sensitivity of the RT-PCR assay used.

Among anti-HCV negatives there are several reports of small, but substantial, proportions positive for HCV RNA in serum, generally in the range of 2 to 4 per cent (Bukh et al 1993b; Chan et al 1993; Kuhns et al 1994; Seelig et al 1994; Aucella et al 1995; Castelnovo et al 1995) although there are also studies that have found no evidence of HCV RNA among seronegative dialysis patients (DuBois et al 1994; Boero et al 1995; Courouce et al 1995). The finding of these proportions of HCV-antibody-negative patients with detectable serum HCV RNA may be as a result of lack of sensitivity on the part of the antibody assays used, or it may reflect silent carriage, which may itself be more common in these patients because of immunosuppression.

This finding plus the knowledge that chronic HCV infection without elevated biochemical markers of liver dysfunction is common in haemodialysis patients implies that only direct determination of the presence or absence of HCV RNA in the serum is adequate for classification of dialysis patients as HCV infected or HCV uninfected.

Incidence of hepatitis C virus infection among patients on dialysis

Studies of the incidence of HCV infection among haemodialysis patients (table 14) report findings that accord with prevalence studies reviewed above (table 13, see *Tables* section). Incidence varies greatly depending on location and year, from 15 cases per 100 person-years in a Brazilian study covering 1987-90 (Vanderborght et al 1995) and 19.4 per 100 person-years in a Venezuelan centre (Pru et al 1994) to 0 and 0.44 per 100 person-years in two Italian studies (Fabrizi et al 1994; Incandela et al 1994). Where it has been investigated, the same gradient in incidence has been found between HD and CAPD patients as in prevalence studies. There are no published Australian studies of incidence of HCV infection among dialysis patients.

Table 14 Incidence of hepatitis C virus infection among haemodialysis patients

Site	Reference	Year	No. at risk	Seroconverters	Incidence per 100 person-years
Belgium	Stuyver et al (1996)	1991-92	68	25 *(37%)*	
Brazil	Cendoroglo Neto et al (1995a)	1987-90	HD: 83 CAPD: 46	18 *(22%)* 2 *(4.3%)*	15 3
Brazil	Vanderborght et al (1995)				11.5
Croatia	Jankovic et al (1994)		63		4
Hong Kong	Chan et al (1993)		40	3 *(7.5%)*	4.9
Italy	Capra et al (1995)				5.5
Italy	Fabrizi et al (1994)		183	2 *(1.1%)*	0.44
Italy	Incandela et al (1994)		76	0 *(0%)*	0
Italy	Aucella et al (1995)				2.4
Spain	Oliva et al (1995)		42	5 *(12%)*	4
Venezuela	Pru et al (1994)		37	17 *(45.9%)*	19.4

Outbreaks of hepatitis C virus in haemodialysis units

Several outbreaks of HCV infection among patients in haemodialysis units have been described. In 1991-92, 25 out of 68 patients undergoing haemodialysis in a Belgian centre were observed to seroconvert for HCV (Stuyver et al 1996). Of the 25, 20 had a unique sequence motif, demonstrating patient-to-patient spread within the unit; despite intensive investigation, no traceable source or transmission mechanism was proven. In Sweden in 1994, 14 haemodialysis patients with chronic HCV infection were investigated (Allander et al 1994). Sequence analysis showed that five were infected with a common strain, and another two with a different common strain. Investigation showed that transmission was not related to blood transfusions or use of the same dialysis machines, but was related to being dialysed on the same shift, suggesting blood transfer between patients by environmental or staff contact. Investigation of several transmission events in a Japanese haemodialysis unit found that patients at different but proximate consoles were being exposed to HCV (Okuda et al 1995). After exclusion of other possible routes of transmission it was concluded that the likeliest transmission pathway was on contaminated gloves of nursing staff withdrawing needles from patients. There are several other studies similarly describing outbreaks of HCV among haemodialysed patients on the basis of common sequence strains but which could not exactly determine the route of transmission other than to exclude the reuse of contaminated dialysis equipment (Chiaramonte et al 1992; Corcoran et al 1994; Sampietro et al 1995).

One study from Germany, however, found only two isolates with common sequences among 14 HCV-RNA-positive haemodialysis patients, suggesting that nosocomial transmission in this unit was uncommon (Zeuzem et al 1996).

Methods of transmission of hepatitis C virus among haemodialysis patients

Several routes have been hypothesised as responsible for transmission of HCV among dialysis patients: through unrelated risk factors such as IDU, through transfusion of contaminated blood and blood products, nosocomial transmission from patient to patient by several mechanisms (including shared and contaminated equipment, contamination by staff not strictly observing universal precautions, and by patients helping each other on the ward), and through the actual dialysis equipment or process itself.

The role of transfusion in transmission of HCV among dialysed patients is clearly indicated by the following associations with HCV exposure among haemodialysed patients:

- a history of blood transfusion;
- a dose-response relationship with the number of blood transfusions;
- higher rates of HCV exposure among HD compared with CAPD patients; and
- higher rates of HCV exposure among transfused HD patients compared with nontransfused HD patients.

However, the higher prevalences of HCV exposure among nontransfused HD patients and among CAPD patients, and the very strong association of HCV exposure with length of time on dialysis (independent of history of blood transfusion) demonstrate that other mechanisms are also important (Tsuyuguchi 1994).

Several authors have concluded that environmental factors are important in nosocomial transmission of HCV in dialysis units (Irie et al 1994; Cendoroglo Neto et al 1995b; Nakayama et al 1996), with an Italian study concluding that 'with two new needle holes made along the anastomosed blood vessels two to three times per week, the chances of patient exposure to HCV may increase with time' (Irie et al 1994). However, one Japanese study found very low rates of HCV exposure among female dialysis patients who had not received a transfusion, concluding that such exposure is not inevitable (Nakayama et al 1996).

A Venezuelan study found 17 seroconversions among 37 initially negative, indicating that, according to the authors, 'the existence of a route of transmission from patient to patient through the dialysis machine' (Pru et al 1994). The role of dialysis itself has been investigated in two studies, the first in Austria indicating that no HCV RNA (cells or cell particles) passed through dialysis membranes (Hubmann et al 1995). In a second study, from Spain, PCRs performed on haemodialysis ultrafiltrate or peritoneal effluent from HCV-RNA-positive patients were always negative for HCV RNA (Caramelo et al 1994). This same study found no transmission of HCV from HCV serum RNA-positive patients to negative patients sharing dialysis monitors, a finding which was replicated in an Italian study (Gilli et al 1995). Despite a high starting prevalence in the patients on the dialysis ward, no new HCV infections were observed either in patients on separate machines or in patients sharing machines. The authors conclude that, '(t)he possibility of an intradialytic diffusion of HCV appeared to be very low and the treatment of infected patients on separate machines not strictly necessary', and further that universal precautions should be rigorously applied. However, the authors of a Swedish investigation of HCV transmission in a haemodialysis unit have suggested that there may be high frequencies of HCV transmission even where precautions are rigorously applied (Allander et al 1994). They particularly point out that such spread can occur unnoticed if it is not searched for.

Prevention of hepatitis C virus transmission in dialysis units

A decrease in the risk of transmission of HCV through transfusion of blood is the most important method of decreasing risk for dialysis patients. Universal screening of blood donors, decreasing the number of transfusions and increasing the use of erythropoietin all diminish the risk of TA-HCV in these patients (Incandela et al 1994; McIntyre et al 1994; Fujiyama et al 1995). Screening of blood donors for anti-HCV has been shown to have decreased prevalence of HCV antibody in one French HD unit from 43.6 to 21.2 per cent (Simon et al 1994). With these measures in place, nosocomial transmission becomes the largest threat to dialysis patients (Paydas et al 1994), raising the importance of strict adherence to universal precautions (Incandela et al 1994; Dussol et al 1995; Fujiyama et al 1995; Huraib et al 1995). A Saudi Arabian multi-centre study found that 'the major difference between HD centres with low and with high prevalence was the adherence of the staff to universal infection precautions' (Huraib et al 1995).

The need to subject HCV-infected patients to quarantine or isolation in special wards or units has been raised by several authors in the light of continuing HCV transmission among dialysis patients (Aucella et al 1995; Blumberg et al 1995; Dussol et al 1995), and some have found that limited isolation does indeed decrease transmission 0(

Blumberg et al 1995). For instance, an outbreak of HCV infection among HD patients in an Italian unit with .machines without completely disposable dialysate circuits was seen to have been stopped by transferring patients with acute hepatitis to machines with completely disposable circuits (Chiaramonte et al 1992). However, the existence of dialysis patients who had been diagnosed as positive by PCR for HCV RNA in their serum while remaining anti-HCV negative (as indicated above) has been used to question the long-term efficacy of such policies (Fernandez et al 1996). As well, there are logistical implications inherent in such policies which involve the multiplying of separate wards or the application of costly routine testing programs (Jadoul et al 1993).

In conclusion, an Italian group has shown that 'traditional dialysis, employing low-permeability machines and disposable dialysate circuits on machines without an ultrafiltration control device' together with rigorous application of universal precautions can prevent HCV transmission among dialysis patients. Jadoul et al (1993) and Jadoul (1995) have concluded that 'the most cost-effective alternative may be strict adherence to basic barrier precautions: cleaning and disinfecting instruments, machines and surfaces as well as frequent handwashing and the systematic use of gloves'. In the words of a *Lancet* editorial on the subject, 'Now wash your hands' (Heptonstall and Mortimer 1995).

4.2.6 Intravenous anti-D immunoglobulin

Anti-D immunoglobulin is prepared from the plasma of donors with high concentrations of anti-rhesus D antibody. Intravenous anti-D immunoglobulin was first reported to be involved in the transmission of HCV in an outbreak of NANBH that occurred in East Germany between 1978 and 1979 (Dittmann et al 1991). A similar outbreak was also reported in Ireland where 12 women received anti-D immunoglobulin manufactured in 1977 that contained HCV-RNA sequences (Stevens et al 1984; Power et al 1994; Power et al 1995a). Both of these outbreaks were traced to index cases who donated HCV-antibody-positive blood.

Another intravenous preparation implicated in the transmission of HCV was an immunoglobulin product, Gammagard, used to treat primary immunodeficiency disorders such as hypogammaglobulinaemia. In the USA, 43 people with acute HCV infection were reported to the Centers for Disease Control and Prevention (CDC) between 1993 and mid 1994 where the only risk factor for HCV infection was receipt of the intravenous immunoglobulin, Gammagard (Anonymous 1994). Gammagard was subsequently removed worldwide in early 1994. Preliminary epidemiological investigations in the USA have indicated that no other intravenous immunoglobulin products or intramuscular immune globulin have been associated with HCV transmission (Anonymous 1994).

The recent introduction of anti-viral treatments used in the manufacture of immunoglobulin products has substantially reduced the risk of transmission of HCV to recipients of these products.

4.2.7 Hepatitis C virus and dentistry

It is a commonly believed that there are 'large numbers of hepatitis C carriers in whom no route of infection can be identified' (Tibbs 1995). Given the findings of HCV RNA in saliva and higher than expected prevalences of HBV in dentists, some of these cases (if this is indeed the case) may be explained by transmission in the dental setting. There is also the question of the degree to which dental staff are at occupational risk of HCV infection.

Presence of hepatitis C virus in saliva

HCV RNA has been detected in saliva in the dental setting, both with and without blood contamination. In one study of 26 anti-HCV-positive patients, of whom 11 were coinfected with HIV, HCV RNA was detected in the sera of 23 (88%) and in the saliva of 4 (17%) of these viraemic patients. The authors suggest that HCV is present in saliva in

less than 25 per cent of HCV viraemic people, and the virus in saliva is restricted to the cell fraction, so that saliva may serve as a nonparenteral transmission route of HCV but at a low probability, which would be increased by blood contamination of saliva during and after oral surgery (Chen et al 1995). A second study of 21 HCV-seropositive patients with haemophilia attending an Oral Surgery Unit, all of whom were HCV-RNA positive and six of whom were also HIV-antibody positive, found HCV in saliva from 10 of the subjects (8 HIV seronegative, 2 HIV seropositive) (Roy et al 1996).

Prevalence of hepatitis C virus in and risks of transmission to dental staff

For exposure of dental staff to HCV to occur, HCV must be present in the population of dental patients and the dentist must experience an exposure-prone injury. That dentists are at risk of occupational injury conducive to exposure to blood-borne viruses is undoubted. A survey of 310 dental practitioners in Scotland found that 56 per cent of respondents reported at least one such injury within the preceding year, half of which were judged to have constituted a moderate or high risk of transmission to the dental practitioner (Felix et al 1994). That HCV is present in dental populations is equally undoubted: it has been estimated that in an average dental practice in the USA that treats 20 patients each day, one HCV-infected patient will be encountered every 2 weeks (Wisnom and Kelly 1993). A study of 500 dental school patients in the USA found more than 5 per cent were HCV seropositive; it also found that responses to questionnaires of risk factors were not of practical value in predicting who was seropositive (Shopper et al 1995).

Given the presence of HCV in saliva, the prevalence of occupational exposure-prone incidents among dentists and the prevalence of HCV in some dental populations, it would be expected that there would be a high prevalence of HCV exposure among dental staff. There have been four major surveys of dentists and oral surgeons examining prevalence and associations of HCV, and their conclusions are not totally in accord.

In a survey of dental professionals attending the annual meeting of the College of Dental Surgeons of British Columbia, Canada, in June 1990, 401 of 1,995 convention attendees (20%) participated. Fourteen (3.5%) had markers of HBV infection, of whom one (0.25%) was also HCV-seropositive: none was positive for antibody to HIV (Roscoe et al 1991). In Taiwan in 1990-91, 3 of 461 dentists (0.65%) were HCV-seropositive, comparable with the prevalence in healthy blood donors (0.95%) and pregnant women (0.63%), leading to the conclusion that in this area the practice of dentistry carries no increased risk of HCV infection (Kuo et al 1993). Among 456 dentists in the New York City area anti-HCV was found in 8 (1.75%), compared with 1 (0.14%) of 723 controls (OR 12.9, 95% CI 1.7, 573). Seropositive dentists claimed to have treated more IDUs in the week (P=0.04) or month (P=0.03) before the study than did seronegative dentists. In this study, anti-HCV was found in 4 (9.3%) of 43 oral surgeons compared with 4 (0.97%) of 413 other dentists (OR 10.5, 95% CI 1.9, 58) (Klein et al 1991). And lastly, among 343 oral surgeons and 305 general dentists, recruited at national meetings of the American Dental Association, anti-HCV was found in 2.0 and 0.7 per cent, respectively (OR 3.2, P=0.13), associated with older age, longer time in practice, and evidence of past HBV exposure (Thomas et al 1996).

Two other studies that have included dentists along with other HCWs have similarly found low rates of exposure to HCV, even where prevalence is high in the patient population. One study in the USA found anti-HCV prevalence to be 1.6 per cent (95% CI 0.0, 3.2%), similar to volunteer blood donors, despite high degrees of blood exposure in the HCWs (Cooper et al 1992). A survey of hospital-diagnosed acute viral hepatitis in the United States Air Force staff from 1980 to 1989 found an increased risk of HCV for ‘procedurally oriented medical personnel’ (including dentists) when compared to all other occupations, but this increase was not large (RR 1.5, 95% CI 1.1, 1.9).

Taken together, these data tend to confirm high rates of HBV exposure among dental staff, but suggest that the risk of HCV infection is considerably lower: it seems to be increased with risk of blood contamination and degree and frequency of exposure-prone procedure.

Knowledge of transmission of viral pathogens among dental staff

Some researchers have investigated dentists' awareness of the risks of transmission of viral pathogens, and their response to these risks. A survey in British Columbia, Canada, showed that many of the mechanisms, routes and risks for the transmission of viral pathogens in the dental setting were not clearly understood by the dentists surveyed, and recommended continuing education to ensure that compliance with current infection control recommendations be based on a clear understanding of the mechanisms of infection (Epstein et al 1995). The Roscoe et al (1991) survey of dental professionals in British Columbia also assessed compliance with infection control guidelines, and found acceptance to be high, with 92 per cent of participants reporting use of gloves for all patients and 82 per cent reporting use of masks and eye protection.

Risks of patient-to-patient transmission in the dental setting

Returning to the question of whether dental procedures constitute a risk for HCV infection for the patient, there are few studies which have identified a history of dental work as a risk factor among HCV-infected people. In Hangzhou, China, 22 per cent of 1,248 people with acute viral hepatitis were NANBH, and among these cases 'seeing dentist was the main risky factor'[sic] (Sun 1990). A second study in China found that for three (7.5%) of 40 HCV-seropositive patients frequent visits to the dentist were the only discoverable risk factor (Garassini et al 1995). An analysis of data on acute viral hepatitis collected by an Italian surveillance system found that 9 per cent of all cases of acute HCV infection had only a history of dental work as a risk factor in the preceding six months (Piazza et al 1995).

On the basis of Piazza et al (1995), environmental contamination of dental surgeries by HCV was investigated by following 35 anti-HCV and HCV-RNA-positive patients with chronic hepatitis through dental treatment; 328 samples were collected from instruments and surfaces after their dental treatment. Twenty (6.1%) were positive for HCV RNA, including samples from work benches, air turbine handpieces, holders, suction units, forceps, dental mirrors and burs. The authors conclude that 'these data indicate that there is extensive contamination by HCV of dental surgeries after treatment of anti-HCV patients and that if sterilisation and disinfection are inadequate there is the possible risk of transmission to susceptible individuals' (Piazza et al 1995).

4.2.8 Hepatitis C virus and surgery

The existence of HCV infection among surgical patients or surgeons raises the possibility of its transmission in the surgical setting, from patient to surgeon, from surgeon to patient, or from patient to patient. Partly because of the low clinical attack rate with acute HCV infection, there have been few reported outbreaks or transmissions in this setting, but some evidence in some settings suggest surgery can be a risk for HCV transmission. Environmental studies on this subject are lacking.

It has been estimated in the USA that the risk of a surgeon acquiring a disease from one percutaneous exposure is 0.3 to 0.4 per cent for HIV, 6-30 per cent for HBV and 2.7 to 10 per cent for HCV, and that rates of blood contacts vary (particularly with the type of surgery) but may reach up to 11.9 per 100 hours in the operating room (Patz and Jodrey 1995).

Environmental studies

One Japanese study (Higashi et al 1994) found HCV RNA in the irrigating solution aspirated by the ultrasonic dissector system used in liver surgery, correlating with HCV RNA in the serum of the patient operated on. The authors conclude 'that it is necessary to be cautious regarding the transmission of HCV during liver surgery when using the ultrasonic dissector in HCV RNA seropositive patients, because the irrigating solution aspirated by this device appears to be highly infectious' (Higashi et al 1994). Studies in the dental setting have found evidence of

HCV RNA both in patients' saliva (Roy et al 1996) and in the dental environment following dental work on HCV-RNA-positive patients (Piazza et al 1995).

An Australian study of exposure of endoscopic surgeons engaged in transurethral resection using fluoroscein staining of irrigating fluid found that in 17 out of 20 consecutive operations splashes on the face of the surgeon, although few, were visible to the naked eye (Taylor 1990). A Japanese study of 226 ophthalmological patients found HCV antibody in the aqueous humour of 11 (4.9%), but in six eyes of five of these patients, HCV RNA was not found by PCR (Kobayakawa et al 1993). Other than these, there are no reported studies of investigation of HCV RNA in the surgical environment.

Prevalence of hepatitis C virus in surgical populations

In several studies of surgical patients, increased rates of HCV seropositivity have been reported in several studies of presurgical patients in several locales. Associations of HCV seropositivity have been reported as having liver disease or risk factors for HCV infection, especially tattoos, a history of transfusion or a history of IDU. One investigation of risks for HCV infection in a consecutive series of surgical patients in the USA found that a history of IDU was difficult to elicit in this setting, raising doubt about the usefulness of this history as a screen for HCV risk (Simonian et al 1995), but a second in Japan found a history of risk factors for HCV to be very discriminating (HCV prevalence among those with risk factors was 54 per cent, while among those with no discoverable risk it was 1.9%) (Yanaga et al 1995).

Risks to surgeons

Several studies in different locales have reported higher than expected rates of HCV seropositivity among surgeons, although these rates generally are lower than those for HBV. Twenty-seven per cent of 2,887 surgeons at 21 hospitals in moderate to high AIDS incidence areas participated in a voluntary, anonymous serosurvey of blood-borne viruses, of whom 7 (0.9%) had anti-HCV (Murphy et al 1995). The authors concluded that HBV posed the highest risk of infection with a blood-borne pathogen to a surgeon, followed by HCV and HIV (Panlilio et al 1995). Of 343 oral surgeons and 305 general dentists recruited at national meetings of the American Dental Association, 2.0 per cent of the former and 0.7 per cent of the latter were found to be HCV seropositive, compared with 21.2 and 7.8 per cent, respectively, for HBV. HCV seropositivity was associated with age, longer practice, and markers of HBV exposure (Thomas et al 1996). In a study of surgeons in Argentina, the fields of surgery in which there were higher rates of HCV seropositivity were haemodialysis, obstetrics, surgery and intensive care (Frider et al 1994). Similarly in the USA, surgeons at greatest risk are residents and those working in obstetrics and gynaecology (Patz and Jodrey 1995). Contributing risk factors are said to include trauma or emergency orthopaedic procedures, high patient blood loss, long procedures and holding tissue by hand while suturing (Patz and Jodrey 1995).

Potential transmission of hepatitis C virus by surgery

There remains only one proven example of patient-to-patient transmission of HCV in a surgical setting, which occurred in Sydney, Australia, in a surgical setting in a private hospital (Chant et al 1994). Investigation of a cluster of five people with HCV infection, all of whom had surgical procedures in the same session at the same operating theatre, came to the conclusion that four were infected from the other, although the actual path of transmission was not determined.

However, there are two reports in which HCV was transmitted from a surgeon to the patients upon whom surgery was performed. The first was reported from England (Anonymous 1995b). The second involved a cardiac surgeon in Barcelona, Spain, who infected five patients between 1988 and 1994. The viral strain was the same in each case as demonstrated by sequencing of the virus and phylogenetic analysis. The surgeon reported an overall incidence of 20 percutaneous injuries per 100 procedures, but the commonest injury, and the one thought to have been most likely

involved in HCV transmission, occurred during the procedure of tying the wires during closure of the sternum (Esteban et al 1996).

Other than these cases, evidence of surgical transmission of HCV to patients (whether from surgeon to patient or from patient to patient) is indirect, identifying a history of surgery as an independent risk factor in those diagnosed as HCV seropositive. This has been found in several studies, mostly in developing countries. In the Yemen, in a survey of 348 people without liver disease, HCV seropositivity was significantly associated with age and prior surgery (OR 10.1), but was not associated with a history of prior blood transfusion or markers of HBV infection (Scott et al 1992). In Indonesia, HCV seroprevalence among 7,572 healthy volunteer blood donors from 21 of the 27 Indonesian provinces was 2.1 per cent; risk factors for HCV seropositivity included a history of surgery, blood transfusion, intravenous medication, and acupuncture (Sulaiman et al 1995). In Taiwan, among 126 family contacts of 42 HCV-infected patients without histories of parenteral exposure, 21 (17%) were HCV seropositive, and histories of blood transfusion and surgery were the factors significantly associated with HCV infection, suggesting an independent route of infection rather than household contact in these people (Chang et al 1994b). Several studies from Portugal and Spain also have found a history of surgery without transfusion to be an independent risk factor for HCV seropositivity (Barcena Marugan et al 1992a, 1992b; Santos et al 1994; Suarez et al 1994).

It is clear that HCV can be transmitted in the surgical setting; however, the rate at which this happens in any particular population of surgical patients is unknown but clearly low.

4.2.9 Transmission of hepatitis C virus to health care workers

Early evidence of an association between HCV infection and health care employment was provided in a case control study of patients with acute NANBH (Alter et al 1989a). Case control studies of blood donors with HCV antibody have also reported increased risk with health care employment (Kaldor et al 1992; Neal et al 1994). Community-based studies carried out in the USA between 1990 and 1993 report that health care employment represents 2 per cent of people with acute HCV infection (Alter 1995b). In Australia, 1.4 per cent of the 138 incident cases of HCV (notified under an enhanced surveillance for incident cases of HCV trial in 1995) were attributed to needlestick injury among nonIDUs (Andrews and Curran 1996).

Case reports of NANBH after percutaneous exposure were published in the early 1980s, and since the development of the HCV-antibody assay, case reports of HCV seroconversion have been published (Seeff 1991; Tsude et al 1992; Garces et al 1996). In Brisbane, Australia, 7 of 33 HCWs referred to a HCV clinic between 1990 and 1994 were documented as people with occupationally acquired HCV infection.

The risk of HCV transmission to HCWs has been investigated in cohort studies of HCWs negative for HCV antibody on enrolment (table 15), cohort studies of HCWs following percutaneous exposure from source patients who were antibody or RNA positive (tables 16 and 17, respectively), cohort studies of HCWs following nonpercutaneous exposure from source patients who were antibody positive (table 18) and cross-sectional surveys of HCV prevalence among HCWs, not employed and employed in haemodialysis units (tables 19 and 20, respectively).

Table 15 Incidence of hepatitis C virus antibody seroconversion in cohorts of health care workers negative for hepatitis C virus at baseline (enrolment)

Country	Reference	Year	Assay	Number tested at baseline	Number tested at follow-up *(%)*	Incidence *(%)*	95% CI
Italy	Di Nardo et al (1995)	1986-92	EIA2	937	765 *(82)*	1 *(0.13)*	
Italy	Puro et al (1995)	1992-93	EIA2 RIBA	3006	2622 *(87)*	3 *(0.1)*	0.02, 0.34
USA		1987-89	EIA1	50		3 *(6.0)*	
USA		1984-92	EIA1 EIA2 RIBA		556	1 *(0.2)*	

Incidence of HCV antibody was 0.8 per 1,000 person years (95% CI 0.03, 3.6) in a cohort of hospital staff from San Francisco with no self-reported behavioural risk factors followed from 1984 to 1992 (Gerberding 1994). In this study, first-generation HCV-antibody tests were confirmed by testing all seropositives and a random sample of seronegatives with second-generation tests. The single incident in this study occurred in a nurse from the emergency department who could not describe a specific exposure event. Comparison was also made with HIV and HBV; HIV incidence was 0.55 per 1,000 person-years and HBV incidence among never-vaccinated staff was 30.5 per 1,000 person-years.

Transmission of HCV from patient or laboratory material to HCW generally has been documented following percutaneous injuries (tables 16 and 17). HCV incidence in HCWs following percutaneous injury to HCV reported in studies using second-generation or third-generation EIA assays with RIBA confirmatory testing ranged from 0 to 6 per cent. Many of these studies have small sample sizes. The upper limit of the 95 per cent confidence intervals ranged from 3 to 18 per cent. Several studies included some patients with both HCV and HIV infection. There does not appear to be an increased risk of transmission associated with HIV coinfection although sample sizes are very small and the number of studies limited (Hernandez et al 1992; Perez Trallero et al 1994; Puro et al 1995). The level of viraemia, however, does appear to influence transmission. Two studies measured HCV RNA in the source and one study tested a random sample of source sera for HCV RNA; HCV transmission was 2.5, 3.4 and 10.3 per cent of 80, 29 and 68 injuries from a source with HCV RNA, respectively, with no reported transmission from sources negative for HCV RNA (Mitsui et al 1992; Sodeyama et al 1993; Perez Trallero et al 1994).

Table 16 Hepatitis C virus transmission to health care workers following percutaneous injury from a source with hepatitis C virus antibody

Country	Reference	Institution	Assay	Type of injury	No. of sources with HCV antibody	No. sero-conversions *(%)*	95% CI	Comments
Australia	NCHECR (1998)			NSI[A]	28	0 *(0)*	0, 12	
Italy	Puro et al (1995)	H[B](16)	EIA2 RIBA	NSI	97	1 *(0.75)*	0.02, 4.1	
		H (16)	EIA2 RIBA	NSI Sharp	331 105	4 *(1.2)* 0	0.3, 3	Includes 123 sources with HIV antibody (2/123 v. 2/208). Loss to follow-up 9%
Italy	Petrosillo et al (1994)	Dialysis units (9)	EIA2 RIBA2	NSI	61	0	0.0, 6	
Japan	Kiyosawa et al (1991)	UH[C]	EIA1 RIBA	NSI	110	3 *(2.7)*	0.6, 8.0	Loss to follow-up, 44%
Japan	Sodeyama et al (1993)	UH	EIA1	NSI & sharp	90	2 *(2.2)*	0.3, 7.8	
Japan	Mitsui et al (1992)	H	EIA1	NSI	76	7 *(9.2)*	3.8, 18	
Spain	Hernandez et al (1992)	TH[D]	EIA2 RIBA	NSI	81	0	0.0, 4	Includes 38 sources with HIV antibody (0/38 v. 0/43)
Spain	Perez Trallero et al (1994)	H	EIA2 EIA3	NSI	53	1 *(1.9)*	0.1, 10	Includes 42 source with HIV antibody (1/42 v. 0/11)
UK, London	Zuckerman et al (1994)	UH	EIA2 RIBA2	NSI	24	0	0.0, 14	
USA	Lanphear et al (1994)	UH	EIA2 RIBA2	NSI	50	3 *(6.0)*	1.3, 17	Loss to follow-up, 56%

[A]NSI, needlestick injury. [B]H, hospital. [C]UH, university hospital.[D]TH, teaching hospital.

Table 17 Hepatitis C virus transmission to health care workers following percutaneous injury from a source with HCV RNA

Country	Reference	Source with HCV RNA	No. sero-conversions *(%)*	95% CI	Source without HCV RNA	No. sero-conversions	95% CI
Japan	Sodeyama et al (1993)	80	2 *(2.5)*	0.3, 9	10	0	0, 31
Japan	Mitsui et al (1992)	68	7 *(10.3)*	4.3, 21	8	0	0, 37
Spain	Perez Trallero et al (1994)	29[A]	1 *(3.4)*	0.1, 18	13[A]	0	0, 25

[A]All sources with HIV antibody.

In table 18 the studies reporting nonpercutaneous injuries from a source with HCV antibody are summarised. There have been two case reports of HCV transmission through nonpercutaneous exposure; these occurred via blood splash to the eye in a health care worker (Sartori et al 1993) and a prison worker (Rosen 1997).

Several studies have reported the seroprevalence of HCV among HCWs to be generally around less than 1 to 2 per cent except among oral surgeons and haemodialysis staff. Among oral surgeons, HCV antibody prevalence was 9 per cent with first-generation testing and was significantly higher than dentists in the same study (Fabrizi et al 1994). A lower prevalence (2%) was reported among oral surgeons in a later study using second-generation antibody testing (Thomas et al 1996). Some of these studies have shown prevalence to be associated with increasing age (De Brouwer and Lecomte 1994; Puro et al 1995; Thomas et al 1996), increasing length of employment (Jadoul et al 1994; Thomas et al 1996), serological markers for HBV (Polish et al 1993; Puro et al 1995; Thomas et al 1996), and a history of blood transfusion (Polish et al 1993; Petrosillo et al 1995; Puro et al 1995).

Table 18 Hepatitis C virus transmission to health care workers following nonpercutaneous injury from a source with hepatitis C virus antibody

Country or region	Reference	Institution	Assay	Type of injury	Source with HCV antibody	No. of sero-conversions
Australia	NCHECR (1998)	Multi-site: Hospitals		Nonpercutaneous	16	0
Italy	Petrosillo et al (1994)	Dialysis units (9)	EIA2 RIBA2	Mucous membrane Nonintact skin	29 40	0 0
Italy	Petrosillo et al (1995)	Dialysis units (9)	EIA2 RIBA2	Mucous membrane Skin contamination	29 271	0 0
Italy	Puro et al (1995)	Hospitals (16)	EIA2 RIBA EIA2 RIBA	Other than needlestick Mucous membrane Skin contamination	36 85 125	0 0 0
Scandinavia	Sartori et al (1993)	Haemodialysis unit (1)	EIA2 RIBA	Conjunctival splash	1	1
USA	Rosen (1997)	Prison	EIA2	Conjunctival splash	1	1

The risk of transmission of HCV infection depends not only on the likelihood of transmission per blood contact and the frequency of occupational contacts but also on the prevalence of infection among the patient population. The prevalence of HCV among hospitalised patients varies according to specialty and community prevalence. In studies carried out in the dialysis setting, a high-risk environment for transmission of blood-borne viral infections to both patients and health care staff, the prevalence of HCV among patients ranged from 5 to 75 per cent (median). Among hospitalised patients other than those in dialysis units, prevalence was generally less than 2 per cent except in patients in emergency departments and autopsy cases in the USA where prevalence was almost 20 per cent and associated with IDU. HCV prevalence among patients in dialysis units was associated with increased duration of dialysis and blood transfusion. In contrast, other studies have found no association with blood transfusion. HCV prevalences of 11 and 18 per cent have been reported from 159 and 36 patients, respectively, with no history of blood transfusion. Among haemodialysis patients in the USA and Belgium, incidence rates of 2 to 3 per cent have been reported: most new infections were unrelated to blood transfusion (Niu et al 1993; Jadoul et al 1994; Peco Antic et al 1994).

Table 19 Hepatitis C virus antibody prevalence among health care workers (other than staff employed in haemodialysis units)

Country	Reference	Assay	Health care facility	No. of HCWs	With HCV antibody(%)	Comment
Belgium	De Brouwer & Lecomte (1994)	EIA3 RIBA3	University hospital	2031	1.48	Non-significant increase with age
France	Germanaud et al (1994)	EIA2 RIBA2	Medical and nursing staff	430	4 (0.9)	Hospital office workers, 1.7%
Germany	Jochen (1992)	EIA2 RIBA	Hospital employees	1033	0.58	
India, Bombay	Amarapurkar (1994)	Not reported	Hospital staff	90	0	
Italy	De Luca et al (1992)	Not reported	Hospital staff	945	45 (4.8)	Factory workers 10%
Italy	Petrosillo et al (1995)	EIA1 Matrix assay	Public hospitals (5)	5813	116 (2)	Associated with history of blood transfusion; No association with occupational or behavioural risk factors
Italy	Puro et al (1995)	EIA2 RIBA	Hospitals (16)	3006	2.2	Associated with previous acute hepatitis, blood transfusions, older age, and housekeeping occupation
Italy	Di Nardo et al (1995)	Not reported	Psychiatric hospital	937	0.85	
Japan	Nakashima et al (1992)	EIA1 RIBA GOR EIA	Acupuncturists Medical staff Nursing staff Other HCWs	183 115 670 310	5.5 4.3 2.2 0.0	No association with age
South Africa	Soni et al (1993)	EIA2 NA[A]	Nurses	212	0	Antenatal patients, 0 of 100
Taiwan	Kuo et al (1993)	EIA2	Dentists	363	0.8	
UK	Herbert et al (1992)	EIA2	Dental surgeons	94	0	
UK	Zuckerman et al (1994)	EIA2 RIBA2	Hospital staff	1053	0.28	No association with age. Anonymous survey.
USA	Gerberding (1994)	EIA2 RIBA	Hospital staff	851	1.1	
USA	Polish et al (1993)	EIA1 NA	Hospital staff	677	1.1	Significant association with HBV core antibody, needlestick, blood transfusion
USA	Thomas et al (1993)	EIA1 EIA2 RIBA	Primary care facility & tertiary referral centre	943	7(0.7)	Voluntary anonymous survey. Response rate 90%.

Table 19 continued next page

Country	Reference	Assay	Health care facility	No. of HCWs	With HCV antibody(%)	Comment
USA	Thomas et al (1996)	EIA2 RIBA	Oral surgeons General dentists	343 305	2.0 0.7	Associated with older age, more years of practice and serological markers for HBV invection
USA	Goetz et al (1995)	EIA2 RIBA	Liver transplant unit Other HCWs	57 184	5 0	Voluntary anonymous survey. No association with sex, age, race, length of occupation.
USA	Panlilio et al (1995)	EIA1 RIBA	Surgeons at 21 hospitals	740	7 (0.9)	27% response rate
USA	Gershon et al (1995)	Not reported	Funeral practitioners	130	0	50% response
USA	Klein et al (1991)	EIA1 RIBA	Oral surgeons Dentists	43 413	9.3 1.0	

[A]NA, neutralising assay.

Table 20 Hepatitis C virus antibody prevalence among staff employed in haemodialysis units

Country	Reference	Assay	No. of HCWs	With HCV antibody (%)	Comment
Belgium	Vanderschueren et al (1991)	EIA1	35	0	
Egypt	el Gohary et al (1995)			7.7	Urban blood donors 14.5% 2 rural communities 15%
Italy	Besso et al (1992)	EIA1 EIA2	55	3.6	
Japan	Oguchi et al (1992)	EIA1 EIA2 at 2 units	150	2	
Japan	Oguchi et al (1992)	EIA2	150	2.0	
Japan	Fujiyama et al (1995)	EIA 2	216	2.3	
New Zealand	Blackmore et al (1992)	EIA1 EIA2	20	0	
Taiwan	Lin et al (1991)	EIA1	69	2.9	
USA	Niu et al (1993)	EIA1	142	1.0	Cumulative incidence=0% over 18 months
USA	Forseter et al (1993)	EIA RIBA1	29	3.5	
USA	Jadoul et al (1994)	EIA2 RIBA	120	4.1	Associated with longer employment in unit

4.2.10 Conclusion

Transmission of HCV infection in the health care setting depends on the likelihood of acquiring infection after blood contact from a source with HCV infection, the frequency of blood contact and the prevalence of HCV infection in the patient population. Current evidence suggests that the risk of transmission of HCV through percutaneous injury from an infected patient is higher than that for HIV but lower than that for HBV. From a limited number of studies it would appear that risk of HCV transmission is associated with level of viraemia.

The transmission studies are limited by nonreporting of incidents within the hospital setting, loss to follow-up of HCWs and possible selection biases in the testing of sources. Further studies are required to estimate the risk of transmission following blood contact with a source with HCV viraemia.

4.3 Sexual transmission of hepatitis C virus

HCV is known to be present in genital tract secretions. Other blood-borne viruses such as HBV and HIV can be sexually transmitted, so the sexual route of transmission for HCV is plausible.

Research to date on sexual transmission of HCV can be divided into three areas. Firstly, studies have searched for HCV in genital tract secretions among people known to be seropositive for HCV. Such research can only demonstrate the theoretical possibility of sexual transmission of HCV. Secondly, populations at increased risk of STDs, such as sex workers, male homosexuals and STD clinic attenders, have been studied for their rate of HCV seropositivity. Thirdly, and most directly, stable sexual partners of known HCV-positive individuals have been studied. These studies can be further classified as cross-sectional, in which the HCV prevalence of current sexual partners of HCV positives is measured, and longitudinal, in which HCV-negative partners of HCV-positive patients are followed and the rate of seroconversion calculated. The prevalence of HCV in the study populations is then compared to that in the 'general population'. Blood donors are often used as the 'general population' comparison, although it is acknowledged that this group may underestimate the true rate of anti-HCV seropositivity in the general population because of donor deferral policies.

4.3.1 Hepatitis C virus in body fluids

If HCV is sexually transmitted, the virus needs to be present in secretions of the genital tract (table 21). This has been studied in individuals known to be seropositive for HCV RNA. In such individuals, one study has confirmed that 100% of specimens (10/10) of first-day menstrual blood of serum HCV-RNA-positive women with chronic hepatitis were positive for HCV RNA (Silverman et al 1994). Whether HCV is present in semen is more controversial. In men positive for serum HCV RNA, rates of semen positivity have varied from 0 (0/14) (Fried et al 1992) to 24 per cent (4/17) (al Dhahry et al 1993). The rate of positivity of saliva is also uncertain, with two reports suggesting rates of 0 (al Dhahry et al 1993) and 48 per cent (Donahue et al 1991).

Table 21 Hepatitis C virus in body fluids

Country	Reference	Assay	No. of subjects	Body fluid	Per cent HCV-RNA positive	Comments
Italy	Fiore et al (1995)	HCV RNA	11	Serum	919	All subjects coinfected with HIV
				Semen		
Taiwan	Liou et al (1992)	HCV RNA	34	Serum	100	8 patients with HCV but who were serum HCV-RNA negative were negative in all fluids tested
			7	Ascites	100	
			31	Saliva	48	
			17	Semen	24	
			29	Urine	7	
USA, Maryland	Fried et al (1992)	HCV RNA	14	Serum	100	
				Saliva	0	
				Semen	0	
USA, Michigan	Silverman et al (1994)	HCV RNA	10	Menstrual blood	100 in serum and menstrual blood	Day 1 of period. All women had chronic hepatitis.

From these data, it appears that in persons who are serum HCV-RNA positive, HCV is present in menstrual blood in a very high proportion of cases. Semen appears to carry the virus in a smaller proportion of cases, but is nevertheless positive in some individuals. Thus, there is biological plausibility for sexual transmission of HCV. Contrary to most other STDs, male-to-female transmission may be less effective than female-to-male transmission, at least if sexual intercourse occurs during menstruation, because of the likely higher infectivity of menstrual blood than of semen.

4.3.2 Studies in populations at high risk of sexually transmissible diseases

High rates of STDs may be found in certain populations (table 22). These may include commercial sex workers, male homosexuals and STD clinic attenders. High rates of HCV would be expected in these populations if HCV were sexually transmitted. Studies in populations at high risk of STDs are of limited use if they do not also collect data on other known means of transmission of HCV, such as IDU and tattooing. This is especially important as these behaviours may be common in populations at high risk of STDs. Even studies that attempt to take into account the effect of IDU on the data may be biased if, as is likely, study participants are reluctant to admit to past or present IDU. For this reason, results that are ‘adjusted’ for IDU still need to be viewed with caution.

Table 22 Hepatitis C virus in populations at high risk of sexually transmissible diseases

Country	Reference	Assay	Population	Results (% positive for HCV)
Australia, Victoria	Crofts et al (1994)	EIA2 HCV RNA	Currently active IDU	Homosexuality not related to HCV, whereas it was to HBV and to HIV
Belgium	Vanderschueren et al (1991)	EIA1	81 IDU	47
			114 prostitutes	3.5
			132 healthy homosexuals	0.8
			31 HIV+ homosexuals	0
Brazil, Goiania	Martins et al (1995)	EIA2, IA[A]	1378 children/adolescents.	0/280 at day care (age <9) positive. 1/607 public school students (0.2%), 7/491 (1.4%) of adolescents, 6.9% in those aged 17-20. Prevalence related to multiple sexual partners, but not to STD history, in univariate analyses (also to IDU, tattooing, blood transfusion).
Brazil, Rio de Janeiro	Edelenyi Pinto et al (1993)	EIA1, RIBA2	2494 voluntary blood donors	2.1
			202 HIV infected homosexuals	8.0
Cameroon	Ndumbe & Skalsky (1993)	EIA 2 RIBA2	Pregnant women	5.5
			Sickle cell patients	31
			Prostitutes	15
			Blood donors	6 , 5 if HIV+. 7 if serologically positive for syphilis, 4 if negative for syphilis.
Denmark	Westh et al (1993)	?	147 homosexual men	1.4
			123 IDU	98
Finland	Kolho et al (1992)	EIA1, RIBA2	Blood donors	In positive donors there was no association with sexual risk behaviour.
Hong Kong	Chan et al (1992)	EIA1	Homosexuals	0
			Female prostitutes	0
Italy, Bologna	Ricchi et al (1992)	EIA1	Homosexual men	6.9. Association with markers of HBV, HIV, HCV-positive partner, >20 partners past year.
				No adjustment for IDU.
Italy, Milan	Salvaggio et al (1993)	EIA2	151 female IDU	74 in HIV+, 74 in HIV-. Anti-HCV associated with STDs and number of sexual partners in HIV negative but not positive women.
Italy, North	Marranconi et al (1994)	EIA2, RIBA2	Pregnant women	Sexual contacts with IDU, OR=19
Japan, Fukoaka	Nakashima et al (1992)	EIA1	Female prostitutes	6.2
		RIBA1	Females with STD	6.1
			Males with STD	2.9
			Controls	1.5. Prevalence rose with age. Patients with a history of syphilis had higher incidence.
Japan	Utsumi (1995)	EIA2	201 prisoners	Frequent, aggressive or promiscuous sexual behaviour associated on univariate analysis.
Netherlands	van Doornum et al (1991)	EIA1, RIBA1	468 heterosexual STD clinic attenders	1.5

Table 22 continued next page

Country	Reference	Assay	Population	Results (% positive for HCV)
New Zealand	Chetwynd et al (1995)	EIA2, HCV RNA	116 IDU attending a methadone program.	84 HCV positive, and 66 PCR positive. No relationship with sexual practices (not specified how this was measured).
Somalia	Watts et al (1994)	EIA1/2 RIBA 2	236 female prostitutes, 80 STD patients, 79 male soldiers	No association with syphilis or HIV serology
South Africa	Schoub et al (1992	EIA2	STD clinic (272)	1.8
		RIBA2	Family planning (148)	0.7
			Blue collar workers (246)	3.3
			New blood donors (117)	0.9
Spain, Seville	Lissen et al (1993)	EIA 2	310 female prostitutes	6.4
		RIBA2	88 clients of prostitutes	6.8
			168 homosexual men	4.2
			147 heterosexual partners of HCV+400 blood donors	7.4
				1.2
Sweden	Shev et al (1995)	EIA2	51 anti-HCV and HCV RNA positive blood donors and matched controls	History of STD significantly associated with anti-HCV (P<0.001). HSV2[B] serology also associated (P=0.015).
UK	Tedder et al (1991)	EIA1, RIBA1	Genitourinary clinic	Association with HIV, HBV, lifetime no. of STDs in homosexual men, age.
			275 homosexuals	2.2
			771 heterosexuals	0.4
UK, England	Neal et al (1994)	EIA?1 RIBA2	Blood donors	No association with multiple sex partners.
USA, Atlanta	Weinstock et al (1993)	?EIA1, NA[A]	Inner city STD clinic	7.7. In univariate analysis, sex with IDU and history of gonorrhoea were associated with risk, but these were not present after adjusting for confounders.
USA, Baltimore	Donahue et al (1991)	EIA1	500 multi-transfused patients	4
		RIBA1	225 IDU	85
			Homosexual men	1.6
USA, Baltimore	Thomas et al (1994)	EIA1, NA	1257 Non-IDU STD patients	Syphilis, HBV serology, and >1 male sex partner in last month (in females) all associated with HCV positivity
USA, Baltimore	Thomas et al (1995b)	EIA2	1039 non-IDU patients at a STD clinic	Risk factors for HCV included male homosexuality, greater numbers of lifetime sex partners. Females whose sexual partners were anti-HCV positive were 3.7 times more likely to be anti-HCV positive.
USA, Florida	Daikos et al (1994)	EIA2, RIBA2	Inner city heterosexuals, IDU excluded	>10 heterosex. partner OR=3.7
				Sex > 1x/week OR=3.3
USA, North Carolina	Fiscus et al (1994)	EIA1, RIBA2	STD clinic attenders	Homosexuality, syphilis serology, history of syphilis not related to anti-HCV

Table 22 continued overleaf

Country	Reference	Assay	Population	Results (% positive for HCV)
USA, San Francisco	Osmond et al (1993a)	EIA1, RIBA2	Homosexual men	4.6 (cf 81% for HBV). After controlling for IDU, weak associations with >50 sex partners per year, >25 oral receptive partners per year, >25 anal partners/y HBV more strongly associated with these.
USA, San Francisco	Osmond et al (1993b)	RIBA2	Couples recruited for a study of heterosexual HIV transmission.	64 in IDU. Not correlated with history of STDs, sexual behaviour, numbers of sexual partners.

[A] NA, neutralisation assay.

[B]HSV2, herpes simplex virus type 2.

4.3.3 Commercial sex workers

Some studies have found a higher prevalence of HCV in female sex workers compared with the general population. This has ranged from 15 per cent in Cameroon (Ndumbe and Skalsky 1993), 6.4 per cent in Spain (Lissen et al 1993), to 6.2 per cent in Japan (Nakashima et al 1992). The results from Cameroon are difficult to interpret as only blood that was negative for HBV surface antigen was tested. A high prevalence (6.8%) was also found in male clients of female sex workers in Spain (Lissen et al 1993). In contrast, studies of commercial sex workers in Somalia (Watts et al 1994) and Hong Kong (GC Chan et al 1992) have found rates of seropositivity no higher than in the background population.

Risk factors for seropositivity to HCV have also been studied in these sex workers. Number of sexual partners per year was not a risk factor in Spain (Lissen et al 1993). In Japan, sex workers who had worked for more than one year had a higher prevalence than those who had been involved for less than one year (8.1 v. 1.4%), but as age is strongly related to risk of HCV in many studies, this may be related to age rather than duration of prostitution (Nakashima et al 1992). In Ghent, Belgium, those sex workers who reported a history of at least one episode of syphilis had a significantly higher prevalence of HCV. However, no data were available on IDU or history of blood transfusion in these sex workers (Vanderschueren et al 1991). In Somalia, no association between HCV and syphilis or HIV positivity was found (Watts et al 1994).

In summary, the prevalence of HCV infection in commercial sex workers has often been found to be somewhat higher than in the general population, but it is difficult to be certain whether this may be accounted for by IDU among commercial sex workers. However, an association with other STDs, particularly syphilis, among sex workers who deny IDU suggests that sexual transmission may occur, at a low rate.

4.3.4 Homosexual males

High rates of STDs have been reported in homosexual males. Rates of HCV infection, however, are inconsistently raised in this population. Although homosexuality has been associated with HCV seropositivity in some studies (Ricchi et al 1992; Edelenyi Pinto et al 1993; Thomas et al 1995b) it is not in most studies (Donahue et al 1991; Tedder et al 1991; Vanderschueren et al 1991; GC Chan et al 1992; Westh et al 1993; Fiscus et al 1994). Of those studies which have attempted to account for the effect of IDU on the data collected on male homosexuals, any association with sexual behaviour is lessened after adjustment, although a weak relationship may still exist (Osmond et al 1993b). Among IDU, homosexuality does not appear to be a risk factor for HCV seropositivity (Crofts et al 1994), suggesting that IDU is the more important risk factor. A recent report has suggested there is a high level of nonspecific anti-HCV reactivity among homosexual males (ie EIA2 positive, RIBA2 negative) so the true

seroprevalence in homosexual males may be lower than described in studies not using RIBA2 confirmatory tests (Andreu et al 1994).

These data suggest that HCV is inefficiently, if at all, transmitted sexually among male homosexuals.

4.3.5 Attenders of sexually transmissible disease clinics

Many seroprevalence surveys have been performed among people attending STD clinics, and other studies have examined risk factors for HCV seropositivity in these populations. Factors associated with seropositivity have included a greater number of sexual partners (Thomas et al 1994), known HCV-positive sexual partners (Thomas et al 1994), positive syphilis serology (Thomas et al 1995a), and positive HBV serology (Thomas et al 1995a). Factors not associated with HCV have included positive syphilis serology (Fiscus et al 1994; Watts et al 1994). A study that accounted for the effect of IDU on the data found that much of the association with STDs disappeared when IDU was accounted for (Weinstock et al 1993).

4.3.6 Studies of sexual partners of HCV-positive individuals

The most reliable means of assessing sexual transmission of HCV is to follow-up known HCV- negative sexual partners of HCV-positive individuals, and to calculate their rate of seroconversion to HCV. Alternatively, the rate of anti-HCV seropositivity among partners of known HCV-positives may be calculated (table 23, see *Tables* section). This method is a less reliable indicator of sexual behaviour because of past behaviours that may be inaccurately recalled. Examples of such behaviours include sharing of needles for recreational or medical drug use, or other activities which led to blood-to-blood contact.

Studies of sexual partners of people with haemophilia have shown generally low rates of seropositivity in spouses, of 0 to 3 per cent (Eyster et al 1991; Brettler et al 1992; Kolho and Krusius 1992; Brackmann et al 1993; Hallam et al 1993). Risk factors for seropositivity in these spouses included HIV seropositivity in the person with haemophilia, and known risk factors for HCV infection in the partner. A possible explanation for the very low seroprevalence in these partners is that the couples use condoms frequently. However, the rate of HCV seropositivity is much lower than that for HIV, so condoms are unlikely to be the primary explanation for the low rates of infection in spouses.

Sexual partners of people who are HCV positive through IDU or other, often unknown, means have shown higher rates of seropositivity. Several studies have shown seroprevalence rates of 20 per cent or more in sexual partners (eg Kao et al 1992; Napoli et al 1993; Oshita et al 1993; Coltorti et al 1994; Gabrielli et al 1994; Shev et al 1995a). However, others have found seroprevalence rates of 5 per cent or less (GC Chan et al 1992; Gordon et al 1992; Bresters et al 1993; Scully et al 1993; Garcia Bengoechea et al 1994; Diaz et al 1995; Meisel et al 1995). It is difficult to be certain in these cases whether the high rate in the partner is due to sexual transmission, or due to other shared behaviours, such as IDU, or shared needles used for medical purposes. Factors associated with seroconcordance in sexual relationships have included sharing of toiletry items (Gordon et al 1992; Diaz et al 1995), IDU (David et al 1995), and HIV seropositivity in the index case (Lissen et al 1993; Gabrielli et al 1994; Soto et al 1994). Longer duration of a sexual relationship has also been found to be related to seroconcordance (Kao et al 1992; Coltorti et al 1994; Garcia Bengoechea et al 1994), but duration of partnership is confounded with age, which may be associated with other behaviours that lead to HCV infection.

Thus, the results of partner studies are somewhat conflicting. The most reliable studies, in female partners of males with haemophilia, suggest very low rates of transmission. Other studies are prone to bias due to unknown or unadmitted shared behavioural factors between sexual partners.

4.3.7 Discussion

Sexual transmission of HCV is less efficient than for HIV, HBV, and most other sexually transmissible agents. The most reliable studies suggest that the rate of transmission is low, but it seems likely that a low rate of sexual transmission of HCV does occur. The most reliable studies, in long-term sexual partners of HCV-infected people with haemophilia, suggest that 3 per cent or less of long-term sexual partners become infected. The relatively low rate of HCV in male homosexuals suggests that anal sex is not a high risk behaviour for HCV transmission. Although one review concluded that sexual transmission of HCV is absent or rare (van der Poel et al 1994), another has suggested that nonparenteral transmission (including sexual transmission) may still be significant (Alter 1995b). There is no evidence that the use of condoms will prevent HCV transmission, although the use of condoms is often recommended (Tibbs 1995).

4.4 Vertical transmission of hepatitis C virus

Other blood-borne viruses such as HBV and HIV are known to be transmitted vertically from mother to child. However, compared to the amount of research on parenteral and sexual transmission, comparatively little research has been undertaken into mother-to-infant transmission of HCV, and most studies have been small scale.

Vertical transmission studies follow babies born to HCV-positive mothers and determine the rate of infection in the infant. Comparison of studies is hampered by differences in definitions of infection of infants. Early studies (1990 and before) tended to define infection as the persistence of anti-HCV antibody beyond three to six months of age, whereas later studies have used serum HCV-RNA presence in the infant as being indicative of infection. The evidence is summarised in table 24 (see *Tables* section), and possible risk factors for transmission are reviewed in the text. In addition to direct studies of vertical transmission, studies reporting rates of HCV infection in children in communities with high levels of HCV infection in adults were reviewed.

4.4.1 Rate of vertical transmission

In mothers who are otherwise well, the rate of vertical transmission of HCV is low, probably less than 5 per cent. Studies which have found higher rates than this have generally been of HIV-coinfected women.

Further evidence that vertical transmission occurs at a low rate comes from a Japanese community survey of HCV (Hayashi et al 1995). Although the prevalence of anti-HCV in children of positive mothers was 18 per cent, this rate was similar to the rate in the same age group of the general population. Furthermore, all HCV-positive children of HCV- positive mothers were aged more than 20. The prevalence of anti-HCV in 292 persons aged less than 20 was 0. The prevalence in women of child-bearing age was 4 per cent in those aged 20 to 39, and 10 per cent in those aged 40 to 49.

4.4.2 Possible risk factors for vertical transmission

Breast feeding

HCV RNA has been detected in human breast milk by some investigators (Uehara et al 1993; Turnbull and Sugano 1994), although not by others (Kurauchi et al 1993). A later report suggests that HCV RNA is found in breast milk only when maternal viraemia is high (Zimmermann et al 1995). No association of risk of transmission with breast feeding was reported in one study (Paccagnini et al 1995) although another found a longer duration of breast feeding in mothers whose infants became infected (Ohto et al 1994). Transmission of HCV by breast feeding remains a theoretical possibility in women with high levels of viraemia, but appears to occur at very low frequency.

Method of delivery

HCV RNA has been found in vaginal secretions of pregnant women (Kurauchi et al 1993), and one study has suggested lower rates of HCV transmission in mothers who undergo caesarean section (Paccagnini et al 1995). This study also

reported that some infants who did become HCV infected and were vaginally delivered were HCV-RNA negative at birth, suggesting that infection may have occurred late in pregnancy or during delivery.

Maternal level of hepatitis C virus RNA

A high level of maternal HCV RNA has emerged as the strongest risk factor for vertical transmission of HCV. Higher levels of transmission (often of around 10%) are reported in those studies that have separately analysed transmission rates in HCV-RNA-positive mothers. Transmission has not been demonstrated to occur when the mother is negative for HCV RNA. Transmission is also more likely when the mother is seropositive for HIV, which may result in increased viral levels of HCV through immune suppression. Whether HIV infection is an independent risk factor for HCV transmission is unclear.

Hepatitis C virus genotype

One study has suggested that only HCV subtypes 1b or 3a, which are more pathogenic in adults, are transmitted to babies (Zuccotti et al 1995).

Discussion

Mother-to-infant transmission occurs from 0 to 10 per cent of infected mothers, most likely in less than 5 per cent of infected mothers. It is much more likely to occur when levels of HCV RNA are high, and in HIV-infected mothers. Transmission appears not to occur when HCV RNA is undetectable in the mother, and may be less likely to occur when the baby is delivered by caesarean section. The marked variation in results of studies may possibly be explained by differences in HCV RNA levels in mothers between studies, or possibly by differences in HCV genotypes. Vertical transmission of HCV has been inadequately researched and these estimates should be seen as preliminary.

4.5 Household transmission of hepatitis C virus

The existence of nonparenteral routes of transmission of HCV has been suggested because of the relatively high proportion of people infected with HCV who have no identifiable parenteral risk factors. For example, of 342 consecutive anti-HCV-positive patients presenting to a liver clinic at a major Australian metropolitan general hospital, 27 per cent had no definite percutaneous risk factor (Strasser et al 1995).

Most studies identified in this report were cross-sectional surveys of the HCV status of family members of known anti-HCV positive people. In many studies, the HCV prevalence was then compared to the prevalence in a control group, or to available figures from blood donors. These studies usually found higher prevalence levels than in blood donors, but this is a biased comparison because of the donor deferral policies practised by most blood banks.

Other studies reviewed included genetic studies of whether individuals within the same family are infected with the same strain of the virus, and studies of specific risk factors that may have led to household transmission.

4.5.1 Rate of household transmission

There has been considerable debate about the rate of household transmission of HCV, and of whether this route of transmission exists at all. Studies reporting the rate of seropositivity in the household contacts of people who are HCV positive have been summarised in table 25 (see *Tables* section). A problem with studies of household transmission is that members of a household often share behavioural characteristics that put them at risk of HCV, particularly IDU, and that they may be reluctant to admit to these behaviours. Although many of these studies have found a higher than background prevalence of HCV, there is considerable debate about whether a higher rate of HCV in family members of HCV-positive index cases truly represents nonpercutaneous transmission. Most studies have found much higher prevalence in older household contacts, and rates in children which are similar to background rates. This may be because the shared

behavioural factors which led to transmission are no longer relevant. For example, two Japanese studies in regions with high levels of HCV endemicity have found higher rates in older people, and very low rates in children without other risk factors (Hayashi et al 1995; Nakashima et al 1995). The use of nonsterile injecting equipment in medical care has been implicated as a possible cause of the high seroprevalence of HCV in these areas. Studies in people infected with HCV through medical procedures (people with haemophilia, dialysis patients) have found no evidence of household transmission (Brackmann et al 1993; Hou et al 1995).

Honda et al (1993) found a greater degree of HCV nucleotide homology among family members with HCV than with infected nonfamily members in Japan, suggesting that intrafamilial transmission had occurred. This has not been confirmed by others, who have found no clustering of genotypes between spouses (Nakashima et al 1995).

4.5.2 Possible routes of household transmission

Ritual blood exchange

Atrah et al (1994) found that of 52 blood donors in England who were HCV positive, 14 per cent gave a history of ritual blood exchange during childhood or early adult life (the practice of having 'blood brothers' or 'blood sisters') and denied other risk factors.

Sharing of nonsterile medical equipment

Sharing of nonsterile injecting equipment within families as a part of medical care has been implicated as a cause of horizontal transmission in Italy where it was a common practice until the 1970s (Buscarini et al 1993; Frosi et al 1995). In Japan, sterile injection equipment is still not used in some parts of the country, and this, combined with the Japanese usually being given drug treatment by injection, may explain the very high rates of HCV in parts of Japan (Hayashi et al 1995; Nakashima et al 1995). Many other studies of household transmission have not investigated this route of transmission, and this route may explain the apparently high rate of horizontal transmission in Japan and Italy. This route may explain the strong relationship of anti-HCV positivity with age in these countries, because the medical use of nonsterile injecting equipment has probably decreased recently.

Razors

The presence of very high levels of HCV infection (38%) in 37 Sicilian barbers who shave themselves with the same instruments they use to shave their customers suggests that sharing of shaving equipment may be a risk factor for acquisition (Tumminelli et al 1995).

Saliva

HCV RNA has been detected in the saliva, although at lower titre than in serum (Wang et al 1991; Liou et al 1992). The epidemiology of HCV infection does not support a role for transmission by saliva.

Discussion

Families of known anti-HCV positive patients often have rates of HCV positivity which are higher than in the local general population. In most cases, this appears to be explained by shared behavioural characteristics (especially IDU), or by sharing of nonsterile medical injecting equipment. There is no strong evidence that there are nonpercutaneous means of household transmission. Potential means of transmission by blood-to-blood contact, such as sharing of razors or toothbrushes, have not been shown to be important epidemiologically, but remain potential means of transmission.

4.6 Tattooing and skin penetration

Tattooing is the practice of making indelible patterns on the skin by inserting pigments through punctures made with sharp instruments. In modern professional tattooing, electrical tattooing machines with combinations of solid needles and numerous coloured pigments are used. During tattooing, dye from the layer on the needles is spattered loosely on the skin surface, before being tapped into the skin by the rapid pricking action of the needles. Spattered dye tends to obliterate the design ahead of the needle, so it is frequently necessary for the tattooist to wipe away excess dye and any blood that has exuded to the surface of the skin. Periodically, the tattooist sprays the area with a cleaning solution and the excess solution, dye and blood are wiped away, generally with a disposable tissue. As the tattooist moves the needles over the design on the skin, the layer of dye on the needle is replenished by frequently dipping the tip into the dye container. Depending on the size and the complexity of the tattoo design, the process can take between minutes and hours, and is completed sometimes over several sittings (Long and Rickman 1994). Since tattooing necessarily involves breaching of the epithelium, bleeding and reuse of equipment, there is the potential for risk of transmission of pathogens - patient-to-patient, operator-to-patient and patient-to-operator. Bleeding is less profuse than in other forms of skin penetration, but nevertheless the possibility for transmission of pathogens pertains.

Since 1947, blood-borne hepatitis viruses have emerged as the most serious and well-documented infections attributed to tattooing (Smith 1950; Long and Rickman 1994; Mercer and Davies 1991). Between 1947 and 1980, reports were published relating to 20 outbreaks and over 300 cases of viral hepatitis, most presumed to be due to HBV (Hopkins et al 1973; Limentani et al 1979; Harrison and Noah 1980; Silvers and Gelb 1991; Loimer and Werner 1992). In most of the reported cases, tattooists had used the same needle for several customers without adequate sterilisation (Long and Rickman 1994). Other noted defects in hygiene in tattooing procedures have included (Davis 1995):

- tattoo needles being immersed in chlorhexidine between clients but not sterilised;
- pigments being reused;
- bowls used for surgical spirit being emptied but not changed between clients;
- tattooists not washing their hands between clients; and
- gauze swabs being reused on other clients.

Interest in blood-borne viruses has increased due to the discovery and reported effects of HIV, continuing transmission of HBV despite availability of an effective vaccine, and the availability of a test for HCV which has revealed the extent of infection with this virus. Case reports (Abilgaard and Peterslund 1991; Thompson et al 1996), research studies (Holsen et al 1993; Ko et al 1992) and the results of routine blood-donor screening (Kaldor et al 1992; Neal et al 1994) have all implicated tattooing as a risk for transmission of HCV. An Italian surveillance scheme that evaluated the role of ear-piercing, tattooing, attendance at a chiropodist or manicurist and barber shop from 1985 to 1993 found that tattooing, ear piercing and barber shop shaving were all associated with NANBH (56% of 1991-93 cases were HCV positive), while attendance at a chiropodist or manicurist was only associated with HBV. The authors argue that although the incidence of infections declined by half during 1991-93, because many in the population are exposed, the role of beauty treatments should not be underestimated (Mele et al 1995). Another study found that Sicilian barbers had a higher prevalence of HCV antibodies (14/37=38%, 11 RIBA positive, 3 indeterminate), compared to 0/50, age and gender matched, new blood donors from the same region. This supports the authors' hypothesis that barbers who use a traditional shaving technique with nondisposable and unsterilised blades and haemostatic sticks might transmit infection - including to themselves if they use those same instruments on themselves (Tumminelli et al 1995).

Identification of the exposure risk for an infection acquired at some unknown time in the past is very difficult. Although HCV is generally acquired by parenteral routes, there are people for whom no risk factor can be elicited (Estaban et al

1991). Of 342 consecutive patients referred to the liver clinic at St Vincent's Hospital in Melbourne, 20 (6%) reported tattooing as their only percutaneous risk factor (Strasser et al 1995). Davies reported that 5 of 13 tattooed donors at the Sydney Red Cross Blood Bank who were positive as identified by third-generation EIA and immunoblot assay reported tattooing as their only risk factor (Davis 1995). Several other studies have implicated tattooing as the only discoverable risk factor in proportions of those with HCV investigated: 12.1 per cent of HCV-positive blood donors in a series in Argentina (Sookoian et al 1997), a similar series in Hong Kong (Prescott et al 1996), and in a patient series in Taiwan (Li et al 1996).

Yet for many of those for whom tattooing was (initially) considered to be a risk for having acquired HCV, other potential sources of exposure exist. Moreover, there have been dramatic reductions in the prevalence of HCV infection in tattooed donors since testing was introduced - a function not only of removing prevalent infections from the donor pool but also probably reflecting increased community consciousness about the strong association between HCV and IDU acting to decrease donor deferral where past IDU exists. The figures from Victoria (Australia) are shown in Figure 1.

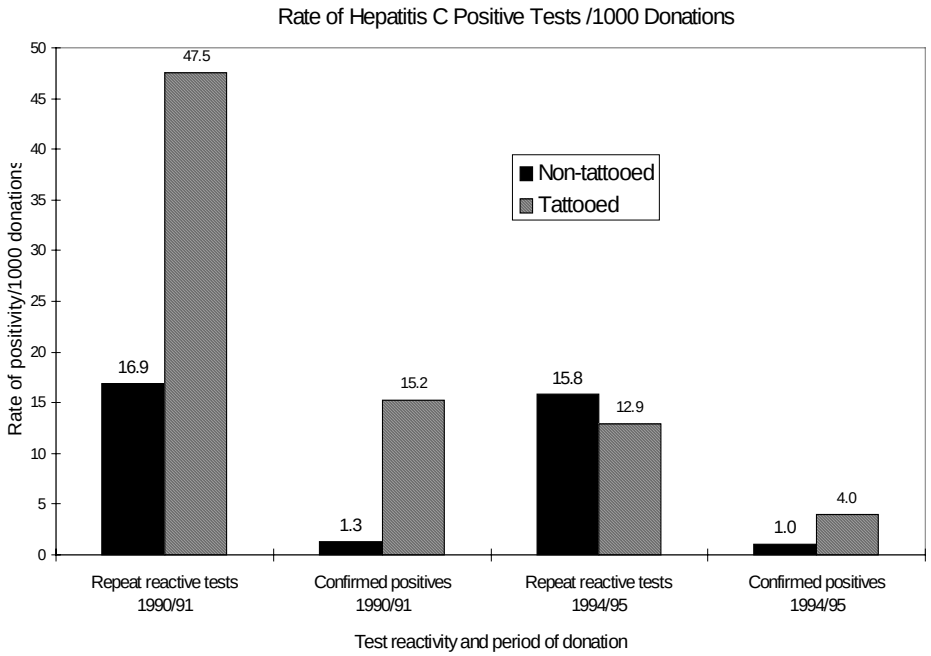


Figure 1. Rate of hepatitis C-positive tests per 1000 donations.

A particular deficiency in current data systems is the dearth of information on the tattooing experience of those with HCV attributed to tattooing: where they were tattooed, how long ago and how many tattoos or occasions of tattooing they have experienced. An unpublished study of blood donors at the Melbourne Red Cross Blood Bank attempted to obtain such information, and all donors with a reactive HCV test who were interviewed over 13 months were asked about their tattooing experience (S. Thompson, personal communication). Of 29 donors interviewed, most had been tattooed at registered premises, spanning a range of years, many before 1984. Many who reported tattooing outside a registered premises had tattooed themselves, in circumstances unlikely to result in transmission of HCV. Half of those interviewed had only one or two tattoos and had few occasions of tattooing, and after comprehensive testing, many of

these donors were determined to be 'biological false positives'. There was no clear dose-response relationship with tattooing, although all the confirmed positives had more than one tattoo, and interestingly all three people with indeterminate results all had more than five tattoos. Some donors lacked any recollection of the circumstances surrounding tattooing episodes suggesting that at least some people have obtunded consciousness at the time tattooing is done. There are studies that suggest that problematic groups, groups with poorer health, and groups with a greater risk of contracting infectious diseases have a higher prevalence of tattoos. Groups with which tattooing is associated include IDU, prostitutes, incarcerated persons and individuals with personality disorders (Rukstinat 1941; Goldstein 1979; Grumet 1983; Silvers and Gelb 1991; Loimer and Werner 1992; Watson et al 1973; Crofts et al 1996). In the absence of any disclosed risk factor, it can not be assumed that a tattooed blood donor's exposure is necessarily due to their tattooing experience.

Surveillance undertaken through the Communicable Diseases Network for incident cases of HCV in Australia during 1995, identified 138 incident HCV infections. (An incident case was defined as documented seroconversion to HCV where the previous negative was within 12 months of a positive test result, or a positive test result was associated with clinical hepatitis where other causes of the hepatitis have been excluded). Numerous problems were identified with the surveillance - variable methods of case ascertainment, response bias and perhaps duplicate notifications. Only one person (0.7%) reported skin penetration in a nonmedical setting (type not specified) as their sole risk factor, with 22 people (16%) having no risk factors indicated, and IDU accounting for the overwhelming majority (105/116, 91%) of reports, with 18 cases having both skin penetration in a nonmedical setting plus IDU (Anon et al 1995). These results highlight the importance of IDU as a risk factor and the confounding which occurs if skin penetration procedures are elicited in isolation from those infected with HCV.

Although tattooing is recognised as a risk factor for transmission of HCV, the efficiency with which transmission occurs is unknown. Some information might be gained by determining the occupational risk to tattooists, although requirements for informed consent make a representative serosurvey of tattooists difficult to achieve today. However, sera stored at Fairfield Infectious Diseases Hospital from a serosurvey of tattooists undertaken in Melbourne in 1984 to test for HIV provided the opportunity to determine the prevalence of serological markers of HBV and HCV in tattooists at that time. The serum specimens had been obtained from five unregistered and 36/37 (97%) of the registered tattooists operating in 1984, and thus provide an unbiased picture of the prevalence of HBV and HCV infection in this group in 1984, although no information was available about other risk factors in those tested. Serological status for HBV (HBsAg, anti-HBs, anti-HBc in standard assays) or HCV (anti-HCV reactivity in second-generation and third-generation tests, confirmed by RIBA) was determined. No serum was HIV positive or HBsAg positive. Of 35 specimens tested for HCV-specific antibody, only two (5.6%) were positive despite markers of HBV in 48.6 per cent of the same sera. Despite frequent needlestick injuries reported by tattooists at the time, the low seroprevalence of HCV in this group suggests that HCV may not be efficiently transmitted by intradermal inoculation using solid bore tattooing needles (Thompson et al 1997).

Since skin penetration procedures provide potential for the spread of blood-borne viruses, performing these procedures necessitates adequate control of infection. Knowledge of the characteristics of blood-borne viruses has enabled health agencies to develop guidelines on safe practices and infection control aimed at limiting spread of these viruses, although such guidelines are not necessarily well understood or well adhered to.

There are concerns about the practice of infection control in registered tattooing and skin penetration premises throughout Australia, but relatively few formal studies have been undertaken. The most detailed assessment of infection control in tattooing premises has been undertaken in Victoria. Registration of tattooing is based on the premises and often only involves inspection of the physical condition and facilities of the building. Operators are not licensed, and no training in infection control is necessary to become a tattooist. Through examination of historical records it is apparent that hygiene has improved in registered premises since the days when HBV cases attributed to tattooing were not uncommon (Goudey and Thompson 1994a). Tattooists chosen as part of a random sample of registered tattooing

premises were surveyed for self-reported compliance with infection control practices specified in the Victorian *Standards of Practice for Tattooing* (Health Department Victoria 1993) and some were observed while tattooing. Of 35 respondents, 94 per cent reported that they believed their practice fully met the *Standards*, yet 19 per cent of tattooists did not have a copy of the *Standards* at their premises. There was considerable discrepancy between self-reported practice and the practices observed. Few tattooists understood or implemented universal precautions and although most wore gloves, there was low use of eye and clothing protection. Tattooists touched many surfaces that were not cleaned or disinfected between clients. Glutaraldehyde was not often used for disinfecting equipment, ultrasound cleaners were generally operated without lids and at no premises was equipment used that had been cleaned according to the *Standards* and sterilised in an autoclave that had passed a sterilisation test (Goudey and Thompson 1994b). There is nothing to suggest that circumstances in Victoria are dissimilar to those in other parts of Australia. Tattooists found it difficult to understand why each State and Territory has different standards and they seek and follow advice from a multiplicity of sources: health departments, Environmental Health Officers (EHOs), government and medical publications, magazines, other tattooists, tattooing associations both in Australia and other countries, equipment and material suppliers. Inconsistent, contradictory, misleading or misunderstood advice provides a cogent reason to work towards uniform national skin penetration guidelines. While demonstrable problems with infection control occur, the potential for transmission of blood- borne pathogens exists and tattooing will continue to be a potential means of HCV transmission.

The deficiencies in knowledge of some tattooists regarding infectious diseases and infection control can largely be explained by the lack of suitable training opportunities available to the industry. The situation in Victoria is similar to those identified in other States and Territories and there is an urgent need for training of both tattooists and the EHOs who supervise them. Studies in Central and Southern Sydney in 1991, in Brisbane, Darwin and Canberra in 1993 and in Victoria in 1994 support appropriate training and education for skin penetration operators and tattooists (Drake 1993; Edwards et al 1993; Kallir Preece 1993; Trott 1993; Bouwman et al 1994). An infection control course designed for staff working for general practitioners, hairdressers, tattooists and other relevant services has been approved to be delivered at the Sydney Institute of Technology (Long and Rickman 1994; NSW TAFE Commission). Similar courses are required elsewhere, and cogent arguments exist for establishment of national standards for skin penetration.

4.7 Hepatitis C virus infection in prisoners

Among the small number of published studies of HCV infection in prisoners, HCV antibody prevalence was generally high (15-46%) compared with the prevalence among blood donors (<0.5%). The high HCV prevalence was attributed predominantly to a history of IDU reported by a substantial proportion of prisoners.

In Australia, HCV-antibody testing of 3,627 people received into prisons in Victoria from October 1991 through September 1992 indicated an HCV prevalence of 39 per cent (Crofts et al 1995). Prevalence of HCV antibody was significantly higher in women (66.7%) than in men (36.9%) and in people who reported a history of IDU (63.6 cf 16.0% among those with no reported history of IDU). Among 119 prisoners received into prison on more than one occasion over the 12 months who were initially HCV-antibody negative, 10 males were subsequently found to have HCV antibody, giving an incidence rate of 18.3 per 100 person-years. Risk factors for incident HCV infection were young age (22.2 v. 26.2 y) and a history of IDU (80 v. 36%). A high HCV antibody prevalence (30.8%) had previously been documented among Victorian prisoners (Fairley et al 1990) and HCV prevalence among IDU in Victoria in 1990-92 was 68 per cent (Crofts et al 1994). Among 408 people tested for HCV antibody at entry into New South Wales prisons in 1994, 37 per cent had HCV antibody; HCV antibody prevalence among those with a history of IDU, previous imprisonment and those who reported IDU during a previous imprisonment was 66 per cent, 48 per cent and 77 per cent, respectively (Butler et al 1997).

Among 265 male prisoners received into prisons in Maryland, USA, for whom serum specimens were available both at reception and at follow-up, prevalence of HCV antibody at reception in 1985-86 was 38.1 per cent (Vlahov et al 1993). HCV prevalence may, however, have been underestimated because it was measured among volunteers who were in prison for at least one year. HCV prevalence was significantly higher among prisoners aged 25 years or older (55%) than among prisoners younger than 25 years (20%), and was significantly higher among black prisoners (43%) compared with nonblack prisoners (29%). Among 164 prisoners who were initially HCV-antibody negative, two seroconverted, giving an incidence of 1.1 per 100 person-years in prison.

Of 70 prisoners (mean age, 28.4 y), received into a national prison in Norway in October-December 1991 and tested for HCV antibody using a second-generation EIA, 46 per cent had HCV antibody (Holsen et al 1993). Both a history of IDU and presence of tattoos were associated with HCV infection.

Voluntary testing for HCV antibody among male prisoners in a medium security prison in Ontario, Canada, carried out in June 1995, indicated a prevalence of HCV antibody of 27.9 per cent (Pearson et al 1995). In an earlier study of male prisoners in British Columbia, Canada, HCV antibody prevalence was 25.5 per cent (Prefontaine and Chaudhary 1990). HCV prevalence among prisoners held in a long-stay penitentiary for women who were voluntarily tested in June 1994 was 39.8 per cent (Ford et al 1995a, 1995b).

HCV infection in 756 prisoners in Naples, Italy, was assessed in serum samples collected between July 1992 and December 1994 using a second-generation RIBA (Chiron) (De Mercato et al 1995). In this population (mean age, 34.7 y), no history of IDU was reported and men who reported a history of male homosexual contact were excluded. Prevalence of HCV antibody was 15.5 per cent and was similar for males and females. Prevalence of HCV antibody increased from 7.6 per cent among those imprisoned for less than three years to 21.6 per cent among those imprisoned for more than six years.

In a random sample of prisoners held in the only reception centre in Connecticut, USA, for women, prevalence of HCV antibody was 32 per cent (Fennie et al 1996). HCV antibody prevalence was 76 per cent among women who reported a history of IDU, whereas among women whose only reported risk for HCV antibody was sexual contact with an IDU, prevalence was 46 per cent. Incidence of HCV, estimated among initially HCV-antibody negative IDU women, who were received into prison at least twice over one year, was 52 per 100 person-years (3/13).

Among 250 young (mean age, 23 y) British prisoners with a history of sharing drug injecting equipment, HCV antibody prevalence was 17.2 per cent (Mohanty and Biswas 1996). Among 157 IDUs in Mid-Glamorgan, UK, HCV antibody prevalence was significantly higher among those with a history of imprisonment (46%) compared with those with no history of imprisonment (29%) (McBride et al 1994). In Greece, prevalence of HCV antibody among 450 IDUs in prison remained higher than 80 per cent in 1991-95.

4.8 Hepatitis C virus-RNA load

There are several techniques that can be used to quantify HCV by RT-PCR, including competitive PCR, end-point titration, branched DNA assay and internal standard RNA. Many of the techniques have potential disadvantages, including lack of resolving power of titre-based assays, poor sensitivity of branched-chain DNA assays, and time-consuming preparation of competitive RNA templates.

Many studies addressing the question of whether viral load correlates with the degree of liver injury have measured the amount of HCV in serum. It has been argued that HCV RNA should be measured directly from liver tissue, because serum levels may be contributed to and be influenced by extrahepatic sources, and immune complexes in the serum may provide interference (McGuinness et al 1996). Mannucci et al (1990b) have reported also that sample-to-sample variation occurs in detectable HCV genome molecules in serum compared to plasma from the same patient. This suggests that serum

specimens, although widely used for qualitative molecular investigation of HCV-infected patients, may not provide reliable quantitative data on HCV viraemia from these patients.

Several studies that have looked at viral load and its relationship to liver disease have been cross-sectional single-point analyses. However, tissue injury may be related to virus release from infected cells, so ideally studies need to examine fluctuations of liver damage and HCV-RNA levels over time.

HCV-RNA-positive hepatocytes were more frequently detected in specimens with advanced periportal, bridging and intralobular necrosis but showed no correlation with the extent of inflammatory cell infiltration (Haruna et al 1993). These findings suggest a close correlation between the detection of HCV RNA in hepatocytes and advanced necrosis of the specimens. The average number of HCV-RNA molecules per millilitre of serum was found to be greater than 10^7 in patients with HCV-associated hepatitis, cirrhosis or HCC (Hagiwara et al 1993; Gretch et al 1994).

4.8.1 Level of infectivity among people with hepatitis C virus infection: the role of polymerase chain reaction

The counselling of people with HCV infection would be assisted by an effective measure of their risk of transmitting HCV in various settings. The development of PCR methods for detecting HCV RNA has provided a potential means of assessing anti-HCV positive people in terms of their level of infectivity. Factors such as level of viraemia and HIV coinfection may also be predictive of transmission risk.

Published studies that examined HCV transmission from anti-HCV-positive individuals were reviewed. Anti-HCV-positive individuals were tested for evidence of HCV viraemia by PCR for HCV RNA. Studies were included if HCV-PCR status of sources corresponding to cases of HCV exposure was recorded. Estimates of number of those exposed to HCV-PCR- positive and HCV-PCR-negative sources were required in those studies with differential source or exposed numbers, such as two retrospective vertical transmission studies (Meisel et al 1995; Power et al 1995a). Transmission rates were calculated separately for exposure to HCV-PCR-positive and HCV-PCR-negative sources. Pooled estimates of HCV transmission rates were made for different modes of transmission. Additional information such as level of viraemia and coinfection with HIV was also sought, and the effect of these factors on transmission efficiency examined.

Identification of anti-HCV was generally with EIA and confirmatory RIBA, although first-generation, second-generation and third-generation assays were used in various studies. Detection of HCV RNA was by PCR with nested primers derived from the 5' noncoding region of the HCV genome.

A total of 29 articles published between 1992 and 1996 met the above criteria. Most of these studies examined vertical HCV transmission (*n*=21), with the remainder examining HCV transmission following transfusion of blood products (*n*=3), bone marrow or solid organ transplantation (*n*=3), and needlestick exposure (*n*=2) (Dore et al 1997).

4.8.2 Vertical transmission studies

In the vertical transmission studies, the percentage of anti-HCV-positive mothers who were also HCV-PCR-positive varied from 46 to 100 per cent, with a pooled estimate of 54 per cent (table 26). Among 903 children born to mothers with a positive HCV PCR, the HCV transmission rate varied from 0 to 42 per cent, with a combined rate of 6.2 per cent (95% CI 4.6, 7.8%). In contrast, no case of HCV transmission was reported among 735 children born to mothers who were HCV-PCR negative (95% CI 0.0, 0.4%) (table 26). Among HCV-PCR-positive mothers, other factors that were reported to influence HCV transmission were level of viraemia (Lin et al 1994; Ohto et al 1994; Matsubara et al 1995; Moriya et al 1995; Zanetti et al 1995a), and coinfection with HIV (Paccagnini et al 1995; Zanetti et al 1995a; Zuccotti et al 1995). The pooled HCV transmission rate from HIV/HCV-antibody-positive mothers was 16 per cent (95% CI 12, 20%) (Latt et al 1994). In contrast, a HCV transmission rate of 1.9 per cent (95% CI 1.2, 2.6%) was seen among children born to mothers with HIV seronegative or unknown status (Dore et al 1997) (data not included in table 26).

Table 26 Studies of mother-to-child transmission of hepatitis C virus

Study	Country	No. of subjects (Mother/infant)	Source positive by PCR (%)	Transmission of HCV [proportion (%)]		
				Positive by PCR	Negative by PCR	HIV-Ab positive or HCV-Ab positive
Fischler et al (1996)	Sweden	55/58	75	0/40	0/18	0/2
Pipan et al (1996)	Italy	25/25	72	0/18	0/7	No HIV
Sabatino et al (1996)	Italy	30/30	33	3/10 (30)	0/20	No HIV
Giacchino et al (1995)	Italy	31/31	61	2/19 (11)	0/12	No HIV
Manzini et al (1995)	Italy	45/45	63	0/27	0/16	1/18 (6)[A]
Matsubara et al (1995)	Germany	29/31	66	3/21 (14)	0/10	No HIV
Meisel et al (1995)[B]	Germany	55/55[C]	57	1/23 (4)	0/32	No HIV
Moriya et al (1995)	Japan	84/87	100[D]	2/87 (2)	-	No HIV
Paccagnini et al (1995)	Italy	37/37[E]	62	9/23 (39)	0/14	12/53 (23)
Power et al (1995a)[B]	Ireland	545/840	46	7/386[F] (2)	0/454[F]	NA[G]
Resti et al (1995)	Italy	22/22	55	5/12 (42)	0/10	No HIV
Zanetti et al (1995a)	Italy	116/116	55	8/64 (13)	0/52	8/22 (36)
Zuccotti et al (1995)	Italy	37/37	57	6/21 (29)	0/16	4/20 (20)
Lin et al (1994)	Taiwan	15/15	100[D]	1/15 (7)	-[H]	No HIV
Ohto et al (1994)	Japan	53/54	58	3/32 (9)	0/22	NA
Kurauchi et al (1993)	Japan	16/16	94	0/15	0/1	No HIV
Lam et al (1993)	Scotland	56/66	59	4/38 (11)	0/28	3/58 (5)
Roudot-Thoraval et al (1993)	France	17/18	47	0/8	0/10	No HIV
Uehara et al (1993)	Japan	12/12	58	1/7 (14)	0/5	NA
Reinus et al (1992)	USA	23/24	70	0/16	0/8	0/4 (0)
Wejstal et al (1992)	Sweden	14/21	100[D]	1/21 (5)	-[H]	No HIV
Total		1317/1640	54[I] (648/1204)	56/903 (6.2; 95% CI, 0.0-0.4%)	28/177 (15.8; 95% CI, 11.8-19.8%)	16/122 (13)

[A] Transmission case from HIV-positive mother of unknown status of HCV by PCR.

[B] Retrospective analyses of children born after infection of mothers with HCV from anti-D immunoglobulin.

[C] Numbers of mothers corresponding to these 55 perinatally exposed children (subgroup of tested children) not known and may be < 55.

[D] Only mothers with evidence of chronic HCV infection selected.

[E] HCV RNA determination performed on only 37/70 mothers in study.

[F] Estimated number from proportion positive by PCR (46%) in total cohort infected from anti-D immunoglobulin.

[G] NA, not applicable.

[H] Not measured.

[I] Excludes studies where only mothers with chronic HCV infection selected.

In five of seven vertical transmission studies in which quantitation of HCV viraemia was reported, transmission was associated with higher level viraemia (Lin et al 1994; Ohto et al 1994; Matsubara et al 1995; Moriya et al 1995; Zanetti et al 1995a). One study demonstrated a significantly higher transmission rate among vaginally delivered infants compared with infants delivered by caesarean section (32% v 6%) (Paccagnini et al 1995) but showed no association between risk of transmission and breast-feeding. The only case of HCV transmission reported by Lin et al (1994) was associated with a maternal HCV-RNA level of 10^{10} copies/mL, as opposed to levels of 10^5-10^6 copies/mL among seven nontransmitting mothers with detectable HCV RNA. The HCV-RNA levels reported by Ohto et al (1994) were significantly higher among HCV transmitting mothers (mean +/- s.d., $10^{6.4+/-0.5}$ copies/mL) than nontransmitting mothers ($10^{4.4+/-1.5}$ copies/mL) (P<0.001). Zanetti et al (1995a) reported a mean HCV-RNA level among eight transmitting mothers (all coinfected with HIV) of $10^{7.1}$ copies/mL, as opposed to $10^{6.7}$ copies/mL among 10 nontransmitting HIV-coinfected or HCV-coinfected mothers, and $10^{5.9}$ copies/mL among 10 nontransmitting mothers with HCV alone.

4.8.3 Other hepatitis C virus transmission studies

Three studies examining HCV transmission from anti-HCV positive transplant donors to anti-HCV-negative recipients (table 27) gave a transmission rate of 21/27 (78%) (95% CI 72, 94%) from HCV-PCR-positive donors, as opposed to 0 (95% CI 0, 15%) from HCV-PCR-negative donors (Pereira et al 1992; Roth et al 1992; Shuhart et al 1994). Three studies of HCV transmission following transfusion of blood products from anti-HCV-positive donors demonstrated a rate of 83 per cent (95% CI 74, 92%) from EIA-positive, HCV-PCR-positive donors, as opposed to 0 among 97 recipients of blood components from EIA-positive, HCV-PCR-negative donors (Norda et al 1995; Vrielink et al 1995; Foberg et al 1996).

Table 27 Studies of transmission of hepatitis C virus related to transplantation and blood transfusion

Study	Country	No. of subjects	Source positive by PCR (%)	Transmission of HCV [proportion (%)]	
}				Positive by PCR	Negative by PCR
Foberg et al (1996)[A]	Sweden	12/36 (blood donor/recipients)	75	21/27 (78)	0/9
Norda et al (1995)[A]	Sweden	21/39 (blood donor/recipients)	33	11/11 (100)	0/26[B]
Vrielink et al (1995)[A]	Netherlands	71/94 (blood donor/recipients)	31	26/32 (81)	0/62 [C]
Shuhart et al (1994)	USA	12/12 (bone marrow donor/recipients)	58	7/7 (100)	0/5
Pereira et al (1992)	USA	11/16 organ (heart, liver, kidney) donor/recipients	82	13/13 (100)	0/3
Roth et al (1992)	USA	21 kidney transplant recipients	33	1/7 (14)	0/14
Total		**148/218**	**68**	**79/97 (81.4%; 95% CI 72.3-88.6%)**	**0/119 (0.0; 95% CI 0.0-2.5%)**

[A] Retrospective studies of donors positive for antibody to HCV and their multiple recipients of blood component.

[B] Two recipient cases excluded: one recipient found to be positive for antibody to HCV and positive by PCR but had received over 100 blood components from donors of unknown HCV status (2 other recipients from same donor negative by PCR had no evidence of infection). Further recipient was ELISA positive but negative by PCR and had also received previous blood components from donors of unknown HCV status.

[C] Excludes those who received EIA-positive (first generation), RIBA-negative blood (n=78) as probable false positive EIA results.

Although several studies have examined prevalence and incidence of HCV among HCWs, only two studies (table 28) have reported on HCV-antibody and HCV-PCR status in source cases of needlestick exposures to HCWs (Mitsui et al 1992; Sodeyama et al 1993). Combining these two studies, the HCV transmission rates following needlestick exposure to anti-HCV-positive patients were 6.1 per cent (95% CI 2.3, 9.9%) for HCV-PCR-positive patients, and 0 (95% CI 0.0, 18.5%) following exposure to HCV-PCR-negative patients.

Table 28 Studies of transmission of hepatitis C virus related to occupational exposure

Country	Reference	No. of subjects	HCV-PCR positive (source) (%)	HCV transmission to HCWs from patients who were:	
				HCV-PCR positive	HCV-PCR negative
Japan	Mitsui et al (1992)	74	92	7/68 (10%)	0/8 (0%)
Japan	Sodeyama et al (1993)	90	89	2/80 (2.5%)	0/10 (0%)
Total		164	90	9/148 (6.1%)	0/18 (0%)

4.8.4 Discussion

The absence of PCR-detectable HCV viraemia appears to indicate an extremely low risk of HCV transmission. In the 29 studies examined, a total of 874 people were exposed to sources positive for HCV antibody, but negative by HCV PCR, through vertical, transplant, blood transfusion and needlestick exposures. Among these people, no HCV transmission was reported. In contrast, 148 cases of HCV transmission occurred among the 1,148 people exposed to a HCV-PCR-positive source. Pooled rates of transmission from HCV-PCR-positive sources were 4.5 per cent following perinatal exposure, 6.1 per cent following needlestick exposure, 78 per cent following transplant exposure and 83 per cent following transfusion of blood products.

Based on vertical transmission studies, level of viraemia and coinfection with HIV were also risk factors for HCV transmission. For mothers coinfected with HIV, transmission occurred in 16 per cent of cases, whereas the rate of transmission from those HIV seronegative or of unknown status was less than 2 per cent. Most vertical HCV transmissions occurred when the maternal HCV-RNA level was greater than 10^6 copies/mL.

The importance of individual characteristics associated with an increased likelihood of transmitting HCV in various settings was highlighted by Alter (1994). However, this editorial also asserted that advice to anti-HCV-positive people on their level of infectivity could not be based on PCR testing for detection of HCV viraemia. The possibility of both false positive and false negative PCR results (Busch et al 1992), the difficulty of interpretation of results and the lack of widespread availability of PCR testing were put forward as supportive arguments. A particular concern was that a person with very low-level viraemia could still transmit HCV if the inoculum was large enough.

However, rapid developments in PCR technology have overcome many of these concerns. The sensitivity of HCV PCR has been optimised through the use of PCR primers based on the very highly conserved 5' noncoding region of the HCV genome (Garson 1994). Thus, improved standardisation of PCR technology together with ongoing monitoring by national reference laboratories should limit the possibility of false negative results. The findings from our report also support the high sensitivity of HCV PCR, at least in the setting of research laboratories where specimens generally were tested in duplicate.

The main drawback of extreme sensitivity of PCR technology is an enhanced possibility of contamination and, thus, suboptimal specificity. This has been emphasised by an international HCV-PCR-quality assurance survey which detected

false positive results from many laboratories (Zaaijer et al 1993). Although increased vigilance to limit contamination and continued monitoring of specificity of HCV PCR are required, an occasional false positive HCV PCR result does not alter the finding of absent HCV transmission from people with negative HCV PCR and the implications arising from such a finding.

The labour intensiveness of inhouse PCR technology, in particular inhouse nested PCR, has limited the availability of HCV PCR. However, new methods such as nucleic acid amplification system (NASBA) and the Amplicor kit (Roche Diagnostic Systems, Basel, Switzerland) enable testing of many specimens in a single day, and have equal sensitivity and specificity to the inhouse PCR methods (Lunel et al 1995).

This review of published studies of HCV transmission strongly supports the use of PCR testing for determination of level of infectivity. Even in situations where the HCV inoculum was large, such as following blood transfusion, HCV transmission from an anti-HCV-positive, PCR-negative person was not documented.

Despite the improvements in PCR technology outlined, it is recommended that a person with HCV infection is counselled on the basis of a persistently positive or negative HCV PCR (at least two tests over a three month period), rather than a single assessment of PCR status. Even greater consistency would be required in a person receiving or having received IFN therapy due to the fluctuation in HCV-PCR status among this group. The greatest benefit would be in identifying those persons anti-HCV positive, who have no biochemical or clinical evidence of chronic infection, and who are persistently HCV-PCR negative. This group of people could be counselled as to their lack of infectivity, and most probable lack of chronic HCV infection, with HCV PCR playing a similar role to that of HBV surface antigen in defining infectivity and chronic HBV carriage status.

Pregnant women, or women considering becoming pregnant who are anti-HCV positive, could be offered HCV-PCR testing to assist in determining their risk of transmitting HCV to their children. Women with a persistently negative HCV PCR could be reassured that their risk of transmitting HCV perinatally was extremely low, if not zero.

Determination of HCV-PCR status would also be useful following a needlestick exposure to blood or body fluid from an anti-HCV positive patient. If the source patient had no biochemical or clinical evidence of chronic HCV infection and was negative on HCV PCR testing, an exposed HCW could be informed that the risk of acquiring HCV was negligible. This information could allay significant anxiety over the next three to six months required before postexposure anti-HCV testing is concluded.

The recent reports of HCV transmission from two cardiothoracic surgeons to their patients has placed increased scrutiny on HCWs who are anti-HCV positive (Anonymous 1994; Esteban et al 1996). In some situations, surgeons are already prevented from performing exposure-prone procedures if found to be anti-HCV positive. HCV-PCR testing could be useful in assessing the potential for transmission from HCWs. Surgeons who are persistently HCV-PCR negative would not be required to undertake measures in addition to the normal universal precautions for infection control.

Although HCV transmission efficiency through sexual contact appears to be low, many people who are anti-HCV positive are counselled to use condoms. A person found to be HCV-PCR negative could be advised that the risk of transmitting HCV sexually was negligible.

In summary, it appears that there is virtually no risk of HCV transmission in the absence of HCV viraemia as detected by PCR. This finding has important implications in regard to counselling both those people at risk of transmitting HCV, and people exposed to anti-HCV-positive sources. Additional investigation of HCV transmission based on clinical stage of HCV infection, level of HCV viraemia and HCV genotype is required to further define level of infectivity in various settings.

5 Pathogenesis and natural history

A schematic outline of events involved in the natural history of HCV infection is shown in Figure 2.

Figure 2. Aspects of the natural history of hepatitis C virus infection.

5.1 Acute hepatitis C virus infection

Acute HCV infection usually produces initially only a mild illness and is often totally asymptomatic, although fulminant hepatitis can occur rarely. In the transfusion setting where acute onset is best documented, 70 to 80 per cent of cases are anicteric and asymptomatic. Alter (1995a) describes a National Institutes of Health (Bethesda, MD, USA) series of 86 consecutive cases of posttransfusion hepatitis, of which only 30 per cent had a bilirubin concentration greater than 2.5 mg/dL and where the mean peak ALT was 708 U/L. Most patients had very mild illness and none had a protracted, severe, acute illness. In community-acquired infection, where people with HCV are generally identified and defined because of presentation with overt clinical illness, 70 per cent of people were icteric; 4 per cent had an ALT between 2.5 and 5 times the upper limit of normal (ULN); 22 per cent had an ALT 6-15 times ULN patients. Because the community-acquired cases had to be ill to seek treatment, they are not useful in defining the clinical spectrum of acute HCV infection. However, they show that HCV can present as an acute overt hepatitis that can not be clinically distinguished from acute cases of HAV and HBV. By extrapolation from transfusion studies, clinically apparent illness occurs in no more than 25 per cent of HCV infections (Alter 1995a).

Seroconversion to HCV can take as long as 26 weeks following infection (Alter et al 1989b), although with second-generation assays the mean time between infection and the development of a detectable antibody response is more often about two to three weeks (Aach et al 1991; Mattsson et al 1992). HCV RNA can be detected in the serum even earlier, as soon as one week after infection (Farci et al 1991).

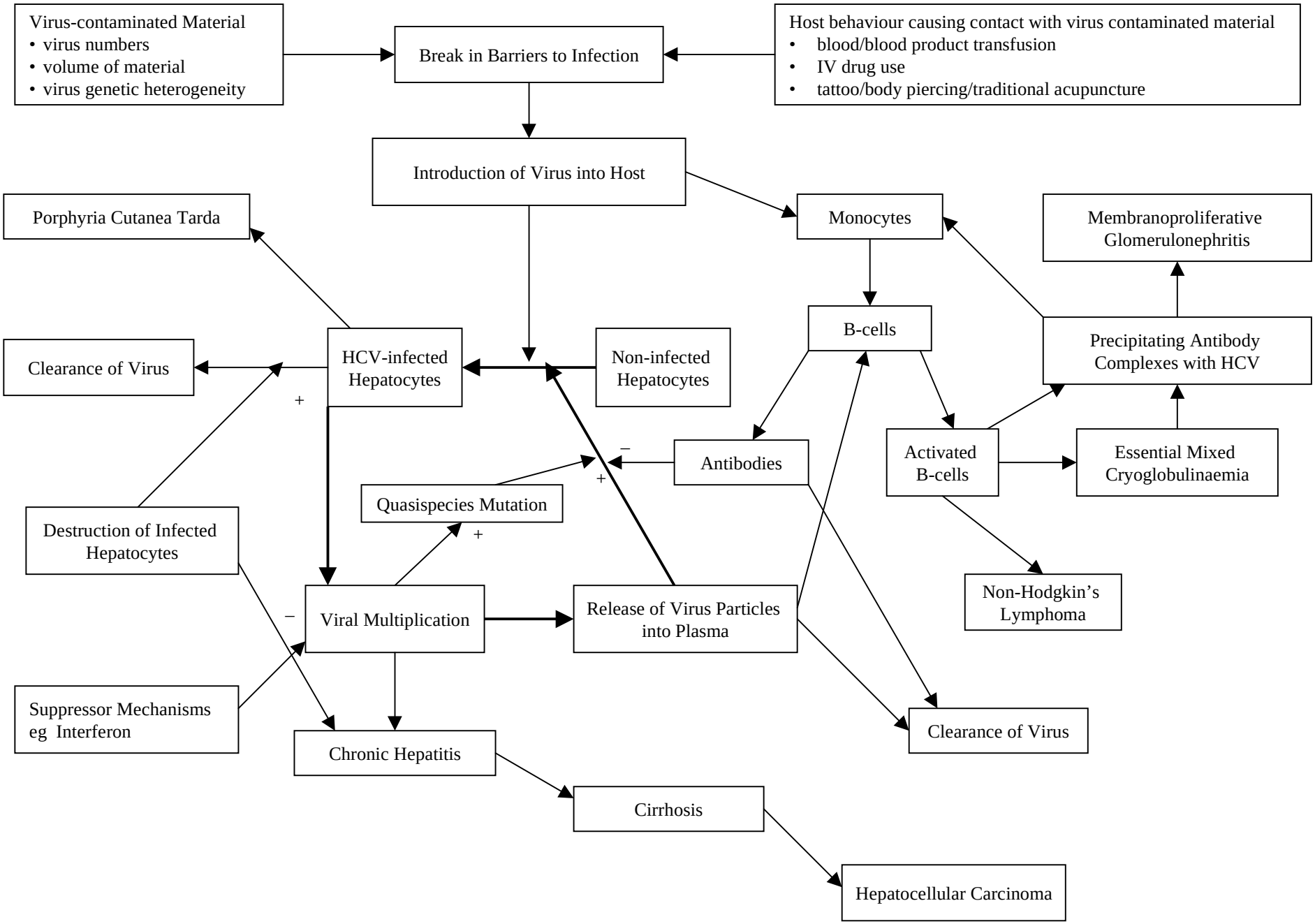
Brunetto et al (1994) quotes Alberti (1991) and Alter (1991) as showing that anti-HCV detected during the convalescent phase of an acute self-limited HCV hepatitis becomes negative after one to four years, and its persistence indicates a chronic HCV infection. He also implies that posttransfusion hepatitis proceeds to a higher number of cases than community- acquired, sporadic hepatitis.

5.2 Fulminant hepatic failure

Documented fulminant HCV infection is extremely rare, although HCV appears to be the causative agent of a substantial number of cases of fulminant hepatic failure (FHF) previously classified as indeterminant (Viladomiu et al 1992). The mechanism by which it occurs is obscure. In-depth study of the few cases has unequivocally established:

- the acute appearance of HCV RNA coincides with the onset of fulminant disease;
- high levels of viraemia (10^7 HCV-RNA equivalents/mL); and
- HCV genotype and sequence was not unique, suggesting that disease is related to viral burden or host response rather than virus genotype.

Viral hepatitis is the most common cause of FHF, followed by drug overdoses or drug-induced hepatotoxicities. Some patients with FHF of presumed viral cause (40-60%) have negative serological markers for HAV and HBV,


Virus-contaminated Material
• virus numbers
• volume of material
• virus genetic heterogeneity
Break in Barriers to Infection
Host behaviour causing contact with virus contaminated material
• blood/blood product transfusion
• IV drug use
• tattoo/body piercing/traditional acupuncture
Introduction of Virus into Host
Porphyria Cutanea Tarda
Monocytes
Membranoproliferative Glomerulonephritis
B-cells
Precipitating Antibody Complexes with HCV
Clearance of Virus
HCV-infected Hepatocytes
Non-infected Hepatocytes
+
Antibodies
Activated B-cells
Essential Mixed Cryoglobulinaemia
Quasispecies Mutation
+
Destruction of Infected Hepatocytes
Non-Hodgkin's Lymphoma
Viral Multiplication
Release of Virus Particles into Plasma
Suppressor Mechanisms eg Interferon
Clearance of Virus
Chronic Hepatitis
Cirrhosis
Hepatocellular Carcinoma

being classified as of NANBH or indeterminate cause. The role of HCV in FHF is controversial. Reported series of FHF of indeterminate cause have shown a prevalence of HCV RNA by PCR of from 0 to 12 per cent in the USA and Europe, but is substantially higher in Asian series (Villamil et al 1995). However, Villamil et al (1995) found that HCV appears to be the causative agent of a substantial number of cases of FHF classified as indeterminate in the Los Angeles area, and suggested that differences in patient populations or risk factors may explain the discordant incidences of HCV infection in FHF observed among different programs. In many patients with FHF, anti-HCV remains negative although HCV RNA is detected; some of these patients go on to develop histological hepatitis after liver transplantation, sometimes severe and sufficient to require retransplantation.

HCV RNA, rather than serological tests, should be used to establish the presence of infection, because anti-HCV seroconversion may take weeks after acute infection. Also, if an overwhelming immunological response occurs in fulminant HCV, analogous to the one that occurs in HBV (table 29), then the amount of virus present may be small and be detected only in liver. Hence, the amount of virus should be measured in both serum and liver using PCR as the most sensitive test available. Biopsy should show massive hepatocellular necrosis with an absence of significant fibrosis to distinguish acute hepatic failure due to HCV from HCV CLD with superimposed acute liver failure due to some unrelated cause (Terrault and Wright 1995b).

Table 29 Serum hepatitis C virus and anti-hepatitis C virus in fulminant hepatic failure of indeterminate cause and fulminant hepatic failure due to hepatitis B virus infection

From Villamil et al (1995).

Reference	Indeterminate cause		HBV infection	
	HCV-RNA+	Anti-HCV (+)	HCV-RNA+	Anti-HCV (+)
Chu et al (1994)	5/11 (45%)	1/11 (9%)	9/51 (18%)	6/51 (12%)
Feray et al (1993)	0/23	0/23	8/17 (47%)	0/17
Ferraz et al (1993)	0/15	0/15	0/4	0/4
Liang et al (1993b)	1/17 (6%)	0/17	NR[A]	NR
Munoz et al (1992)	1/18 (6%)	NR	0/16	NR
Sallie et al (1991)	0/30	0/30	NR	NR
Theilmann et al (1992)	1/8 (12%)	0/8	0/4	0/4
Villamil et al (1995)	9/15 (60%)	6/16 (37%)	2/7 (29%)	1/7 (14%)
Wright et al (1992)	0/6	0/17	1/4 (25%)	1/4 (25%)
Yanagi et al (1991)	3/7 (43%)	2/7 (29%)	3/8 (37%)	3/8 (37%)
Yoshiba et al (1991)	10/17 (59%)	9/17 (53%)	0/5	0/5

[A]NR, not recorded.

5.3 Progression to chronicity

A wide range of chronicities has been reported for HCV infection in different studies, and may be explained in part by differences in length of follow-up, irregular fluctuations of ALT, and the difficulty of diagnosing the extent and progression of disease without serial liver biopsies. Much of our current knowledge about the natural history of chronic HCV infection is based upon cross-sectional data, and it is difficult to predict the course in a patient seen at

one point in time. Longitudinal data often derive from those infected as a result of blood transfusion. It is clear that progressive HCV disease can occur without symptoms and although serological test results do not predict histology, patients who are not viraemic, or whose RIBA results are indeterminate, are less likely to have significant liver disease on biopsy.

There is continuing debate about whether there is such a person as a healthy carrier of HCV, some people having persistently detectable HCV RNA but no symptoms or signs of liver disease. It is likely that persistent viraemia corresponds to mild hepatitis with an inflammatory portal response and a variable lobular inflammation with parenchymal apoptoses. For example, Chemello et al (1993) took liver biopsy samples of 23 patients and found that all patients with viraemia (HCV-RNA positive on PCR analysis) had CLD detectable on biopsy, whereas seven HCV-RNA negative cases had normal liver histology (Chemello et al 1993). Lymphoid infiltrates can occur in the portal inflammatory infiltrate and periportal necrosis is usually mild (Dhillon and Dusheiko 1995). The infiltrate generally consists of T cells, and is similar in chronic active and chronic persistent patterns of HCV infection, although it varies in intensity. Prieto et al (1995) studied 98 blood donors found positive for anti-HCV (second-generation EIA confirmed using RIBA2) by liver biopsy, PCR for HCV RNA and a panel of liver injury tests. Almost all (97%) of the anti-HCV-positive blood donors had some type of histological abnormality: 22 (22%) had minimal changes; 1 (1%) had chronic lobular hepatitis; 40 (41%) had CPH; and 32 (33%) had chronic active hepatitis (CAH). Only three subjects had a normal liver histology. HCV RNA was detectable in the serum in 65 per cent. HCV RNA in serum was detectable in none of the donors with a normal liver histology, in 36 per cent ((CI 17, 59%) of those with minimal changes, in 70 per cent (CI 53, 83%) of those with CPH, and in 87 per cent (CI 71, 96%) of those with CAH (P=0.00001). HCV RNA was detectable in 75 per cent of the donors with elevated (>45 U/L) ALT values and in 59 per cent of those with normal ALT levels (P=not significant). The incidence of chronic hepatitis was higher in HCV-RNA-positive than in HCV-RNA-negative donors (88 v. 50%; P=0.00005). Age older than 50 years (OR=17.5), an elevated ALT (OR=74.4) and serum HCV RNA (OR=18.9) were independently associated with the presence of chronic hepatitis. The authors suggested that the detection of HCV RNA in 36 per cent of the donors with minimal changes on biopsy, all of them with normal ALT levels, suggests that a healthy carrier state may exist. However, Gunji et al (1992) followed four patients who were persistently HCV-RNA positive for three years with monthly serology and reported that despite persistent viraemia, the subjects consistently had normal ALT levels and a liver biopsy was normal. Yuki et al (1996) used branched-chain DNA to quantitate HCV RNA and found a significant inverse relationship between levels of viraemia and the duration of aminotransferase normalisation (r=-0.46, P<0.01). They interpret their findings to indicate that biochemical remission of HCV infection may be frequent in haemodialysis patients and may be related to viral attenuation, but unfortunately no liver histology was available.

Shindo et al (1995) investigated HCV titres, HCV-RNA levels in liver and serum, genetic variability in the hypervariable region (HVR) of the genome, the form of the virus in the circulation, and liver histology in 21 anti-HCV-positive patients with sustained normal liver biochemical values. Titre of anti-HCV was determined by second-generation anti-HCV-passive haemagglutination assay, and HCV-RNA levels were semiquantified by RT-PCR. In 19 (90%) of the 21 subjects who had a higher titre of anti-HCV [>2], HCV RNA was detected in both serum and liver samples, and histological examination showed minimal or mild chronic hepatitis in all (Allander et al 1994). In the remaining two patients who had a lower titre of anti-HCV, HCV RNA was not detected in serum and liver samples, and liver histology was normal. Anti-HCV titres and HCV-RNA levels in serum and liver in the 19 HCV-RNA-positive patients were compared with those levels in the 41 patients with biopsy-proven chronic HCV infection and elevated serum ALT levels as a control group. There were no significant differences in viral levels in serum and liver between the two groups. Anti-HCV-positive patients with normal liver biochemical values had quasispecies of the HCV genome similar to the patients with chronic HCV disease. The authors argue that since both

groups have similar virological characteristics, but different patterns of serum ALT levels and histological findings, the two groups may have different immune responses to the virus.

ALTs that are normal for many months or years can then unpredictably increase many fold. It is not known whether changes in HCV during infection or mutation to a particular variant affect different episodes of the disease, but sequence changes in the envelope protein may correlate with exacerbations in hepatitis (Gunji et al 1992).

Kurosaki et al (1995a) using SSCP analysis found 13 amino acids in the 5' end of the HVR were completely identical in three sequences of free HCV, whereas there were three and seven amino-acid differences in two sequences of antibody-bound HCV. This suggests that isolated specific epitopes for envelope antibodies exist within the HVR, and that a portion of the circulating virus population is captured by HVR antibodies to form immune complexes and cryoprecipitants, while the others with different HVR sequences escape from the antibodies. The escape mutant in the HVR may be related to the persistence of HCV infection.

Following transfusion, chronic HCV infection is believed to be the result in about 70-80 per cent of patients with acute HCV infection (Iwarson 1994). Since around only 5 per cent of acute HBV infections that occur in adults lead to chronic carriage, the number of chronic carriers following acute HCV infection is more than ten times the number following acute HBV infection. There is no evidence to suggest that the progression to chronicity is different with different ways of contracting the disease.

Chronic HCV is said to have a variable course that in some people is rather indolent. The time elapsing between diagnosis of chronic hepatitis, cirrhosis and HCC appears to be 10, 20 and 30 years, respectively (Kiyosawa et al 1990) and 14, 20 and 30 years, respectively (Tong et al 1995). Such follow-up studies that have been reported so far have found a wide variation in proportions developing liver disease (table 30). Factors that promote chronicity and progression of HCV-related disease remain unclear. Postulated factors include age at infection, route of transmission, duration of infection, serum ALT levels, viral load, genotype, alcohol consumption and coinfection with other blood borne viruses (Gordon et al 1993; Strasser et al 1995; Kobayashi and Thomas 1996; Mangia et al 1997; Schiff 1997; Seeff 1997). Seeff (1997) grouped factors into virus related (viral dose, viral load and quasispecies), host related (age, race, sex) and other (alcohol, viral coinfection, environmental, smoking).

Viral load at the time of infection may influence progression of disease. There is, however, little conclusive evidence to date. Those acquiring infection through IDU would appear to acquire a lesser dose at the time of infection than those infected through contaminated blood products acquired, and this may be a factor involved in the possibly more benign nature of HCV in the former group. This requires further evaluation.

The role of genotype is also unclear with several studies reporting increased pathogenicity in those infected with subtype 1, in particular subtype 1b. Silini et al (1996) studied three groups of patients: 593 patients with chronic hepatitis, 166 patients with HCC and cirrhosis, and 219 patients with cirrhosis but without HCC. A cross-sectional study of frequency distribution and a case-control analysis were performed. They concluded that HCV type 1b is overrepresented in patients with cirrhosis and HCC and significantly influences the risk of HCC in cirrhosis, independent of sex, age, and Child's class. Kobayashi et al (1996) examined 140 patients with chronic HCV. Deterioration of the grade of liver histology during the follow-up period was seen in 68 per cent of the patients with genotype 1 as compared with 41 per cent of those with genotype 2 ($P<0.01$). In addition the mean serum HCV-RNA titre was significantly higher in the patients with genotype 1 than in those with genotype 2 ($P<0.001$). The authors conclude that more severe progression of chronic HCV is seen in genotype 1b. Several other studies have, however, refuted any connection between genotype and severity and progression of disease, in particular any connection between genotype and progression to HCC (Romeo et al 1996; Benvegnu et al 1997).

Age is another factor that appears to influence outcome. The National Heart, Lung and Blood Institute study (Seeff 1994) reports that HCV infection in those older than 55 years was associated with an increased mortality with the

opposite outcome noted in those infected at < 55 years. Age may also play a role in those already chronically infected and may be associated with clinical decline beyond the two decade mark (Seeff 1997).

Coinfection with HIV (see section 5.9.2) causes an increase in progression to liver disease and is associated with increased levels of HCV viraemia (Cribier et al 1995). Coinfection does not appear to cause an increased rate of progression of HIV (Quan et al 1993).

The presence of chronic HBV in addition to chronic HCV appears to increase the severity of disease and risk of HCC (see section 5.9.1). Benvegnu et al (1994) followed 290 consecutive cirrhotic patients for 46.3±21.4 months. HCC developed in 32 patients (11.0%). By multivariate analysis, age (P<0.01), positivity for HBsAg and HCV antibodies (P<0.05), male sex (P<0.05), and previous alcohol abuse (P<0.08) were independently related to tumour appearance. The authors conclude that although male sex and previous alcohol abuse are risk factors for HCC in cirrhosis, concurrent HBV and HCV infection determines the highest risk of developing HCC. This increased risk of disease, in particular HCC, has been noted in other studies (Chiba et al 1996; Tsai et al 1997). However, the viruses also have an inverse relationship, in that the presence of HCV appears to suppress HBV replication (Fong et al 1991).

Several studies (Tanaka et al 1996; Petrik et al 1998) indicate that HGV coinfection has no important effects on histological features in chronic HCV carriers and that it is unlikely that HGV infection causes chronic liver disease.

Alcohol is increasingly recognised as being important in progression to cirrhosis and HCC (see section 5.6). Alcohol in excess of 10 g/day is associated with increased HCV RNA and aminotransferase levels, the mechanism of which is not well understood (Schiff 1997). It is unknown whether HCV and alcohol are independent risk factors for chronic liver disease or whether they act synergistically. However, patients with HCV should be encouraged to restrict alcohol intake.

Table 30 Results of long-term histological follow-up of posttransfusion hepatitis C virus infection

From Alberti et al (1995).

Country	Reference	No. of patients	Years of follow-up (mean)	Findings at end of follow-up		
				CPH (%)	CAH/CPH (%)	HCC (%)
Italy	Tremolada et al (1992)	104	1-15 (7.5)	30	69	1
Japan	Takahashi et al (1993)	100	5-32 (11)	34	42	19
Japan	Yousuf et al (1992)	62	5-15 (8.8)	25	23	52

Long-term histological follow-up reveals bile duct damage, lymphoid aggregates or follicles and lobular inflammation in a substantial proportion of patients. The lymphoid involvement suggests that an immunological mechanism for liver injury may be involved.

5.4 Long-term consequences

There remain unanswered questions regarding the natural history of chronic HCV infection. Some patients, even those with cirrhosis, appear to do very well over long intervals, whereas others progress rapidly to a fatal outcome within a decade. Whether this is related to the virulence of the viral strain, levels of virus in the liver, host immune response or genetic susceptibility or to other cofactors that increase the severity of HCV infection is still unclear.

Determining the natural history of HCV is difficult, principally due to the problems of identifying those with incident infection, the long latent period before development of liver-related disease and the difficulties of following up the largest affected group, IDUs, over long periods of time. Therefore, much of the reported data are on transfusion-acquired diseases and are based on cross-sectional, retrospective studies with their inevitable biases in estimation of rates and proportions of disease progression. Despite this a great deal of information has been gathered over the past 15 years that provides considerable insight into the natural history of HCV.

Several studies have prospectively followed persons with transfusion-acquired NANBH from onset of acute disease. In the USA, Koretz et al (1993) reported on long-term follow-up (mean of 16 y after disease onset) of 80 patients who developed TA-hepatitis in the 1970s. They found that eight patients (10%) in the entire population had developed clinical evidence of hepatic failure. Life-table analysis showed that the probability of developing clinical evidence of cirrhosis in patients with chronic HCV infection was 20 per cent after a mean interval of 16 years. Two patients whose cirrhosis had been documented for over a decade had no evidence of hepatic failure, suggesting the often indolent nature of cirrhosis in HCV-infected individuals. Also from the USA, Di Bisceglie et al (1991a) reported on outcomes of subjects with acute NANBH post heart surgery. Thirty-nine subjects were followed from between 1 and 24 years (mean 9.7 y). About 20 per cent developed cirrhosis by the end of follow-up and 12 per cent developed end stage liver disease. No cases of HCC or liver-related deaths were reported. Most patients with histological evidence of cirrhosis or CAH had minimal clinical evidence of liver disease within the time frame of the study. From Europe, Hopf et al (1990) followed 86 patients in Germany for a mean of eight years (range 3-20 y). Clinical symptoms were noted in 4.7 per cent and cirrhosis identified in 24 per cent. The development of cirrhosis required many years. In Italy, Tremolada et al (1992) reported on 135 patients who developed NANBH mostly after cardiac surgery and who were followed up for a mean of 7.6 years (range 1-15 y). Of the 65 patients who underwent biopsy at the end of follow-up, 32 per cent had developed cirrhosis. One subject (0.7%) developed HCC. Age was a significant correlation with development of cirrhosis in this group. Mattsson et al (1993) reported on Swedish subjects who had acute NANBH in 1978. After 13 years of follow-up, 8 per cent of subjects had cirrhosis with no cases of HCC and no liver-related deaths. In summary, in the above studies at the end of follow-up, cirrhosis was identified in 8 to 32 per cent of subjects, HCC detected in 0.7 and 1.3 per cent in two studies and mortality from liver- related disease ranged from 1.6 to 6 per cent.

In the National Heart and Lung Blood Institute study of TA-NANBH, Seeff et al (1992) followed post-TA-hepatitis cases and controls from five major prospective studies that defined posttransfusion NANBH in the 1970s. Although there was a small but significant excess of liver-related mortality in the hepatitis population, the study found little difference in overall mortality. The five studies were primarily of older individuals undergoing open heart surgery. For most, their life expectancy was less than the 18 years follow-up interval in Seeff et al (1992), independent of patient's liver disease. Although HCV is generally persistent, it is indolent, with a natural history measured in decades. Because so many deaths were caused by cardiac and other disease in an older population and because the natural history of HCV is measured in decades, it is not a good study in which to determine the outcome of chronic HCV infection in those infected at a younger age. More recently (Seeff 1994) there have been morbidity data - 30 per cent of those with NANBH/HCV infection had evidence of chronic hepatitis as compared with 1 per cent of

controls, and of the 40 patients who at the time of the survey had liver biopsies, two-thirds had severe histological lesions including CAH, cirrhosis and HCC (Seeff 1994).

5.4.1 Studies of outcome of chronic hepatitis C virus infection in people with already established chronic liver disease

Several studies have reported on outcomes in HCV-infected individuals with chronic hepatitis. Yano et al (1993) reported 30 per cent cirrhosis and 15 per cent HCC on Japanese blood donors with chronic hepatitis after a mean follow-up of eight years. The extremely high incidence of HCC in this group was also reflected by Takahashi et al (1993) who followed 333 Japanese patients with chronic hepatitis for 11 years. Cirrhosis developed in 42 per cent and HCC in 19 per cent. The very high rates of liver-related sequelae in these studies undoubtedly reflect that in Japan chronic HCV is common and appears strongly related to HCC (Seeff 1997). From the USA, Tong et al (1995) reported on 131 patients of whom 101 were biopsied (the others had signs of cirrhosis and abnormal coagulation tests). The mean age of subjects at transfusion was 35 years (range 1-76 y) and at the time of initial assessment, 57 years. The mean duration of follow-up after evaluation was 3.9 years (range 1-15 y). Over 46 per cent of subjects had cirrhosis and 10.6 per cent had HCC. Liver-related deaths during the course of the study were 15.3 per cent. The authors also identified posttransfusion chronic hepatitis at 13.7±10.9 years, cirrhosis 20.6±11.8 years and HCC 28.3±11.5 years later. Similar results were found by Castells et al (1995) who studied serum samples from 191 consecutive patients diagnosed with cirrhosis and HCC in a Barcelona hospital, Spain, between 1988 and 1993, using stored sera, and found 148 were positive for anti-HCV on second-generation EIA (152 on third-generation EIA), confirmed by second-generation RIBA (Dhillon and Dusheiko 1995). Only 14 (7.4%) were HBsAg positive, 8 (4%) of whom had dual infections. Of the 29 anti-HCV-positive patients with a history of transfusion, the mean interval (± s.d.) between transfusion date and diagnosis of cirrhosis was 24±12.5 years and that of HCC was 26.8±12.4 years. Poynard et al (1997) assessed the natural history of liver fibrosis progression in HCV and the factors associated with this progression by recruiting 2,235 patients with a biopsy sample compatible with chronic hepatitis. The median rate of fibrosis progression per year was 0.133 fibrosis unit (95% CI 0.125-0.143) Three independent factors were associated with an increased rate of fibrosis progression: age at infection >40 years, daily alcohol consumption of 50 g or more, and male sex. There was no association between fibrosis progression and HCV genotype. The median estimated duration of infection for progression to cirrhosis was 30 years (28-32 y), ranging from 13 years in men infected after the age of 40, to 42 years in women who did not drink alcohol and were infected before the age of 40. Without treatment, 377 (33%) patients had an expected median time to cirrhosis of less than 20 years, and 356 (31%) will never progress to cirrhosis or will not progress for at least 50 years. Hu and Tong (1999) investigated a total of 112 patients with compensated HCV-cirrhosis and a documented history of either intravenous drug abuse or transfusion. The mean follow-up interval was 4.5 (2-7.7) years. The cumulative probabilities for decompensation and development of HCC were 22.2 per cent and 10.1 per cent in five years, with an estimated yearly incidence of 4.4 and 2.0 per cent, respectively. The incidence of decompensation was significantly lower in patients treated with IFN, but age may have played a contributory role. In contrast, neither HCC development nor mortality was significantly altered by IFN therapy. The authors conclude that once decompensation develops disease is progressive. Further studies are required to determine the efficacy of IFN on clinical outcomes in this group of patients.

These studies highlight the serious sequelae that can be expected in those with established HCV chronic hepatitis. However, as they only report on individuals with established liver disease, and do not include those with asymptomatic HCV disease who will not progress, they cannot give estimates of rates of progression to sequelae. This can only be achieved through prospective follow-up studies with determination of disease onset dates.

5.4.2 Studies in subjects with community acquired hepatitis C virus

Determining the natural history of community acquired HCV is difficult and little has been published to date. A group in Melbourne reported pilot results (Rodger et al 1999) of a retrospective cohort study examining the long-term outcomes of HCV in a cohort who acquired infection through IDU in the early 1970s. Stored serum from 1971 to 1975 was found to be strongly reactive for antibody to HCV in 238 subjects. The pilot results indicated that HCV-antibody-positive individuals followed up to date were at increased risk of liver-related pathology, but few (7%) had progressed to cirrhotic liver disease after a mean follow-up of 25 years. This differs from findings of transfusion-related studies and suggests, within the limitations of the study, that the natural history of community acquired HCV may be more benign. The final results of the study are expected to be published shortly. Another study also tested stored sera samples, this time of 10,000 airforce recruits in the 1950s (Seeff 1997), and is tracing the recruits. The results of this study are not yet published.

5.4.3 Other studies

HCV infection following administration of anti-D immunoglobulin has been reported. In Ireland, 417 (0.8%) of 53,178 recipients of anti-D in 1977 were found to be anti-HCV positive (Power et al 1995b). At follow-up 232 were assessed. Serum ALT was normal in 37.6 per cent and liver biopsy specimens revealed mild to moderate chronic hepatitis in 38 per cent and severe hepatitis in 6 per cent. Only 2.4 per cent had features suggestive of early cirrhosis (Seeff 1997). To assess progression of disease in this group, Albloushi et al (1998) followed 30 patients who underwent two liver biopsies about two years apart, 17 and 19 years after initial infection with the infected immunoglobulin. In the initial 1994 biopsies, one patient showed cirrhosis (stage 6/6) and six patients (20%) had developed moderate fibrosis (stage 3-4/6). There was no significant histological disease progression between two biopsy specimens over two years. The results suggest that the prognosis in such cases could be guardedly optimistic in this homogenous cohort of healthy women infected at a young age.

5.5 Hepatocellular carcinoma

HCC is one of the commonest carcinomas worldwide, although it is less common in Western countries than in Asia, South Europe and Africa. An aetiological association between chronic HBV infection and HCC has been known for some time, and is thought to be mediated partly through the capacity for HBV DNA to integrate into host DNA. Although replicative intermediates of HCV RNA do not insert into cellular DNA, there is increasing evidence to support a strong association between chronic infection with HCV and the occurrence of HCC. Although the pathogenesis of HCV-related HCC is unknown, it almost always arises in association with cirrhosis or chronic hepatitis. Because there is no evidence that the virus is directly carcinogenic, it appears that HCV induces malignant transformation indirectly by causing chronic necroinflammatory hepatic disease and continued regenerative attempts that eventually are responsible for tumour formation.

Evidence for the link between HCV infection and HCC is provided by case-control studies, case series and by longitudinal studies (tables 31-39). The proportion of patients with HCC who have circulating antibody to HCV shows a pronounced geographical variation. In regions where HBV infection is endemic and is the major risk factor for HCC, antibody to HCV is present in the serum of a smaller proportion of patients (6-39%), with RRs of 7 (95% CI 1.6, 39) in Taiwan and 6 (95% CI 0.5, 69) in Senegal. In Japan, Spain and Italy, antibody to HCV is present in 47 to 83 per cent of the patients, with RRs of 52 (95% CI 24, 114) in Japanese and 69 (95% CI 15, 308) in Italian carriers of the virus. Comparatively low prevalences (13-35%) have been recorded for the remaining geographical regions for which information is available, with RRs of 10.4 (95% CI 4, 26) in Greece and 10.5 (95% CI 3.5, 31) in North America. For tables 31-39, see *Tables* section.

5.5.1 Interaction between hepatitis B and hepatitis C viruses in causation of hepatocellular carcinoma

There is uncertainty regarding the interaction of HCV and HBV in hepatocellular carcinogenesis. Many reports have suggested that anti-HCV antibodies are present appreciably more often in HBsAg-negative patients than with HBsAg-positive patients with HCC (table 40) (Simonetti et al 1989; Hasan et al 1990; Saito et al 1990; Jeng and Tsai 1991; Tanaka et al 1991; Bukh et al 1993a).

Table 40 Prevalence of hepatitis B virus markers and anti-hepatitis C virus among people with hepatocellular carcinoma from different countries or regions

Country or region	Reference	Total no. of cases	Percentage of people with:			Percentage of anti-HCV(+) in HCC in people with:	
			HBsAg+	Any HBV marker (+)	Anti-HCV+	HBsAg+	HBsAg-
China	Jeng & Tsai (1991)	129	63	NM[A]	37	24	60
France	Ducreux et al (1990)	74	NM	43	28	47	14
Italy	Colombo et al (1991b)	132	31	80	65	54	70
Italy	Levrero et al (1991)	167	32	68	58	28	72
Italy	Trevisani et al (1995)	166	20	47	72	47	78
Italy	Simonetti et al (1992)	200	62	NM	76	58	79
Japan	Nishioka et al (1991)	180	42	NM		15	76
Japan	Shiratori et al (1995)	205	11		71		
Japan	Tanaka et al (1991)	91	21	NM	51	5	63
Mozambique	Dazza et al (1993)	189	66	98	37	NM	NM
Southern Africa	Kew et al (1990)	380	48	81	29	26	32
Spain	Bruix et al (1989)	96	9	NM	75	56	77
Taiwan	Lee et al (1992)	326	75	97	13	4	37
Taiwan	Lee et al (1991b)	26	75	NM	13	35	55
Taiwan	Yu et al (1991)	127				8	29
USA	Hasan et al (1990)	87	32	NM	45	14	53

[A]NM, not measured.

These results may provide some support for reports that HBsAg is cleared when superinfection with HCV occurs, or suggest that HCV protects against superinfection with HBV which goes on to chronic HBsAg carriage. Bukh et al (1993a) found that very few patients with HBsAg in serum had HCV detectable, despite the presence of anti-HCV. There are also many reports which show that HBV DNA can be found in the liver tissue of some patients who are HBsAg negative (Brechot et al 1982; Sakamoto et al 1988; Dodd 1995). A few reports have not found any significant difference in HCV prevalence in patients with HCC related to the HBsAg status (Bruix et al 1989; Colombo et al 1989; Vargas et al 1990), but there is a consistent trend to a higher prevalence of HCV in patients who are HBsAg negative.

Of the many studies on HCC, relatively few have reported the risks for HCC in individuals positive for HBsAg separately from those with anti-HCV and from those with both (Kaklamani et al 1991; Yu et al 1991; Chuang et al 1992; Yuki et al 1992). Because HBsAg carriage is usually acquired early in life, the results suggest that HCV superinfection in HBV carriers may synergistically increase the risk of HCC developing. However, there are other studies which have reported that HBV and HCV act as completely independent risk factors for HCC (Nalpas et al 1991; Simonetti et al 1992).

HBV and HCV can interact with chronic alcohol consumption, and there is circumstantial evidence of a high prevalence of HBV and HCV infection in people with alcoholism. The high prevalence of HCV infection with cirrhosis in people with alcoholism (40-50%), relative to those with minimal liver damage (about 20%) suggests that HCV infection might be involved in the development of cirrhosis in some of these patients, and might also account for the high prevalence of anti-HCV (50%) in people with alcoholism with HCC (Brechot 1996).

Coinfection with HBV and HCV might influence HCC at two levels: there is *in vitro* evidence for decreased replication of both HBV DNA and HCV RNA in patients infected by two viruses. *In vitro* expression of the HCV capsid also diminishes encapsidation of the HBV pregenome (Brechot 1996).

There is some evidence for an interaction between HCV and HBV in hepatocellular carcinogenesis, but this remains to be proved (tables 41 and 42). There appears to be a negative correlation between markers for HBV and HCV (figure 3). In most populations, HCC develops at an older age in patients with HCV-induced tumours than in those with HBV-induced tumours.

Table 41 Effect of hepatitis C virus infection on risk of hepatocellular carcinoma in hepatitis B-(HBsAg)-positive individuals

Country	Reference	No.	HCC			Control			OR if anti-HCV positive	95% confidence interval	
			HCV +ve	HCV -ve	HCV +ve *(%)*	HCV +ve	HCV-ve	HCV +ve *(%)*		Lower	Upper
Italy	Stroffolini et al (1992)	96	5	11	*31*	0	80	*0.0*	Undefined	5.58	Undefined
Taiwan	CC Chang et al (1994)	34	1	23	*4.2*	0	10	*0.0*	Undefined	0.1	Undefined
Taiwan	Tsai et al (1994c)	140	12	100	*10.7*	1	27	*3.6*	3.24	0.44	143.6
Taiwan	Chuang et al (1992)	208	12	87	*12.1*	5	104	*4.6*	2.87	0.89	10.76
Combined M-H Weighted Odds Ratio		478	30	221	*12.0*	6	221	*2.6*	4.55	2.15	19.4

Table 42 Effect of hepatitis C virus infection on risk of hepatocellular carcinoma in hepatitis B-(HBsAg)-negative individuals

Country	Reference	No.	HCC			Control			OR if anti-HCV positive	95% confidence interval	
			HCV +ve	HCV -ve	HCV +ve *(%)*	HCV +ve	HCV -ve	HCV +ve *(%)*		Lower	Upper
Italy	Stroffolini et al (1992)	68	38	11	*77.6*	13	6	*68.4*	1.59	0.4	5.89
Taiwan	CC Chang et al (1994)	156	4	10	*28.6*	4	138	*2.8*	13.8	2.15	83.4
Taiwan	Lee et al (1991a)	160	23	15	*60.5*	2	120	*1.6*	92	18.8	836
Taiwan	Chuang et al (1992)	304	13	16	*44.8*	8	267	*2.9*	27.12	8.74	85.4
Combined M-H Weighted Odds Ratio		688	78	52	*60.0*	27	531	*4.8*	12	8.73	29.8

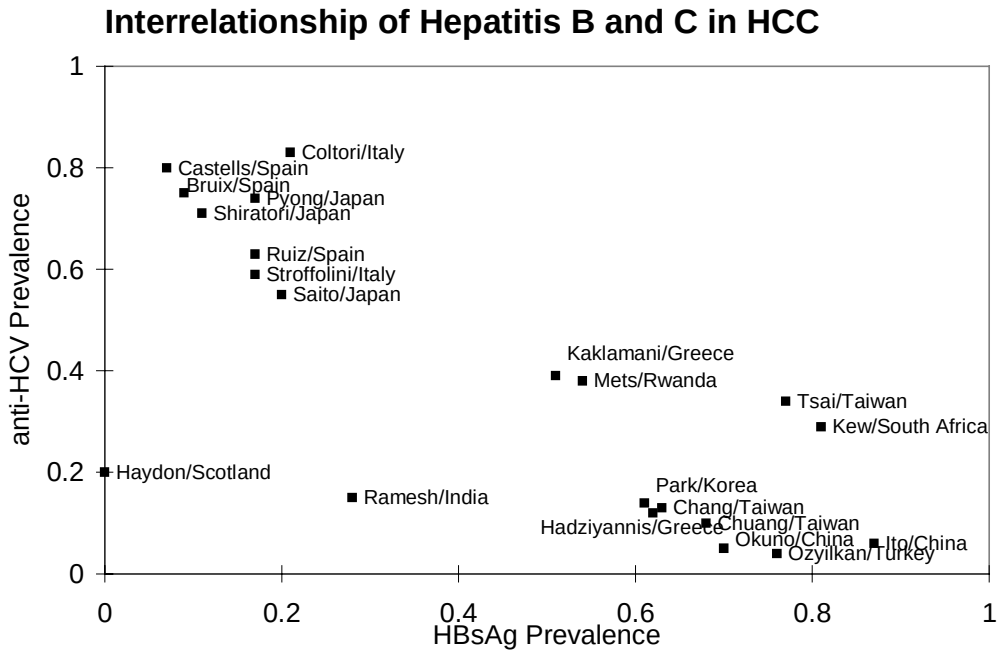


Figure 3. Interrelationship of hepatitis B and hepatitis C in hepatocellular carcinoma.

One of the difficulties in attributing magnitude of risk associated with particular serostatus is that exposure or infectivity as measured in the serum does not precisely reflect findings in liver tissue. For example, De Mitri et al (1995) examined cancerous and noncancerous liver tissue and serum samples from 19 HBsAg-negative patients with HCC without cirrhosis. Thirteen were HCV-RNA positive. Seven of 19 patients were HBV-DNA positive in cancerous and noncancerous liver tissue. HCV antibody status did not match HCV-RNA status, HBsAg-negative patients were not necessarily HBV-DNA negative, and HCC occurred in patients with HCV without the intermediate step of cirrhosis. Liang et al (1993a) in the USA studied 91 HBsAg-negative patients with HCC. These patients did not have other predisposing factors for HCC for evidence of HCV or HBV infection, using PCR to detect HCV RNA and HBV DNA in serum and liver. HCV antibodies were measured with second-generation immunoassays. Twenty-six (29%) of these patients carried low levels of HBV DNA in either serum, liver/tumour tissue or both. The authors found that 53 of 91 patients (58%) exhibited evidence of HCV infection. When the data were combined, 14 patients (15%) had evidence of HBV and HCV coinfection, whereas 12 (13%) were infected with HBV alone and 39 (43%) had HCV only. Twenty-six (29%) had no markers of HBV or HCV infection. All patients with identifiable viral markers had coexisting CLD. The authors concluded that HCV or occult HBV infections account for most (71%) HCC of unknown pathogenesis in the USA. Paterlini et al (1993), using a combination of serological and PCR assays, investigated the association between HCV and HBV infections and primary liver cancer in 24 HBsAg-negative patients living in France. Eleven of 22 patients tested had HBV DNA in the serum; 5 patients were anti-HBc positive and anti-HBs positive. Patients with HBV viraemia had HBV DNA sequences in both tumorous and nontumorous liver specimens. Selective loss of part of the HBV genome in the tumorous tissue of two of these patients suggested HBV DNA persistence in clonally expanded malignant cells. The presence of HCV-RNA and HBV-DNA sequences was tested for in serum and in tumorous and nontumorous liver samples. Twelve patients had anti-HCV, and HCV-RNA sequences were found in the serum samples of all anti-HCV-positive patients and none of the patients who were negative. Patients with HCV viraemia had HCV-RNA genomic sequences and presumed replicative intermediates in both tumorous and nontumorous specimens. Sequence analysis of a hypervariable region in the E2/NS1 gene of HCV showed significant variations between the viral molecules isolated from the nontumorous, tumorous and serum samples. This eliminated the hypothesis of the contamination of the tumour by nontumorous cells and serum particles and assessed that liver tumour cells did contain HCV-RNA genomes. Only 4 of the 22 patients were negative for both viruses. Thelu et al (1992) tested 40 Caucasian patients with HCC: 19 were anti-HCV positive and 21 were anti-HCV negative. Only 4/19 (21%) of anti-HCV-positive patients were HCV-RNA positive: all four had C33-c-positive and C22-3-positive bands, but C100-3 and 5-1-1 bands were present in one and two patients, respectively. The only HBV marker was anti-HBcAb in two patients. Only one of the patients who was anti-HCV negative had HCV RNA detected by PCR. The findings suggest that HCV RNA is uncommon in the serum of Caucasian patients with HCC, which may be accounted for by the contribution of alcohol to underlying cirrhosis in the patients or to the absence of viraemia at a final stage of the disease. Diamantis et al (1994) studied paired samples (tumour, nontumour) from 38 patients using PCR for HBV and HCV. Coinfection for HBV and HCV in liver was seen in nine patients, only three of whom had anti-HCV in serum. One of these three was HBsAg negative in serum while the other two and four of the other six from this group were HBsAg positive. One patient with anti-HCV in serum and no HBsAg had no HCV RNA in liver tissue and HBV DNA was detected. Twenty-seven patients were infected with HBV only, but only 25 of these had HBsAg detectable in serum. HCV was detected as the only agent in one patient. The results suggest that in a hyperendemic area, HBV is closely associated with the development of HCC, but that infection with HCV may play a secondary role. Even where PCR results between serum and liver are not discordant, serum HCV genotyping may not reflect the viral population infecting the liver of a given patient (Castillo et al 1995).

Table 43 Association of hepatocellular carcinoma with infection with hepatitis B virus or hepatitis C virus

All patients were HBsAg negative.

	Serum	Liver	Reference
HBV DNA	11/22	37/63	Paterlini et al (1993)
	12/54	Not tested	Ruiz et al (1992)
	24/105	14/38	Liang et al (1992)
	Not tested	5/12	Gerber et al (1992)
	4/31	9/31	Sheu et al (1992)
	Not tested	8/12	Unsal et al (1994)
	3/22	11/22	Ramesh et al (1994)
HCV RNA	11/22	5/5 (HCV+)	Paterlini et al (1993)
	42/68	Not tested	Ruiz et al (1992)
	40/90	7/9 (HCV+)	Liang et al (1992)
	Not tested	11/20	Gerber et al (1992)
	17/31	18/31	Sheu et al (1992)

Koike et al (1995) suggest an explanation for this. They measured HBV-DNA and HCV-RNA levels in the sera of patients positive for both HBsAg and HCV antibody to characterise the state of dual infection with HBV and HCV. Among 27 patients who showed evidence of double infection, 21 (77.8%) had detectable levels of only either HBV or HCV genome in their sera, 2 (7.4%) showed none of the viral genomes, and 4 (14.8%) had both HBV DNA and HCV RNA. In the 4 patients with both HBV DNA and HCV RNA, the titres of HCV RNA or HBV DNA were lower than those in the patients with HCV RNA or HBV DNA alone. In some patients with chronic hepatitis, the viruses appeared to replicate in turn in the course of the disease. Their results suggest that the viruses show alternating dominance in replication in most patients who have dual infection with HBV and HCV, probably due to interference of the viruses.

Studies seem to suggest that HBV-associated HCC tends to evolve more frequently in a noncirrhotic liver and also at younger ages, and perhaps HCV-associated HCC emerges more often in an advanced cirrhotic liver in older individuals and grows in a less aggressive manner (Okuda 1995). For example, in a series of 205 consecutive Japanese patients with HCC admitted during 1990-93, 71 per cent of the patients showed positivity for HCV antibody alone, 13 per cent showed positivity both for HCV and HBV antibodies, 11 per cent were positive for HBsAg alone and absence of both HCV and HBV antibody occurred in 4 per cent only (Shiratori et al 1995). Positivity to both HCV antibody and HBsAg was demonstrated in 1 per cent only. Mean detection age (± s.d.) of HCVAb-positive HCC as well as both HCV and HBV antibody-positive HCC was 62±7 years, in contrast to 52±13 years in HCC with HBsAg (P<0.05). The male-to-female ratio among HCVAb-positive HCC was 3.3:1, in contrast to 5.5:1 among the HCV/HBVAb-positive HCC and 7:1 among HBsAg-positive HCC, but there was no significant difference in the gender distribution between these groups. More than 60 per cent of HCVAb-positive HCC and HCV/HBVAb-positive HCC were classified into the stage of Child B and C, whereas 65 per cent of HBsAg-positive HCC was at the stage of Child A. The severity of liver disease was confirmed by liver histology, indicating that more than 70 per cent of the HCVAb-positive HCC and the HCV/HBVAb-positive HCC showed cirrhosis, in contrast to 50 per cent among the HBsAg-positive HCC. Three-year survival rate of HCVAb-positive HCC and HBV/HCVAb-positive HCC was 68 and 56 per cent, respectively, in contrast to 47 per cent in HBsAg-positive HCC.

5.5.2 Time between exposure and development of hepatocellular carcinoma in hepatitis C virus-positive patients

Blood transfusion

A history of blood transfusion may be associated with HCV infection, although blood transfusion appears no longer to be a major route of HCV transmission. The mean time between first transfusion and the development of HCC has been 25.2 years (USA, Yu et al 1990); 22 years (Japan, Saito et al 1990); 27 years (Japan, Nishioka et al 1991); and 29 years (Japan, Kiyosawa et al 1990). Tremolada et al (1990) report the well-documented case of HCV infection which progressed through CAH and cirrhosis to HCC 13 years after transfusion. Kiyosawa described a case of a 70-year-old nonalcoholic man who developed HCC 18 years after chronic NANBH following a blood transfusion, with five liver biopsies sequentially taken from year 5 to 15 showing, in order: unresolved viral hepatitis, CPH, CAH, CAH with bridging necrosis and postnecrotic cirrhosis (Kiyosawa et al 1984). Close correlations have been demonstrated between blood transfusion, NANBH and anti-HCC in patients with TA-HCC (Kiyosawa et al 1990).

Tanaka et al (1991) used cross-sectional data on seropositivity among 422 HCC patients, cancer registry data and data on age-specific population prevalence to estimate the five-year age-specific incidence rates of HCV-linked HCC. Using these risks, the cumulative risk (ie the probability of contracting HCC within the following 15 y in 50-y-old carriers) was estimated as 28 per cent for males and 6 per cent for females (Tanaka et al 1991).

Castells et al (1995) investigated the prevalence of anti-HCV and the interval between HCV infection and HCC among 191 consecutive patients with cirrhosis and hepatocellular carcinoma. Of the 29 anti-HCV-positive patients with previous transfusion, the interval between the date of blood transfusion and the diagnosis of hepatic cirrhosis was (mean±s.d.) 24±12.5 years and that of HCC was 26.8±12.4 years, showing the slow sequential progression from HCV infection through cirrhosis and HCC.

Prospective studies of hepatocellular carcinoma development

Ikeda et al (1993) prospectively studied 795 consecutive patients with viral or alcoholic cirrhosis for 2 to 17 years (median, 5.8 y). During the observation period, HCC developed in 221 patients. Cumulative appearance rates of HCC were 19.4, 44.3 and 58.2 per cent at the end of year 5, 10 and 15, respectively. When classified by the type of hepatitis virus infection, the appearance rates of HCC in 180 patients with only HBsAg and in 349 patients with only antibodies to HCV were: 14.2 and 21.5 per cent at year 5; 27.2 and 53.2 per cent at year 10; and 27.2 and 75.2 per cent at year 15, respectively. A Cox proportional hazard model identified that αFP levels (P<0.001), age (P<0.001), positive HCV antibodies (P<0.002), total alcohol intake (P<0.005) and indocyanine-green retention rate (P=0.05) were independently associated with the appearance rates of HCC. Whereas age and indocyanine-green retention rate were independent predictors for the appearance rate of liver tumour in the subgroup of HBsAg-positive patients, αFP levels, age and past alcohol consumption were independent predictors in the group of HCV antibody-positive patients. The authors believe these epidemiological results suggest that some differences exist in the activity and modes of cancer promotion between HBV infection and HCV infection.

Ganne Carrie et al (1996) prospectively followed 151 hospitalised patients with histologically proven cirrhosis from 1987-90 until June 1994 by which time 31 had developed HCC. Six variables summarised predictive information of HCC: age greater than or equal to 50 years (P=0.01); male (P=0.01); large EV (P=0.03); prothrombin activity <70 per cent (P=0.04); serum αFP levels greater than or equal to 15 ng/L (P=0.06); and anti-HCV antibodies (P=0.08). A clinicobiological predictive score identified two groups of patients at low (n=67; 3-y cumulative incidence, 0%) and high risk for HCC (n=84; 3-y cumulative incidence, 24%). The predictive value of this score was confirmed using an independent population of 49 patients with cirrhosis. Furthermore, liver large-cell dysplasia (LCD) had an additional predictive value in high-risk patients (P=10^{-4}), which thus helped to define a subgroup at very high risk for

HCC (*n*=12; 3-y cumulative incidence, 72%). The authors concluded that in Western patients with cirrhosis, a limited number of usual variables can identify a group of patients at high risk for HCC and that liver biopsy allows for determination a subgroup of patients at very high risk for HCC.

Mechanism of carcinogenesis

The means by which HCV causes HCC has been an active area of research, and it seems likely that HBV and HCV act via different mechanisms. HCV persists in hepatocytes during malignant transformation, and some HCC appear to support replication and expression of HCV (Gerber 1993; Horiike et al 1993; Haruna et al 1994). One mechanism suggested for carcinogenesis is that the cellular inflammatory infiltrates, present in the liver in both chronic HBV and chronic HCV infection, are associated with premature hepatocellular death, possibly by apoptosis, leading to regeneration of hepatocytes and, thus, an overall increase in the rate of proliferation and cell turnover of the hepatocyte population. At the same time, inflammatory cells, particularly monocytes and macrophages, present in the liver, generate free hydroxy radicals, which are capable of damaging cellular DNA, and may be the proximate cause of malignant transformation. Much of the intrahepatic inflammatory response may be nonspecific and cytokine-mediated (particularly IFN-γ). Although hypothetical, this mechanism of viral carcinogenesis is consistent with the observation that HCC commonly develops in both HBV and HCV infections against a background of chronic hepatic inflammation and cirrhosis (Lemon and Brown 1994).

Although in most cases the noncancerous tissue of HCC patients is cirrhotic, HCC can arise in HCV infection without an intermediate step of cirrhosis (Sbolli et al 1990; Jeng and Tsai 1991; Levrero et al 1991; Simonetti et al 1992), suggesting that HCV could be exerting some direct effect on the development of HCC. El-Refaie et al (1996) reported four cases of HCV-RNA-positive, HBsAg-negative, HBV-DNA-negative HCC in patients without cirrhosis in 66 consecutive cases of HCC undergoing surgical resection. Theise et al (1993) reported an incidental small HCC in a patient with chronic HCV infection without cirrhosis. The existence of portal triads and the Meyenburg complexes within the lesion and atypical subnodules suggested that the carcinoma has arisen in the context of a macroregenerative nodule rather than the whole nodule being an early, spreading carcinoma. They argue that macroregenerative nodules are precursor lesions in the development of HCC. Although often thought of as being large cirrhotic nodules, the authors suggest that they may be lesions that develop in the context of CLD, parallel to, but independently of, cirrhosis. Moreover, the development of carcinoma within the nodule suggests that macroregenerative nodules may be involved in carcinogenesis in noncirrhotic livers.

HCC may be multicentric in occurrence, and patterns of loss of heterozygosity on chromosome 16 in multiple HCCs suggest that they have an independent clonal origin. Multicentric tumours are associated with a low disease-free three-year survival rate (Tsuda et al 1992; Takenaka et al 1994).

Mutant p53 has been found in a wide variety of human malignancies including carcinomas of the lung, breast and colon. Laurent Puig et al (1992) examined immunohistochemically a large series of liver tumours from Caucasian patients with different risk factors for expression of the p53 mutant to assess its prevalence and the relationships between p53 overexpression and clinicopathological data. Nine of 58 specimens were found to have detectable evidence of p53 gene mutation, and p53 was more frequent in patients with serological HBV and HCV markers than patients without these markers (P=0.046). The authors concluded that p53-positive HCC is rare in patients exposed to a low dietary aflatoxin intake and that p53 mutation seems to occur at a late stage of the tumorous process and could contribute to an aggressive tumorous phenotype. Teramoto et al (1994) reported that p53 abnormalities in HCC correlated with the grade of cancer cell atypia which advanced with tumour growth. Using PCR techniques on cancerous and noncancerous regions of the liver, patients who had been infected with either HBV or HCV showed an incidence of p53 abnormalities (45%) higher than those infected by neither (13%). However, the detection rate of these viruses was lower in the HCC region (33%) than that in the noncancerous region (56%) in cases with mutated p53. There was a difference in pattern of p53 mutational changes in patients depending upon whether they were

infected by HBV or by HCV. Two of three HBV-infected patients had a transversional change of nucleotide at the G:C site to T:A. However, four of eight patients with HCV had a transitional change of nucleotide of p53, indicating that HCV infections affect carcinogenic pathways causing p53 abnormalities independently. Yumoto et al (1995) have also reported that loss of heterozygosity (LoH) on every chromosome and the p53 mutation is observed more frequently in more advanced tumours. Genetic changes accumulated with the increase of the histopathological grade, suggesting that the accumulation of genetic changes in multiple tumour suppressor genes is involved in HCC progression (Yumoto et al 1995).

Tarao et al (1994) examined whether the pathogenesis of carcinoma that increased proliferation of tissue cells correlates with the development of carcinoma, by increased rate of random mutations and by promotion. Patients were studied by the *in vitro* uptake of bromodeoxyuridine in biopsied liver specimens and were followed prospectively for 3 years. Nine of 14 (64.3%) of the cirrhotic patients with high-DNA synthesis activity developed HCC in the 3 years, in contrast to only 2/14 (14.3%) of the cirrhotic patients with low-DNA synthesis activity ($P<0.05$). Niu et al (1995) showed that HCV viral replication occurs both in the tumour tissue and nontumour tissue of HCC. Viral replication was established by showing the presence of minus strand HCV RNA by PCR amplification, after excluding residual reverse transcriptase activity of Taq polymerase. No minus strand was found in serum-derived virion RNA. PCR amplified products from both tumour and nontumour parenchyma were sequenced in the 5' noncoding region and shown to be identical. The finding of a conspicuous inflammatory infiltrate of the tumour tissue was thought to reflect the presence of the virus.

Sullivan and Gerber (1994) sequenced part of the 5' untranslated region of HCV from the tumour tissue and the surrounding nontumorous liver of three patients with HCC. No sequence differences between tumour-derived and liver-derived HCV isolates were detected. Based upon the conservation of the 5' untranslated region of HCV - not only in infected hepatocytes, but also in neoplastic cells - the authors suggest that the regulatory elements at the 5' terminus of the viral genome are important in the pathobiology of HCV.

Based on histological criteria, regenerative nodules in cirrhotic liver have been generally considered to result from hyperplastic proliferation of hepatocytes, but whether these nodules are hyperplastic or neoplastic has not been determined definitively. Aihara et al (1994) undertook clonal analysis of regenerative nodules (n=76) and HCC (n=7) induced by HCV infection. All carcinomas were monoclonal. Clonal analysis of regenerative nodules showed that 43% (33/76) were monoclonal in origin. Adjacent monoclonal nodules showed inactivation of the same allele of the phosphoglycerokinase gene. Because the gene allele is inactivated at random, it is unlikely that each nodule happens to inactivate the same allele; it is more likely that monoclonal cell expansion is initiated before the nodule is established by septum formation. The authors conclude that monoclonal cell expansion is seen in many regenerative nodules in cirrhotic liver, indicating that certain genetic changes have already occurred in these nodules.

Australian studies

There are few reports on HCC from Australia since the advent of testing for HCV. Brotodihardjo et al (1994) from Westmead Hospital in Sydney, Australia, undertook a retrospective case-record review of clinical features of all (122) patients discharged from their 900-bed tertiary-referral teaching hospital with a diagnosis of HCC from January 1979 to March 1993. They aimed to examine the incidence of HCC in western Sydney over this period, assess risk factors for the disease, and to consider the opportunities for improving HCV's usually poor outcome. They reported that the number of cases admitted each year at least doubled between 1979-85 and 1986-92, an apparent increase affecting individuals born in Australia (50% of all patients) as well as immigrants. Cirrhosis was found in 93 per cent at liver biopsy or autopsy. Excessive alcohol intake was an associated risk factor for 46 per cent of Australian-born patients and for 13 per cent of those born in other countries. Among the latter, HCC was associated with markers of HBV infection in 64 per cent. Since HCV tests became available in 1990, five of nine patients tested were anti-HCV positive. Screening of patients known to have cirrhosis detected eight cases of early

HCC. The authors concluded that in Australian-born patients, alcoholic liver disease remains a major aetiological factor and that the role of HCV requires further evaluation. Among immigrants, cirrhosis from chronic viral hepatitis accounts for most cases. The authors suggested that prevention of cirrhosis caused by chronic viral hepatitis should have the greatest long-term effect on prevention of HCC in Australia.

A Victorian study aimed to assess the prevalence of previously identified risk factors for liver disease and infection with HBV and HCV in people with HCC recorded by state-based cancer surveillance (*Victorian Cancer Registry*) and the feasibility of retrospective surveys in determining risk factors for HCC (Thompson et al 1997). A retrospective mailed survey was undertaken of doctors notifying cases of HCC diagnosed in 1991 and 1992. The study documented the high contribution of alcohol to HCC, particularly in Australian-born men. Low rates of testing for HBV and particularly HCV at that time make interpretation of their contribution to HCC uncertain; no cases of HCC due to HBV or HCV were reported in Australian-born patients. Higher rates of HBV carriage in those tested were found in Asian and Mediterranean immigrants. Testing for HCV was known to have occurred for less than one-quarter of subjects and assessment for multiple aetiological risk factors was very uncommon. The authors concluded that the epidemic of HCV necessitates improved surveillance for the sequelae of long-term infection. Alternative approaches to ongoing surveillance require cooperation from clinicians and adequate resources for State cancer registries to supplement the existing passive reporting system with data on exposure.

Screening strategies for early detection of hepatocellular carcinoma

The prognosis for patients with HCC is poor. The five-year survival rate in patients who present with abdominal pain and weight loss is less than 5 per cent, with mean survival measured in months (Wands and Blum 1991). Studies have been undertaken in some countries with a high incidence of HCC to establish screening strategies for early detection of HCC in an attempt to improve prognosis. Screening can be broadly divided into population-based and clinic-based approaches; population-based screening programs have been successful in Japan, China and the USA (Alaska); whereas clinic-based screening has been more relevant in Europe and other parts of the USA (Wands and Blum 1991). Regular ultrasonography and measurement of tumour markers (serum αFP or abnormal prothrombin) are screening tests, and may be supplemented by tests such as CT, magnetic resonance imaging, celiac angiography and CT with angioportography when a tumour is suspected. HCC larger than 2 cm in diameter show a higher frequency of vascular invasion and a higher recurrence rate after resection, so the emphasis is on early detection before vascular invasion (Unoura et al 1993). It has not yet been confirmed in controlled trials that screening has a beneficial effect on survival (Colombo et al 1991a; Sallie and Di Bisceglie 1994), and screening programs in patients with chronic hepatitis are hampered by a significant false-positive detection of HCC.

Treatment of hepatocellular carcinoma

The treatment of hepatitis-related HCC is unsatisfactory, and made more difficult because most cases occur in patients with cirrhosis, meaning patients tolerate surgery poorly. Only a minority of cases are suitable for surgical resection, but this may improve survival in those with small, unifocal lesions. Systemic chemotherapy is generally ineffective, with survival not being improved significantly over conservative management. Intra-arterial chemotherapy with or without chemoembolisation has a reduced risk of toxicity related to chemotherapeutic agents. Injection of pure ethanol into the tumour causes necrosis of the tumour; although this technique is restricted to tumours less than 3 cm in diameter. Liver transplantation is an option but, unfortunately, limited by availability of suitable donors, and the recurrence of HCV in grafts including severe hepatitis in some.

The prevention of virus-related HCC can be summarised (Sherlock 1994):

- universal vaccination against HBV;
- screening blood donors;
- changing life styles, responsible alcohol consumption;
- use of sterile syringes and needles; and
- anti-viral treatment to prevent cirrhosis.

5.6 Hepatitis C virus and alcohol

Both HCV and alcohol are major causes of liver disease, serious morbidity, and mortality in various populations worldwide. It is important to understand how these two factors interact. There has been no suggestion that HCV infection increases the likelihood of high alcohol intake. However, there is strong circumstantial evidence that high alcohol intake increases the likelihood of HCV infection and disease. Several questions arise in relation to HCV and alcohol, as discussed in the following sections.

5.6.1 Association of hepatitis C virus infection and alcohol intake

Ideally, we would like to observe the incidence of HCV in a population-based sample of people in which an accurate measure of alcohol intake over an extended period of time is recorded. There have been studies that have attempted an approximation of this ideal from Portugal (Santos et al 1994) and Japan (Lin Chu et al 1990; Shinzawa et al 1991). The Portuguese study demonstrated the difficulty of this approach, since the absolute numbers of HCV-positive individuals was very small (3/659), as was the number of high-alcohol-intake individuals, and observing sufficient numbers of HCV-positive high-alcohol-intake individuals in order to meaningfully estimate the incidence would require a sample size very much larger. A population-based survey in Japan (n=618) was performed in districts known to have a high rate of liver disease, and HCV-positive rates in the two towns surveyed were 16.6 and 3.7 per cent (Shimizu et al 1992). The differences in the incidence of HCV-positivity could not be explained by differences in alcohol intake. The second study (n=4,491) was undertaken in people older than 35 in one town in Japan having routine health examinations, and 79 per cent of the eligible population was examined during the study. Liver dysfunction was observed in 9.8 per cent of the population, and 36.1 per cent of this group were HCV-positive (Shinzawa et al 1991).

A more common approach to the problem of estimating the rate of HCV infection in the general community and in those with high alcohol intakes is to use convenience samples: the incidence in blood donors in a geographical area compared to the incidence in a secondary-referral clinic or hospital for those being treated for the adverse effects of high alcohol intake (Caldwell et al 1991; Blackmore et al 1992). In both instances, the patients with high alcohol intakes already had alcoholic liver disease as an entry criterion. More often, the researchers simply assume that the rate of HCV infection in the general population is very low. No studies compared patients with high alcohol intakes but no liver disease, with a healthy control population. The studies were all cross-sectional observations.

Despite the shortcomings of the studies, most published observations demonstrated a markedly raised prevalence of evidence of HCV infection in those with high alcohol intake (table 44, see *Tables* section). The reported prevalence of antibodies to HCV was 12 per cent in European and American studies in patients being treated for the adverse effects of high alcohol intake without known alcoholic liver disease or only mild histological changes. The similar prevalence in Japan was 22 per cent. However, several studies did not examine the liver histology, and people with occult cirrhosis may have been included in these groups. In Northern Europe, the prevalence of HCV antibodies in those with severe liver disease and HCC was 12 per cent, in France 32 per cent, in Italy and Spain 36 per cent, in USA 18 per cent, and in Japan 65 per cent. This demonstrates that HCV infection is a common problem in people

with alcoholism, particularly in Japan and Southern Europe, and raises the question of increased susceptibility of people with alcoholism to HCV infection.

It is clear that IDUs in many countries have high prevalences of HCV infection. Users of one type of drug are frequently users of multiple drugs including alcohol, either concurrently or sequentially. Thus, some people with high alcohol intakes have been IDUs, and this may account in some instances for the high rate of HCV in people with alcohol abuse problems in the USA (McHutchison et al 1992; Caplan et al 1995; Mendenhall et al 1993b), Sweden (Bell et al 1992; Verbaan et al 1993), Japan (Ishii et al 1992) and France (Jiang et al 1995). The association may be valid in other countries also, but may not have been thoroughly investigated because of the difficulties of gaining accurate histories of past IDU. Other forms of parenteral transmission, such as tattooing, may be associated with high alcohol intake (Ishii et al 1992). High alcohol intake can be associated with violent behaviours and also with medical interventions such as blood transfusion following haematemesis, both of which could increase exposure to HCV.

An additional explanation for the association of high alcohol intake and HCV infection may be a methodological bias: when high alcohol intake and HCV infection occur in the same person, the rate of progression of liver disease may be higher (see section 5.6.2), and therefore those people may be more likely to be included in the clinic-based prevalence studies than people with only high alcohol intake or HCV infection or neither. Population-based incidence studies which include the subpopulations at risk of high alcohol intake and HCV are required in order to measure the magnitude of this effect

5.6.2 Effect of hepatitis C virus and high alcohol intake

Most studies that attempt to establish the effects of hepatitis C virus and high alcohol intake have made cross-sectional observations in specialist clinics serving people with the adverse effects of high alcohol intake, usually alcoholic liver disease. The greater the degree of liver disease in these people, the higher the prevalence of HCV-infection markers. The studies reported provide considerable circumstantial evidence that the presence of HCV infection is associated with increased severity of liver disease in people with high alcohol intake. Combining the results of the studies (tables 45 to 47) indicates an increased risk of liver disease in people with high alcohol intakes with HCV infection (OR 5.8, 95% CI 3.6, 9.4), increased risk of cirrhosis in those with alcoholic liver disease and HCV infection (OR 3.4, 95% CI 2.1, 5.5), and increased risk of HCC in those with alcoholic cirrhosis and HCV infection (OR 2.5, 95% CI 1.5, 4.2). A multivariate analysis of risk factors in HCC demonstrated that alcohol consumption and HCV infection were independent predictors of the disease. The calculations need to be treated with caution, since they are based on potentially biased populations of uncertain origin. However, they provide support for more definitive studies being performed in order to investigate the interaction of HCV and alcohol on the development of liver disease.

Table 45 Effect of hepatitis C virus infection on risk of liver disease in people with high alcohol intakes

Reference	Disease present		Disease absent		*n*	OR	Lower CI 95%	Upper CI 95%
	Exposure present	Exposure absent	Exposure present	Exposure absent				
Caldwell et al (1993)	10	24	12	36	82	1.25	0.42	3.74
Chang et al (1994a)	37	86	1	43	167	18.50	2.88	767.3
Coelho Little et al (1995)	17	23	6	54	100	6.65	2.12	22.9
Pares et al (1990)	36	59	1	44	140	26.85	4.1	1114
Shimizu et al (1992)	14	60	5	116	195	5.41	1.72	20.0
Combined	114	252	25	293	684	5.8	3.27	9.2

Table 46 Effect of hepatitis C virus infection on risk of cirrhosis in people with alcoholic liver disease

Reference	Disease present		Disease absent		*n*	OR	Lower CI 95%	Upper CI 95%
	Exposure present	Exposure absent	Exposure present	Exposure absent				
Gonzalez Quintela et al (1995)	11	55	1	77	144	15.40	2.09	671.2
Pagani et al (1994)	28	50	17	79	174	2.60	1.23	5.6
Pares et al (1990)	26	35	10	24	95	1.78	0.67	4.82
Shimizu et al (1992)	14	25	1	35	75	19.60	2.6	851.8
Combined	79	165	29	215	488	3.41	2.05	5.8

Table 47 Effect of hepatitis C virus infection on risk of hepatocellular carcinoma in people with alcoholic cirrhosis

Reference	Disease present		Disease absent		*n*	OR	Lower CI 95%	Upper CI 95%
	Exposure present	Exposure absent	Exposure present	Exposure absent				
Pagani et al (1994)	32	23	28	50	133	2.48	1.15	5.4
Shimizu et al (1992)	14	10	14	25	63	2.50	0.78	8.1
Zarski et al (1993)	9	15	4	16	44	2.40	0.52	12.8
Combined	55	48	46	91	240	2.50	1.39	4.4

5.6.3 Effect of abstinence from alcohol in people with hepatitis C virus infection

This question has not been thoroughly addressed. One Japanese study demonstrated a fall in viral RNA levels following in-hospital complete abstinence in patients with alcoholism infected with HCV (Sawada et al 1993). One patient who resumed drinking alcohol showed subsequent rises in HCV-RNA levels. The implication of this observation was that alcohol enhanced HCV replication, although it is possible that the effect was a reduction in release of viral particles rather than reduced production. In people with alcoholic liver disease without evidence of HCV infection, the levels of liver enzymes in the blood fall rapidly following abstinence from alcohol intake, whereas in those people with alcoholic liver disease and HCV infection, normalisation of liver enzyme levels is slower and less complete (Ishii et al 1993; Matsuda et al 1993; Nagata et al 1993; Yokoyama et al 1995). Removal of the main toxic influence on the liver in the former group leads to fall in liver-damage markers, whereas this is less complete when a second toxic influence is present. Nevertheless, improvement in markers of liver damage occurs when people with alcoholic liver disease and HCV infection abstain from alcohol consumption.

Histological improvement as measured by repeat liver biopsy was observed to occur more commonly after alcohol abstinence or reduced intake in people with alcoholic liver disease with HCV infection, although a minority of patients deteriorated despite abstinence (Yoshida et al 1991). Another study confirmed this, and showed that improvement in histology was greatest in those with fewest markers of HCV infection (Ishii et al 1993). These observations would be consistent with various levels of toxic activity of both alcohol and HCV infection producing a range of interactions. These observations suggest that abstinence from alcohol intake reduces progression of liver damage in HCV-infected people.

However, very few studies have been performed, and of these, almost all have been performed in Japan. No studies have been published that directly measure the therapeutic effectiveness of abstinence from alcohol on clinical end-points. The influence of alcohol on the effectiveness of IFN therapy has not been investigated. Thus, although there is a therapy available that might reduce the effect of HCV infection on mortality and morbidity from liver cirrhosis and HCC that has not been thoroughly investigated in long-term follow-up, there should be an unwillingness to recommend a change in lifestyle that might cause additional stress and social disruption to an infected person, if that alcohol abstinence proves to have no influence on health outcomes in people with alcoholic liver disease and HCV infection. It is important that the effect of abstinence on long-term outcomes should be investigated. An even more important question is whether there is any benefit in abstaining from alcohol in HCV-infected individuals whose alcohol consumption is light or moderate.

5.7 Extrahepatic manifestations of hepatitis C virus infection

Gumber and Chopra (1995) reviewed the extrahepatic manifestations of HCV infection identified by mid 1995. They identified conditions where strong evidence for an association exists of a direct pathogenic effect of HCV (essential mixed cryoglobulinaemia, Willems et al 1994), membranoproliferative glomerulonephritis and porphyria cutanea tarda), conditions where good evidence of an association exists but which falls short of proof of pathogenic effect of HCV (Mooren corneal ulcers and autoimmune thyroiditis), and conditions where evidence suggests the possibility of an association with HCV (the Sjögren syndrome, lichen planus and idiopathic pulmonary fibrosis).

A common feature of most of these conditions is that they represent abnormal immune-system activity. HCV is found in peripheral monocytes of most people chronically infected with HCV (Zignego et al 1995). In addition, 36 to 54 per cent of people with HCV CLD are reported to have cryoglobulins that precipitate HCV antigens (Pawlotsky et al 1995a). These cryoglobulins consist of either a monoclonal antibody (type II) or polyclonal antibodies (type III) complexed with anti-Ig(G or M) antibodies, which precipitate when cooled. The cryoglobulins bind and concentrate

HCV virions in the blood. Precipitation of the cryoglobulins in different tissues can lead to skin lesions, vasculitis, peripheral neuropathy, myopathy, and autoimmune hepatitis, among others. About 20 per cent of people with HCV-associated cryoglobulinaemia have symptoms, typically a triad of purpura, weakness and arthralgia. Cryoglobulinaemia is also associated with non-Hodgkin's lymphoma (Pioltelli et al 1996; Zignego et al 1996) and membranoproliferative glomerulonephritis (Pozzato et al 1994b).

Thus, chronic HCV infection can infect both liver and immune cells. The ongoing presence of virus stimulates the immune system including B-cells leading to large quantities of HCV antibodies being produced, which themselves become antigenic targets for antibody production. Neoplastic change can occur in the B-cell lines. This process is likely to progress slowly over years or decades, so the possibility of HCV infection may be overlooked by patient and doctor. The patient may eventually present in many different ways, and there is the danger that the underlying diagnosis of HCV infection is missed, delaying specific therapy and risking cross-infection to other patients using the same health facilities. In particular, patients in whom membranoproliferative glomerulonephritis is the dominant presentation may progress to renal failure and be placed on dialysis, risking cross-infection of other dialysis patients unless scrupulous infection control is practiced. Alternatively, people who present with arthralgias and myopathy may be treated with surgery, local steroid injection or acupuncture, with the risk of transmission to others.

5.8 Paediatric hepatitis C virus infection

In adults, HCV is known to be transmitted through parenteral exposure, primarily through receipt of blood or IDU in about 50% of cases (Alter 1994; Alter 1995a). Other cases of HCV infection, without a reported source of parenteral exposure to HCV, are so-called 'sporadic cases' of HCV infection. The possibility of sexual transmission has been suggested for sporadic cases. The extent to which parenteral exposure and community-acquired HCV infection contribute to HCV infection in children is not known. The outcome of chronic HCV infection in children is also not well described (Doherty 1993).

5.8.1 Prevalence of hepatitis C virus infection in children

Prevalence of HCV infection is low in children without parenteral risk factors for HCV infection (table 48, see *Tables* section). HCV seroprevalence measured by second-generation EIA in school children in Brazil, Italy, Japan and Taiwan indicated that HCV seroprevalence was less than 0.5 per cent. HCV seroprevalence among children transfused during surgery or with orthotopic liver transplantation was much higher than that in children without parenteral risk factors. In Taiwan, HCV seroprevalence was 4 per cent among children transfused during open heart surgery, prior to the introduction of HCV-antibody screening of blood donors. The highest HCV seroprevalence was recorded among multiply-transfused children such as children with thalassaemia or haemophilia or in children surviving malignant disease. In two studies carried out in Italy, HCV seroprevalence among thalassaemic children was about 55 per cent whereas among children with haemophilia in Canada and Australia, HCV seroprevalence was 63 and 74 per cent, respectively. Among children with NANBH and without underlying conditions which may contribute to liver disease, HCV seroprevalence ranged from 36 per cent in Taiwan to 74 per cent in children in Italy. In almost all children with HCV infection, a history of parenteral exposure to HCV was documented.

5.8.2 Natural history of hepatitis C virus infection in children

A few papers have described aspects of the natural history of HCV infection over a relatively short time (table 49, see *Tables* section). Although about 60 per cent of children appeared to progress to chronic HCV infection, measured by persistent elevation of ALT, limited evidence of liver damage was available for most children. Children with thalassaemia had the highest rate of cirrhosis but this may be due to treatment and immunological factors.

5.8.3 Interferon treatment in children with hepatitis C virus infection

In three small studies, IFN treatment in children appeared to be effective in limiting progression to more advanced liver disease (table 50, see *Tables* section). However, further studies need to be carried out to confirm these results.

HCV infection is rare in children except for those with parenteral exposure to HCV. Although the available studies of the natural history of HCV infection in children were limited by the small numbers of children included and the relatively short duration of follow-up, they suggest that in most children, HCV infection is chronic but severe active hepatitis and cirrhosis were rare.

5.9 Coinfections

5.9.1 Coinfection with hepatitis B virus

There is a complex relationship between HBV and HCV which, in terms of pathogenesis, is explored elsewhere in this report. Interaction with acute infection is also complex. Acute HCV infection can enhance the clearance of HBsAg in those chronically infected with HBV (Sheen et al 1994). Acute HBV/HCV coinfection may inhibit the development of chronic HBV infection, whereas the onset of HBV infection may reduce the severity of HCV infection but not its progression to chronicity (Mimms et al 1993). And in a study of people with cirrhosis, 80 per cent had evidence of both HBV and HCV exposure, although most were negative for HBsAg (Villa et al 1995b).

As discussed elsewhere, although HBV and HCV seem to inhibit each other at the molecular level (Francois et al 1994; Ohkawa et al 1994), they seem also to enhance each others' cytopathic effects (Alberti et al 1995). For instance, concurrent HBV and HCV infection confers the greatest risk of HCC (Bertorp 1994).

5.9.2 Coinfection with human immunodeficiency virus

HIV and HCV share similar routes of transmission so individuals at risk of contracting one virus are at risk of the other. Prevalence of HCV in those with HIV varies according to exposure risk. In IDUs, prevalence of HCV in those who are HIV infected ranges from 52 to 95 per cent (Quan et al 1993; Francisci et al 1995). In homosexual or bisexual men, who do not inject drugs, the prevalence ranges from 0 to 12 per cent (Quan et al 1993; Wright et al 1994b).

HCV infection of a person already infected with HIV can lead to a prolonged and/or increased HCV viraemia. For instance, Horvath and Raffanti (1994) found that HCV RNA was quantifiable in 79 per cent of HIV-infected, HCV-seropositive IDUs compared with only 43 per cent of HIV-uninfected; Cribier et al (1995) found mean HCV-RNA levels to be much higher in HIV coinfected people than in those with only HCV infection.

One possible result of this effect is that transmission of HCV from coinfected people may be more efficient. Lissen et al (1993) examined the stable heterosexual partners of index cases who were either HIV/HCV coinfected or only HCV infected, and found that HCV prevalence was 2.2 times higher in the partners of the coinfected than in those infected by HCV alone. Their conclusion was that the efficiency of sexual transmission of HCV is enhanced by concurrent HIV infection.

However, there is some evidence that HIV infection has a deleterious effect both on immune response to HCV and, as a result, on serological diagnosis of HCV exposure. Several studies have found higher rates of indeterminate reactivity to HCV antibody in those with HIV infection than in those without. For example, in one study of people all of whom were HCV-PCR positive, 14.7 per cent of those with HIV infection were seronegative or indeterminate compared with only 4 per cent of those without HIV (Cribier et al 1995).

The effect of HIV/HCV coinfection on pathogenesis and disease progression is still not fully understood. HCV does not appear to adversely influence survival in, or severity of, HIV infection (Quan et al 1993; Wright et al 1994a,

1994b). One study found an inverse relationship between CD4 count and the severity of liver damage, suggesting immunomediation is important in the process of hepatic damage caused by HCV (Guido et al 1994).

There appears to be an increase in the incidence of liver disease in coinfected individuals (Sanchez-Quijano et al 1995; Soto et al 1997). Telfer (1994) reported that the risk of HCV-infected people with haemophilia developing hepatic decompensation after 20 years was 10.8 per cent, and in HCV/HIV-infected individuals the risk increased 21-fold. The authors conclude that HIV infection in those with HCV accelerates progression to cirrhosis and hepatic decompensation, and speculate that this is probably due to enhanced HCV replication in the presence of immune deficiency. Eyster et al (1993) report on a cohort of people with haemophilia. In those coinfected, 9 per cent had liver failure after 10 years of HCV infection compared to 0 per cent in those infected only with HCV. In a UK cohort of coinfected people with haemophilia, Martin (1989) reports that 18 per cent of deaths were due to liver failure and 44 per cent developed cirrhosis over 12 years. This is significant as the expected prevalence of cirrhosis in mono-infected subjects should be 10 to 20 per cent (Seeff 1997) and mortality due to HCV-related liver disease in people with haemophilia infected only with HCV is uncommon (Eyster et al 1993).

The hypothesis for the more severe liver disease seen in coinfected individuals has been well documented, that is, progressive HIV-induced immunosuppression giving rise to an increase in HCV replication which correlates with increased liver damage (Beld et al 1998a). Sherman et al (1993) reported that whereas HCV-RNA levels increased four-fold in those who were HIV negative, they increased 58-fold during the same time period in coinfected subjects. The same study also showed a significant correlation with declining CD4 T cell counts and raised ALT levels.

6 Treatment

6.1 Therapy for hepatitis C virus infection

6.1.1 Interferon therapy in the management of hepatitis C virus infection: efficacy, predictors of response and effect on natural history

Although some people with chronic HCV infection develop a sustained response following IFN therapy, the proportion of responders, factors predictive of response and optimal therapeutic regimes need to be clarified. Of even greater importance is whether IFN therapy can alter favourably the natural history of HCV infection (Terrault and Wright 1995a).

This section summarises information on the efficacy of IFN therapy in the management of acute and chronic HCV infection, including factors predictive of response. It also explores the question of the effect of therapy on the natural history of HCV infection, and outlines further areas for research.

Information abstracted from published reports included type of trial, number of participants, inclusion and exclusion criteria, baseline characteristics including liver histology, type, dose and duration of IFN therapy, initial, complete and sustained response rates, and predictive factors for response. Studies were broadly divided into randomised and nonrandomised trials.

6.1.2 Interferon therapy for chronic hepatitis C virus infection

Inclusion criteria among published trials were similar. These included elevated ALT levels (1.5-2 times greater than normal) for more than six months, age greater than 18 years, and anti-HCV except for early studies among patients with NANBH. Liver biopsies to document chronic hepatitis were performed on most study participants. Exclusion criteria were also remarkably standard including presence of HBsAg, HIV antibody, evidence of other CLD, current drug or high alcohol intake, decompensated cirrhosis, pregnancy, and several biochemical and haematological parameters. In addition to patients with CPH and CAH, most studies included patients with compensated active cirrhosis.

Recombinant IFN-α2a was the predominant formulation of IFN, although recombinant IFN-α2b and natural IFN-α were used in some trials. Earlier trials of IFN efficacy among persons with NANBH and HCV infection included a control or placebo arm, but, in later randomised trials, dose and duration of IFN therapy were compared.

Randomised controlled trials demonstrated a clear benefit (based on normalisation of ALT level) of IFN therapy, with complete response (normal ALT level at completion of therapy) rates of 38 to 69 per cent and sustained response (normal ALT level 6-12 months posttherapy) rates of 19 to 40 per cent in trials where 3 million units (MU) or more of IFN were used, compared with no significant response among control patients (table 51) (Davis et al 1989; Di Bisceglie et al 1989; Diodati et al 1994a; Fernandez et al 1995; Rumi et al 1995). IFN doses of 2 MU or less gave sustained response rates of 10 per cent or lower (Davis et al 1989; Douglas et al 1993). Subsequent randomised studies that compared IFN regimes of different doses and duration produced complete response rates of 27 to 70 per cent, with sustained response rates of 8 to 49 per cent (table 51) (Alberti et al 1993; Attili et al 1994; Caporaso et al 1993; Chemello et al 1995a; Negro et al 1995; Poynard et al 1995). These studies also appeared to demonstrate improved response for longer durations (12-18 months) (Chemello et al 1995a; Poynard et al 1995) and higher doses (6 v. 3 MU) (Caporaso et al 1993; Chemello et al 1995a) of IFN therapy.

Table 51 Randomised trials of the efficacy of interferon therapy for treatment of chronic hepatitis C virus infection

Country	Reference	No. of subjects	Therapy	IR[A]/CR[B] (%)	SR[C] (%)	Comments
France	Poynard et al (1995)	*n*=303 CPH/CAH (*n*=225) CIRR[D] (*n*=75)	IFN-α2b (1) 3 MU[E] 6/12 (2)1-3 MU 18/12* (3) 3 MU 18/12	 38/30 41/27 49/45	 8 10 22	 Histological improvement (at 18/12): 39% (1), 48% (2), 70% (3) *3 MU 6/12 then 1 MU 12/12 Randomisation occurred at 6/12
Italy	Alberti et al (1993)	*n*=234 CPH (*n*=66) CAH (*n*=119) CIRR (*n*=49)	IFN-α2a 3-6 MU 12/12* 3 MU 12/12 6 MU 6/12 IFN-α (natural) 3 MU 6/12	 70/67 58/53 70/70 56/56	 44 27 33 12	 SR: CPH 33%; CAH 35%; CIRR 9.5% * 6 MU 6/12, 3 MU 6/12 86% +ve anti-HCV antibody
Italy	Attili et al (1994)	*n*=62 CAH	IFN-α2a 3 MU 3/12 3 MU 6/12	 63 63	 10 30	
Italy	Caporaso et al (1993)	*n*=81 CAH/CIRR	IFN-α2a 3 MU 6/12 6 MU 6/12	 50 64	 28 41	 CR: CAH 68%; CIRR 32%
Italy	Diodati et al (1994a)	*n*=60 CAH (n=60)	IFN-α2a 1-6 MU 12/12* Controls	 67 /47 3/3	 27 3	 Histological improvement : 28% at 18/12 * 6MU 1/12, 3MU 3/12, 1MU 8/12
Italy	Negro et al (1994)	*n*=135 CPH (*n*=44) CAH (*n*=71) CIRR (*n*=18)	IFN-α2a 6 MU 9/12 6 MU 3/12 x 2*	 46 47	 17 10	 14/14 SRs tested -ve HCV-RNA * 2 3/12 cycles separated by 6/12 with no therapy
Italy	Rumi et al (1995)	*n*=67 CPH (*n*=21) CAH (*n*=30) CIRR (*n*=23)	IFN-α2a (Rof) 3-6 MU 12/12* Controls	 69 0	 40 6	 Histological improvement: IFN, 80%; controls, 32% 8/14 CRs -ve HCV-RNA (23% CR) ALT normal + HCV-RNA-ve: CPH 40% (4/10); CAH 29% (4/14); CIRR 0% (0/11) * 6MU 2/12, 3MU 10/12
Japan	Yokosuka et al (1995)	*n*=66 CPH/CAH (*n*=61) CIRR (*n*=5)	IFN-α2a 3 MU 12/12 3 MU 2/12 Placebo 2/12	 67* 32 4	 67* 4 4	 *57% (12/21) HCV-RNA -ve
Spain	Fernandez et al (1995)	*n*=148	IFN-α2a 6 MU 12/12 IFN-α2b 5 MU 12/12 Controls	63 57 0	 25 19 0	

Table 51 continued next page

Country	Reference	No. of subjects	Therapy	IR[A]/CR[B] (%)	SR[C] (%)	Comments
USA	Davis et al (1989)	*n*=166 CPH (*n*=27) CAH (*n*=41) CIRR (*n*=83)	IFN-α2b 3 MU 6/12 1 MU 6/12 Controls	 38 16 4	 19 8	 Histological improvement : 3 MU=52% (24/46); 1 MU=29% (14/48)
USA	Di Bisceglie et al (1989)	*n*=41 CPH (*n*=3) CAH (*n*=31) CIRR (*n*=7)	IFN-α2b 2 MU 6/12 Placebo 6/12	 62/33 15/5	 10	 Histological improvement: 90% (40% among placebo group)
USA	Douglas et al (1993)	*n*=32 CPH (*n*=4) CAH (*n*=15) CIRR (*n*=10)	IFN-α2a 1.5 MU 6/12 Controls	 25 6	 6	 HCV-RNA -ve in 43% of CRs

[A]IR=normal ALT level during therapy.
[B]CR=normal ALT at completion of therapy.
[C]SR=normal ALT 6/12-12/12 following therapy completion.
[D]CIRR=cirrhosis.
[E]MU=million units of interferon: regimes given three times per week unless otherwise stated

Nonrandomised studies have been limited by the combination of patients treated with different IFN regimes and the relative lack of follow-up; three studies provided no information on sustained response rates. Complete response rates varied from 31 to 69 per cent, while sustained response in those studies with available information ranged from 22 to 41 per cent (table 52).

Table 52 Nonrandomised trials of the efficacy of interferon therapy for treatment of chronic hepatitis C virus infection

Country	Reference	No. of subjects	Therapy	IR[A]/CR[B] (%)	SR[C] (%)	Comments
France	Pawlotsky et al (1994)	*n*=36	IFN-α2a 3 MU[E] 6/12	47/33		10/12 CRs had negative HCV-RNA at 6/12
Italy/Japan	Pozzato et al (1995)	*n*=57 CPH/CAH /CIRR [D]	IFN-α2a 3-6 MU 6/12*	53	30	6 MU 1/12, 3 MU 5/12[A]
Japan	Aiyama et al (1994)	*n*=65 CAH	IFN-α2a IFN-α, IFN-β 3-10 MU 3/12-6/12	75	41	20% -ve HCV-RNA 6/12 posttherapy
Japan	Kanai et al (1992)	*n*=96	IFN-α2a 3 MU 6/12*	31		First week 6 MU daily[A] CR: Genotype II(1b) 20%; III(2a) 67%; IV (2b) 33%
Japan	Kanai et al 1995	*n*=126	IFN-α2a 3 MU 6/12*	50		First week 6 MU daily[A] HCV-RNA negativity at 6/12=33% CR (HCV-RNA -ve): genotype II(1b) 20%; III (2a) 69%; IV (2b) 25%
Japan	Orito et al (1994)	*n*=55 CAH	IFN-α2a 6-9 MU 6/12*	69	22	9 MU daily 2/52, 6 MU x3/week 22/52[A]
Japan	Urushihara et al 1994	*n*=31	IFN-α2a	81	35	10/11 SRs -ve HCV-RNA
Japan	Yoshikawa et al (1994)	*n*=156 CPH (*n*=20) CAH 2a (*n*=96) CAH 2b (*n*=40)	IFN-α2a 9 MU or IFN-α (natural) 3 MU 6/12	69	28	SR: CPH 35%; CAH 2a 35%; CAH 2b 5%

[A]IR=normal ALT level during therapy.
[B]CR=normal ALT at completion of therapy.
[C] SR=normal ALT 6/12-12/12 following therapy completion.
[D]CIRR, cirrhosis.
[E]MU=million units of interferon: regimes given three times per week unless otherwise stated;

In studies where HCV-RNA detection by PCR was performed, response rates based on clearance of HCV viraemia were generally lower compared with rates based on normalisation of ALT (Aiyama et al 1994; Negro et al 1994; Chemello et al 1995c; Kanai et al 1995; Yokosuka et al 1995). One study that produced a sustained response of 41 per cent based on a normal ALT six months posttherapy gave a sustained response of 20 per cent when HCV-RNA negativity was included in the definition (Aiyama et al 1994).

In contrast, a response classified on the basis of histological improvement noted on repeat liver biopsy tended to be higher than that based on ALT normalisation, with improvement of between 48 and 90 per cent at completion of

therapy (Davis et al 1989; Di Bisceglie et al 1989; Chemello et al 1995a; Poynard et al 1995; Rumi et al 1995). However, in the two studies where control or placebo participants underwent repeat liver biopsies, histological improvement was also seen in 32 to 40 per cent (Di Bisceglie et al 1989; Rumi et al 1995).

6.1.3 Predictors of response to interferon therapy

The strongest predictors of response to IFN therapy appear to be HCV genotype and baseline HCV-RNA level (table 53). The poor response to genotype 1b (II) has been demonstrated in several studies (Aiyama et al 1994; Chemello et al 1995c; Poynard et al 1995; Pozzato et al 1995), whereas the benefit of lower HCV viraemia (baseline HCV-RNA level, table 53) in promoting response also appears significant (Aiyama et al 1994; Yoshikawa et al 1994; Kanai et al 1995; Negro et al 1995; Yokosuka et al 1995). Other factors which may be important are age, disease duration and liver histology, with younger age, shorter duration of disease and absence of cirrhosis appearing to predict improved response. Factors which appear not to influence response to IFN therapy are gender, HCV exposure category, and baseline ALT level (table 53).

Table 53 Studies showing possible predictive factors for response to interferon therapy in treatment of chronic illness caused by hepatitis C virus

Predictive factors	References supportive	No association	Higher response
Age	Chemello et al (1995c), Piccinino et al (1993), Poynard et al (1995)	Aiyama et al (1994), Pozzato et al (1995), Saracco et al (1993)	Younger age
ALT level (baseline)	Pozzato et al 1995	Aiyama et al (1994), Di Bisceglie et al (1989), Kanai et al (1995), Saracco et al (1993)	
Anti-HCV core IgM	Negro et al (1995), Pawlotsky et al (1994)		Absent IgM
Disease duration	Chemello et al (1995c), Fernandez et al (1995), Par et al (1995)		Shorter duration
Dose of IFN therapy	Davis et al (1989) (3 v. 1 MU)	Aiyama et al (1994)	Higher dose
	Chemello et al (1995a) (6 v. 3 MU)	Alberti et al (1993) (3 v. 3-6 MU)	
	Caporaso et al (1993) (6 v. 3 MU)	Aach et al (1991)	
	Enriquez et al (1995) (10 v. 5 MU)	Lin et al (1995) (3 v. 5 MU)	
Duration of IFN therapy	Chemello et al (1995a) (12/12 v. 6/12)	Craxi et al (1992) (12/12 v. 6/12)	Longer duration
	Yokosuka et al (1995) (12/12 v. 2/12)		
	Poynard et al (1995) (18/12 v. 6/12)		
	Saracco et al (1993) (12/12 v. 6/12)		
	Aucella et al (1995) (6/12 v. 3/12)		
	Lin et al (1995) (24/12 v. 6/12)		
Exposure category		Aiyama et al (1994), Kanai et al (1995), Pozzato et al (1995), Saracco et al (1993)	
Gender	Par et al (1995)	Aiyama et al (1994), Alberti et al (1993), Chemello et al (1995c), Kanai et al (1995), Piccinino et al (1993), Pozzato et al (1995), Saracco et al (1993)	

Table continued overleaf

Predictive factors	References supportive	No association	Higher response
HCV genotype	Chemello et al (1995c) (2, 3) Orito et al (1994) (serotype II) Pozzato et al (1995) (I,III,IV) Aiyama et al (1994) (III) Poynard et al (1995) (non-1b) Kanai et al (1992) (III)		Non-1b (II) genotype
HCV-RNA level (baseline)	Aiyama et al (1994), Kanai et al (1995), Negro et al (1995), Yokosuka et al (1995), Yoshikawa et al (1994)		Low HCV-RNA level
Liver histology	Aiyama et al (1994), Alberti et al (1993), Caporaso et al (1993), Lin et al (1995), Piccinino et al (1993), Poynard et al (1995), Rumi et al (1995), Saracco et al (1993), Yoshikawa et al (1994)	Chemello et al (1995c), Kanai et al (1995), Pozzato et al (1995), Reichard et al (1994)	Noncirrhosis, less severe CAH
Neutralising anti-IFN antibodies	Diodati et al (1994b)		Absence of anti-IFN antibodies
No. of HCV genotypes	Villa et al (1995a)		Single genotype
Serum iron level	Archer et al (1992)		Lower serum iron
Type of IFN	Chemello et al (1995c) (rec.v. nat)	Aiyama et al (1994) (α v. β)	Recombinant

Table 53 continued overleaf

6.1.4 Interferon therapy for acute hepatitis C virus infection

Randomised controlled trials of IFN therapy in acute HCV infection (table 54) were performed within posttransfusion prospective cohorts. The trials uniformly demonstrated more rapid transaminase resolution and initial reduction in progression to chronic infection among treated patients. Follow-up appeared to demonstrate a relatively limited long-term benefit as level of chronic infection and ALT abnormality rates converged among treatment and control groups. However, a recent meta-analysis of interferon therapy for acute HCV infection, with the addition of further studies, estimated an approximately 30 per cent increased long-term response rate (Quin 1997). The optimum duration of therapy appeared to be 12 weeks, with higher doses (6-10 MU) providing increased response rates (Quin 1997).

Table 54 Randomised trials of interferon therapy in acute hepatitis C virus infection

Adapted from Hoofnagle (1994).

Reference	No. of subjects	Response (normal ALT at 12/12) (%)	
		Interferon	Placebo
Alberti et al (1991)	22	57	37
Omata et al (1991)	20	64	11
Rumi et al (1992)	45	61	42
Viladomiu et al (1992)	28	57	31

6.1.5 Effect of interferon therapy on progression of hepatitis C virus infection

The primary goal of IFN therapy should be to decrease HCV-related morbidity and mortality. Although about 50 per cent of people develop an initial response to IFN therapy, the lack of long-term follow-up has impaired the ability of studies to determine the benefit of IFN therapy in altering the natural history of HCV infection. However, two studies have provided preliminary evidence that progression of chronic HCV infection may be delayed by IFN therapy. In a randomised trial of six months v. 18 months IFN-α2b therapy (Poynard et al 1995), progression to cirrhosis was 16 and 7 per cent, respectively, during 19 to 42 months of follow-up. Although not statistically significant, this halving of progression rate to cirrhosis with prolonged therapy suggests a true effect of IFN therapy on the natural history of chronic HCV infection.

The second study was a randomised controlled trial of the effect of IFN-α on incidence of HCC among patients with compensated cirrhosis (Di Bisceglie et al 1991b). Patients were randomised to IFN-α (6 MU for 3-6 months) or symptomatic treatment. Although only 16 per cent of IFN-treated patients cleared HCV RNA, the rate of progression to HCC during two to seven years of follow-up was 4 per cent as compared with 38 per cent in the control group (P=0.002).

6.1.6 Recent advances in therapy for chronic hepatitis C virus infection

The long-term response rate to interferon therapy of 15 to 20 per cent is obviously suboptimal, and has almost certainly contributed to a poor uptake of treatment for chronic HCV infection. Recent studies, however, have provided optimism that therapeutic advances are approaching. A randomised placebo-controlled study of the addition of ribavirin to interferon therapy demonstrated a sustained response rate (absence of viraemia 6 months posttherapy) of 36 per cent in those treated with the combination therapy compared to 18 per cent in the interferon monotherapy group (Reichard et al 1998). This followed to smaller studies which have also demonstrated a higher sustained response rate for the combination therapy (Chemello et al 1995b; Lai et al 1996).

Trials are also underway to investigate the efficacy of pegylated forms of interferon which would require less frequent dosing (once per week v. standard 3 times per week), and the use of induction dosing with standard interferon (daily dosing for the initial month of therapy). Other classes of therapies such as protease or helicase inhibitors are under investigation, but will be several years before they reach phase III clinical trials.

6.1.7 Interferon therapy trials and use in Australia

A randomised trial of IFN-α2b therapy among 230 patients with histologically proven chronic HCV infection compared three regimes: 3 MU for six months, 5 MU for six months, and 3 MU for two years (Lin et al 1995). The complete response rate (normal ALT at therapy completion) was 64 and 58 per cent for patients treated with 5 MU and 3 MU, respectively, while the sustained response rate (normal ALT 6 months posttherapy) was higher among patients treated for two years (32% v. 17%; P<0.001). Histological stage of disease was the strongest predictor of response, with a complete response rate of 75 per cent among noncirrhotic patients as compared to 42 per cent among those with cirrhosis (P<0.001). Although HCV exposure category was a significant predictive factor for response to IFN therapy in univariate analysis (complete response rates: IDU 71%; blood transfusion 56%; sporadic 43%; P<0.01), it was not independent of histological stage in multivariate analysis.

There are several chronic HCV trials currently recruiting patients in Australia. These include trials investigating the effect of high dose induction interferon (6-9 MU daily for 1 month) (AUSHEP 07), pegylated interferon (multinational), and the efficacy of combination interferon and ribavirin therapy for prior interferon nonresponders (AUSHEP 06) and for treatment-naive patients (AUSHEP 08).

Requirements for prescription of IFN therapy in Australia under the S100 scheme include evidence of chronic HCV infection (positive anti-HCV antibody, abnormal ALT), and absence of current high alcohol intake or current IDU. Excluded from therapy are patients with cirrhosis on liver biopsy and current IDUs, the latter group constituting the largest proportion of people with chronic HCV infection in Australia. IFN therapy available under the S100 scheme consists of 3 MU three times per week for 12 months. Recent changes to the S100 criteria included the removal of HIV coinfection and IDU in the previous 12 months as exclusion criteria, and the increase in recommended therapy duration from six to 12 months.

6.1.8 Discussion

Pooled information from randomised trials of IFN therapy demonstrate a complete response rate to standard regimes (3 MU for 6 months) of about 50 per cent with a sustained response rate of 20 per cent. There is preliminary evidence that more aggressive IFN regimes, including higher doses (6 MU) and/or longer duration (12-24 months) of therapy can provide greater and more sustained response rates. The most important predictive factors for response to IFN therapy are HCV genotype, baseline HCV-RNA level and less advanced histological liver disease. However, if these persons are those least likely to progress to advanced liver disease, targeting of them for IFN therapy may not be a reasonable or cost-effective approach.

Evidence suggests that IFN therapy may be able to significantly alter the natural history of HCV infection and thus reduce long-term morbidity and mortality. These studies need to be replicated in the case of the apparent reduction of HCC among persons with cirrhosis, and provide longer term follow-up in the case of assessing progression of CAH and CPH to cirrhosis. The increased response rates with combination interferon and ribavirin should translate into significant reductions in chronic HCV progression. However, combination therapy is currently only available through a compassionate access scheme.

Future research should include determination of the benefit of interferon and ribavirin combination therapy in people with compensated cirrhosis and people with HIV/HCV coinfection, and the effect of combination therapy in reducing risk of progression to HCC.

6.2 Liver transplantation

In patients with CLD secondary to HCV, the indications for transplant referral are based upon the presence and severity of hepatic decompensation. Patients with cryptogenic cirrhosis should be investigated for HCV infection. Anti-HCV testing may be insufficient, and examination of both serum and liver for HCV RNA may be required. HCV often coexists with other forms of CLD. End-stage cirrhosis related to HCV is a common reason for liver transplantation, although viraemia is known to persist in most cases (Gane et al 1996). Initial graft dysfunction often resolves but liver damage can continue to occur and may lead to recurrent cirrhosis. Recurrence of HCV in the graft can occur within four weeks after liver transplantation for HCV-induced cirrhosis (Konig et al 1992) and acute lobular hepatitis occurs in most patients who are viraemic within the first year (Ascher et al 1994); most of those with histological disease at two to three years follow-up will only have mild hepatitis. Feray et al (1992) proved that the posttransplant infection was recurrence rather than a new infection by showing HCV-RNA sequence homology pretransplant and posttransplant. In a few patients there is rapid clinical and histological progression resulting in subacute liver failure (Lim et al 1994; Schluger et al 1996). There remains a concern that chronic hepatitis leading to graft loss and decreased patient survival may become more common in the later posttransplant period (>5 y). The relatively short follow-up periods in patients with documented HCV infection prior to liver transplantation means that whether chronic hepatitis occurs later has not been clearly established.

Gane et al (1996) investigated the effect of persistent HCV infection after liver transplantation on patient and graft survival and the effects of the HCV genotype and degree of human lymphocyte antigen (HLA) matching between donor and recipient on the severity of recurrent hepatitis. A group of 149 patients with HCV infection who received liver transplants between 1982 and 1994 were followed for a median of 36 months; 623 patients without HCV infection who underwent liver transplantation for end-stage CLD were used as a control group. A total of 528 liver-biopsy specimens from the HCV-infected recipients were reviewed, including 82 obtained one year after transplantation as scheduled and 39 obtained at five years as scheduled. In addition, biopsy specimens were obtained from 91 of the HCV-negative patients five years after transplantation. Cumulative survival rates for the 149 patients with HCV infection were 79 per cent after one year, 74 per cent after three years, and 70 per cent after five years, comparable with rates of 75, 71 and 69 per cent, respectively, in the HCV-negative transplant recipients (P=0.12). Of the 130 patients with HCV infection who survived more than six months after transplantation, 15 (12%) had no evidence of chronic hepatitis on their most recent liver biopsy (median follow-up, 20 months), 70 (54%) had mild chronic hepatitis (median, 35 months), 35 (27%) had moderate chronic hepatitis (median, 35 months) and 10 (8%) had cirrhosis (median, 51 months). Graft loss occurred after a median of 303 days in 27 of the 149 patients, including five with HCV-related cirrhosis and three with HCV-related cholestatic hepatitis. Infection with HCV genotype 1b was associated with more severe graft injury, whereas the primary immunosuppressive regimen used and the extent of HLA mismatching between donors and recipients had no significant effect on this variable.

Feray et al (1995) have also studied the influence of the genotypes of HCV on the severity of recurrent liver disease after liver transplantation. They recognised that the clinical relevance of genotypes remains elusive, and that liver transplantation for HCV-related cirrhosis offers a unique opportunity for prospective studies of this issue. Sixty anti-HCV-positive liver recipients with precise virological and histological assessments had HCV genotype determined with both type-specific capsid primers and a line probe genotyping assay. They found that HCV genotype 1b was the predominant type before transplantation (40/60 patients); after liver transplantation, acute hepatitis and CAH developed more frequently in these patients than in patients infected by other genotypes (31/40 and 24/40 v. 8/20 and 4/20 patients). Actuarial rates of acute hepatitis and CAH were 77 and 59 per cent, respectively, three years after transplantation in patients infected by type 1b and 40 per cent (P=0.008) and 22 per cent (P=0.004) in those infected by other types. There was no statistical relationship between the level of HCV viraemia and HCV genotypes both before and after transplantation. In contrast, after transplantation, serum HCV-RNA values were significantly increased in patients who developed hepatitis after transplantation. This study provides direct evidence that HCV 1b is associated with more aggressive recurrent liver disease than other genotypes.

Schluger et al (1996) described a progressive, severe cholestatic form of hepatitis occurring in 10 of 135 patients with HCV infection who received liver transplants (Schluger et al 1996). The 10 patients experienced severe recurrent HCV infection; 1 died, 1 was awaiting retransplantation, and 8 underwent retransplantation. All 10 developed severe progressive cholestatic hepatitis, with a mean rise in bilirubin to 24.7 mg/dL at the time of retransplantation. Histology at initial recurrence showed mild hepatitis without evidence of rejection. The failed grafts showed either cirrhosis or confluent hepatic necrosis. The onset of cholestasis preceded retransplantation by less than five months, and suggests that a minority of patients with recurrent HCV infection after undergoing liver transplantation develop a severe progressive cholestatic hepatitis and liver failure.

In summary, after liver transplantation for HCV-related cirrhosis, persistent HCV infection can cause severe graft damage, and such damage is more frequent in patients infected with HCV genotype 1b than with other genotypes. After five years, the rates of graft and overall survival are similar between patients with, and those without, HCV infection.

6.2.1 Hepatitis C virus in other transplantation events

HCV can also be acquired *de novo* in the peritransplant period, from donor organs or transfused blood products, and the course of disease may be altered by immunosuppressives in the posttransplant period. The size of the inoculum, ability of the organ to sustain replication, procurement and preservation techniques, and posttransplant immunosuppression may all affect the risk of infection. There is some debate about whether it should be permissible to use organs from HCV-infected donors for HCV-infected recipients.

6.2.2 Mechanism of liver injury

The mechanism of liver injury in HCV-infected transplant recipients is thought to be via direct viral cytopathicity and host-mediated immunity. Among the factors which may influence viral-host interactions are: level of viraemia before transplantation, viral genotype, coinfection with other heterotrophic viruses, amount of immunosuppression in the posttransplant period and host immunocompetence.

6.2.3 Fulminant hepatitis

Another important, if uncommon, reason for liver transplantation is fulminant hepatitis, of which viral hepatitis is the most common cause. The extent to which HCV contributes to FHF has been discussed previously. HCV alone may not be causally responsible for all cases of FHF in which it is found, but acts either as a cofactor or represents an 'innocent bystander' in liver failure due to another aetiology (Terrault and Wright 1995b). An interaction with HBV/hepatitis D virus (HDV) appears to exist.

Haratake et al (1993) looked at predictable factors for estimating prognosis of patients after resection of HCC. One hundred and forty cases of HCC with hepatic resection were observed from 1 to 11 years, and the relationship among various clinicopathological factors, including the mitotic index and anti-HCV, and prognosis was evaluated. Age at the time of operation, positive results for HBV surface antigen or anti-HCV, accompanying cirrhosis, and the degree of tumour necrosis due to transarterial embolisation did not influence the prognosis significantly. Patients with HCV-related cases had a better prognosis than patients with HBV-related cases, and patients with a single and small carcinoma (<2 cm) had a significantly better prognosis than those who had larger and/or multiple tumours. A better prognosis also was observed in the carcinomas with no histological invasion into portal vein branches, low Edmondson grades and low mitotic activities when compared with the counterpart of each group. The mitotic index was correlated best with prognosis in the current study and was a simple examination which was a helpful factor in predicting prognosis.

6.2.4 The Australian Liver Transplant Registry

(From: *Australian Liver Transplant Registry 8th Report*. From the Combined Registries of the Australian Liver Transplant Centres, data to 31 December 1995).

The Australian Liver Transplant Registry (*Australian Liver Transplant Registry 8th Report*) collates the data on all liver transplants undertaken in Australia. The number of new patients receiving a liver transplant has steadily increased from the mid 1980s to the mid 1990s (figure 4).

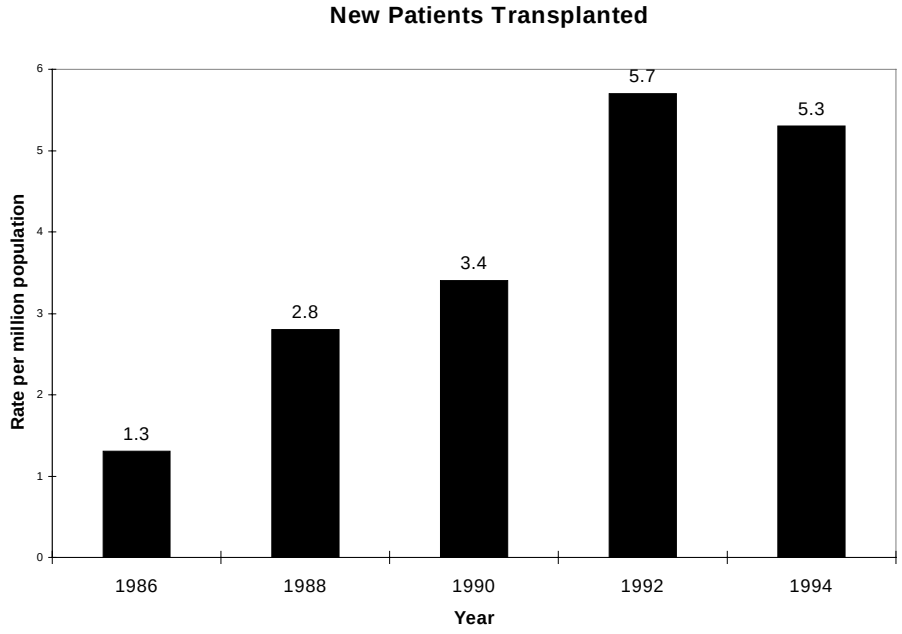


Figure 4. Number of new patients receiving liver transplants per million within the Australian population. From *Australian Liver Transplant Registry 8th Report.*

Until the end of 1995, a total of 890 patients (650 adults and 240 children) had received 974 liver transplants in Australia. Paediatric patients are most commonly transplanted for biliary atresia (72%) or metabolic disorders (14%), although 7 per cent are transplanted following FHF. The effect of viral hepatitis infections is seen in adult patients. Chronic HCV infection as a cause has increased dramatically over the past few years, whereas transplantation for HBV has remained fairly steady from year to year (figure 5).

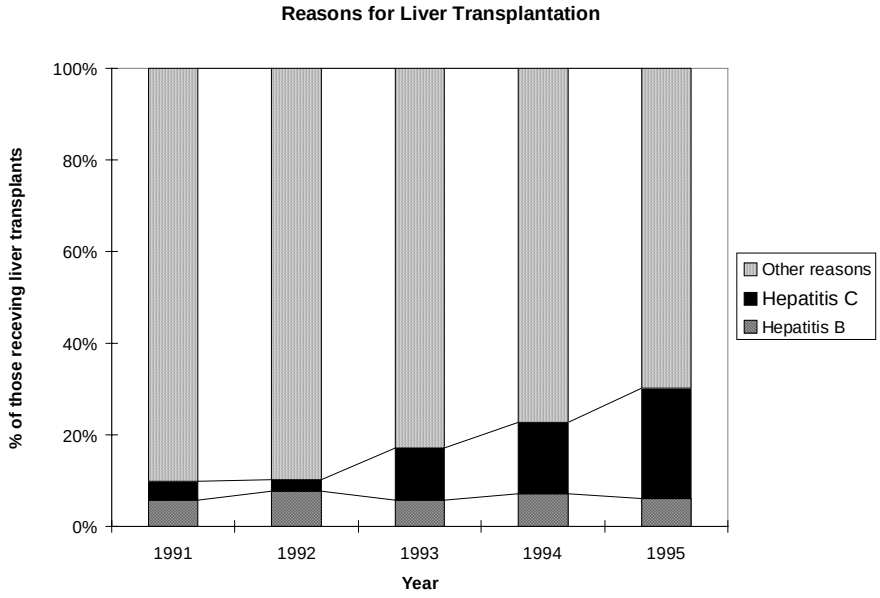


Figure 5. Percentage of liver transplantations as a result of infection with hepatitis B virus and hepatitis C virus.

The actuarial survival figures for the 60 adult patients who have received liver transplants for HCV is 87 per cent at one year, 87 per cent at three years and 79 per cent at five years, better than the figures for all liver transplants combined. Recurrent infection in the graft accounts for some graft losses and patient deaths, and may occur as early as six months after transplantation.

6.2.5 Patients infected with hepatitis C virus referred to Royal Prince Alfred Liver Clinic: characteristics and outcomes

Levy et al (in press) from the Royal Prince Alfred Hospital in Sydney have analysed their experience in assessing and transplanting patients referred to their Unit with HCV-associated cirrhosis. This Unit is the largest liver transplant centre in Australia, and has transplanted nearly half of the HCV infected patients up to the end of 1995.

Twenty-eight of 63 patients (44%) referred received transplants. Of patients referred, 86 per cent were male and 35 per cent consumed alcohol in the harmful/hazardous range, 13 per cent were infected with HBV and 7 per cent had HCC. The reason for the male preponderance in referral is unknown. The routes of infection were considered to be: 26 (41%) IDU; 8 (13%) via blood transfusion; 2 (3%) via tattoo, and in 27 (43%) there was no known risk factor (sporadic). Patients whose acquisition of infection was considered 'sporadic' were more likely to have been born outside of Australia (Egypt 9, Italy 7, Australia 6, other countries, 5) and were an average of 10 years older than those with HCV acquired via IDU ($P<0.001$). Alcohol consumption in the harmful range meant referral at an average age 12 years younger than in those who abstained.

Between mid 1994 and the end of 1995, 21 per cent of patients referred for assessment and 31 per cent of patients transplanted had an underlying diagnosis of HCV cirrhosis. Of the 34 patients accepted for transplantation, four died while on the waiting list and two were to be transplanted. Among those not accepted for transplantation are those with ongoing drug dependence (5) and psychological/psychiatric contraindications (2). HCC developed in one patient in the 18 who had transplantation deferred; and two died of decompensated liver failure. Three-year survival was 84 per cent. Chronic-HCV-related graft dysfunction occurred in 56 per cent (15 patients), of whom 10 had asymptomatic transaminitis, two had cholestatic hepatitis and three had severe HCV infection that progressed onto chronic rejection. HCV genotype 1b tended to be associated with HCV graft dysfunction (5/6 type 1b v. 10/16 in non type 1b).

7 Hepatitis C virus infection in Australia

Detailed information on the size of the HCV epidemic in Australia is lacking. The two main sources of information both provide very partial and biased perspectives on the numbers and characteristics of people infected with, or becoming infected with, HCV in Australia: surveillance for HCV infection; and studies of particular population groups. With the former, the problems revolve around participation in testing and in the difficulties of identifying incident cases; with the latter, estimating the sizes of the populations at risk and deriving representative samples. Further work is needed in these areas to quantify the HCV epidemic in Australia, information vitally necessary to underpin every aspect of the public health response.

7.1 Surveillance data

Between 1991 and 1997, over 57,000 diagnoses of HCV infection were reported to the National Notifiable Diseases Surveillance System (NNDSS) maintained by the Commonwealth Department of Health and Aged Care (CDNANZ, pers. comm. 1998) in States other than New South Wales and South Australia. A further 46,900 HCV diagnoses have been reported in New South Wales to the end of 1997 (Robert Menzies, pers. comm. 1998) and 7,500 in South Australia (STD Control Branch, pers. comm. 1998), the only two States in Australia that forward details of incident HCV diagnoses to the NNDSS, making a total of over 110,000 HCV diagnoses in Australia to the end of 1997. Of annual total notifications to the NNDSS during this period, 67 to 78 per cent of HCV diagnoses were in the age range 20-39, with a male to female ratio of between 1.6 and 1.7 (Crofts et al 1997a). A second system of reporting by sentinel laboratories (CDI Laboratory Reporting Scheme, Lab VISE) received 18,124 reports of diagnosis of HCV exposure from 1990 through September 1995, of which only 11.8 per cent had accompanying risk factor information (Crofts et al 1997a). Of the cases with such data, 86.4 per cent gave the risk as a history of IDU.

These data reflect patterns of testing and of notification far more than they do patterns of infection and transmission, although they are, of course, based on the latter. Such data reveal nothing about the incidence rate for HCV infection in either the general population or any special subgroups. As a response, the Communicable Diseases Network Australia New Zealand undertook a trial enhanced surveillance program for incident infection in 1995 (Andrews and Curran 1996). Based on notification of cases, enhanced callback to assist classification of cases into incident or pre-existing was undertaken with somewhat different emphases by different States and Territories. In the preceding two years, 73 cases (0.4% of all notified cases) had been classified as incident (Crofts et al 1997a); in 1995, under enhanced callback, this rose to 138 cases (0.8% of all notified cases) (Andrews and Curran 1996). This is an annual rate of 7.8 incident cases per 100,000 per year, but the authors of this report point out that this is an unreliable estimate because of, among other factors, ‘variance in the methods used, response bias, and the presence of duplicates among the total HCV notifications’ (Andrews and Curran 1996). The major limitation of this type of surveillance for incident cases, however, is that most acute HCV infections are either asymptomatic or cause nonspecific symptoms which do not get classified as hepatitis and are, therefore, not investigated further (Locarnini and McAnulty 1996). This rate is stated as 75 per cent: ie only 25 per cent of acute cases are icteric (van der Poel et al 1994), but this figure is derived from studies of TA-HCV infection in which those infected received higher infectious doses than would be the case in those infected as a result of IDU. Anecdotal information suggests that the rate of development of jaundice among those IDUs acutely infected with HCV is much lower than 25 per cent.

7.2 Population sizes and prevalence

7.2.1 Blood donors

The prevalence of antibodies to HCV among blood donors has decreased since testing for HCV antibody was introduced in 1990 from 0.7-0.8 per cent in 1987-89 in selected hospitals in Western Australia and New South Wales (Ismay et al 1995), to 0.45 per cent overall and 1.0 per cent in first time donors in Sydney in 1990-91 (Archer et al 1992), to 0.05 per cent in 1994 (Melbourne Red Cross Blood Transfusion Service, unpublished). These rates are likely to be increasingly unrepresentative of the general population because of the selection process involved in donating blood, but they provide a lower boundary of around 100,000 Australians having been exposed to HCV. HCV incidence has been estimated among repeat blood donors in Victoria to be 1.0 per 100,000 (Whyte and Savoia 1997).

7.2.2 Injecting drug users

Published HCV prevalence studies among IDUs in Australia show a range of prevalences between 8 and 94.3 per cent (Crofts et al 1997a). The lower figure is from a study in Perth of recent initiates to IDU; the upper from a study of entrants to methadone maintenance programs in 1994. Most of the cross-sectional surveys of Australian IDUs have found prevalences of HCV antibody between 50 and 70 per cent. Using these data and estimates of the numbers of people who have ever injected drugs in Australia, Crofts et al estimated in 1993 that there were approximately 80,000 people in Australia chronically infected with (not simply exposed to) HCV as a result of IDU (Crofts et al 1993). Subsequently the same authors have raised this estimate to 130,000 on the basis of newer knowledge of the proportions of people exposed who become chronically infected (Crofts et al 1996).

The incidence of HCV among IDUs in Australia has also been measured in several studies. These rates vary from 14 to 38 per 100 person-years, depending on the population studied (Crofts et al 1997a). Using a rate of 20 per 100 person-years, Crofts et al estimated in 1993 that between 8,000 and 10,000 new infections were occurring per year among IDUs (Crofts et al 1993). They have subsequently revised this figure, using an average incidence rate of 15 per 100 person-years, to around 6,000 new infections in Australian IDUs per year (Crofts et al 1997a).

In a combined analysis, based on two cohorts of IDUs in Melbourne and one in Sydney, the incidence of HCV infection among IDUs in the 1980s and early 1990s was estimated to be around 15 new infections per 100 person years of follow-up (Crofts et al 1997a). These studies also provided an indication, although not statistically significant, of a reduction in HCV incidence among IDUs from around 18 infections per 100 person years in IDUs who started injecting before 1987, to 13 infections per 100 person years in IDUs who started injecting since then. This indication coincides with the introduction of needle and syringe exchange programs, and other preventive campaigns, that were aimed at reducing the risk of HIV infection among IDUs. Further evidence of declining incidence in some populations of IDUs in Australia is beginning to accrue (see section 4.1.12).

7.2.3 Antenatal patients

Two studies of HCV antibody prevalence among women receiving antenatal care in Victorian hospitals using the first-generation assay found prevalences of 0.3 and 0.4 per cent (Fairley et al 1990; Williamson et al 1990). A study in South Australia found an overall prevalence of 1.1 per cent (17/1537) in an unselected consecutive series of antenatal patients (Garner et al 1997).

7.2.4 General population

No data have been published on the prevalence of HCV among the general population in Australia, but there has been one population-based survey (as yet unpublished) of the prevalence of risk behaviours and of participation in testing for HCV. In a phone survey of the adult Victorian population, Watson et al found that 11.4 per cent reported having been tested for HCV, 15 per cent reported having had a blood transfusion prior to 1990, 4.4 per cent reported ever having had a tattoo and 2 per cent reported having ever injected drugs (R Watson et al, pers. comm).

7.2.5 Estimates of hepatitis C virus prevalence and incidence

It has been estimated, based on both direct and modelling approaches, that there were around 190,000 people living with HCV antibodies in Australia in 1997 (plausible range 140,000-240,000) (Hepatitis C Virus Projections Working Group 1998). HCV incidence in 1997 was estimated using a mathematical model to be 11,000 new infections (8,500-13,500), 91 per cent of whom were exposed through injecting drugs.

Of all people living with HCV antibodies in Australia in 1997, it was estimated that:

- 8 per cent were exposed to HCV through IDU, 7 per cent through receipt of blood, and 13 per cent through other transmission routes;
- 47,000 (35,000-60,000) had cleared their HCV infection;
- 134,000 (101,000-167,000) had chronic HCV infection, and therefore were at risk of developing cirrhosis;
- 8,500 (4,000-13,000) were living with HCV-related cirrhosis;
- 80 (40-130) people developed HCV-related HCC during 1997; and
- among those people exposed through IDU, 49 per cent were currently injecting.

Projections of the number of people living with HCV-related cirrhosis, or the number of incident cases of HCV-related HCC, indicated that the numbers of both would more than double by 2010.

7.3 Conclusions

The available data suggest that to the end of 1997 about 140,000 to 240,000 people living in Australia have been exposed to HCV at some time, most as a result of IDU. This, together with the surveillance and survey data, suggest that between 46 and 79 per cent of those who have been exposed have been tested for HCV. Of those exposed, 101,000 to 167,000 could be expected to be chronically infected and at risk of end-stage liver disease. Mathematical models suggest that about 11,000 new HCV infections occurred in Australia during 1997, most as a result of IDU.

However, these data are uncertain, partly at least because the sizes of the populations at risk are generally unknown. Further work enabling better estimates of the numbers of people infected and becoming infected with HCV is necessary.

Control of the epidemic of HCV in Australia clearly depends on control of the epidemic among IDUs, the only remaining core group for HCV in this community. There is some suggestive evidence of declines in incidence of HCV among some populations of IDUs, beginning in the late 1980s, and perhaps accelerated from 1993 onwards, but even if these are real phenomena, current HCV incidences in other populations remain extremely high. It has been argued that current strategies are effective in decreasing HCV incidence among IDUs, but that, given the high prevalences the virus has reached in these populations before the institution of control strategies, the dose of current efforts - needle and syringe availability and disposal programs, substitution therapy and peer education - is inadequate (Crofts et al 1999). It would seem that an increase in current strategies, combined with investigation of

new approaches - for example, primary prevention of IDU, support for transitions from injecting to other methods of administration of drugs, and specific HCV-peer education programs - will be necessary to control this ongoing epidemic in Australia (Crofts and Wodak 1999).

Tables

Tables have been numbered consecutively throughout the document. Tables that can be displayed upright (portrait) have been positioned appropriately within the main body of the text. Only tables in landscape format appear in this section of the document.

Table 4 Prevalence of hepatitis C virus among injecting drug users

Region/ country	Reference	Number in sample	Population	% HCV positive	% PCR positive	HIV	HBV core antibody	HBV surface antigen	Assay generation	Year of sample
Asia										
China, Ruili County	Cheng (1993)	79	HIV-infected	92			68			
China, Yunnan	Li et al (1994)	507	DRCs[A]	94.9		66.5				
China	Ye (1993)	177		92.2						
Japan, Hiroshima	Ichimura et al (1995)	47		74.5	44.7	2.1	57.4			
Malaysia	Sinniah & Ooi (1993)			85						
Taiwan	Wu et al (1991)	703		82.2						
Taiwan	Lee et al (1991a)	115		53						
Taiwan	Chen et al (1990)	58	IDUs	81						
Thailand, Chiang Mai	Apichartpiyakul et al (1994)	29		82.8					PCR assay	
Vietnam, Hanoi	Nakata et al (1994)	200		30.5						
Vietnam, HCMC	Nakata et al (1994)	67		86.6						
Australia/New Zealand										
Australia	MacDonald et al (1998)	20	Trawler crew	55.0		0.0				96
NSW, Sydney	Bell et al (1990)	172	MMT clients[B]						1	88-90
NSW, Sydney	van Beek et al (1994)	201	Primary care	58.7		7.2	48.0		2	91-92
NSW, Sydney	van Beek et al (1998)	1078	Primary care	45.0		2.5			2	92-95
Victoria	Crofts et al (1995)	1428	Prison entrants	64.0					1	91-92
Victoria	Crofts et al (1994)	303	Cohort study	68.0	50.0	4.5	47.0	1.8	2	91-92

Table 4 continued overleaf

Region/ country	Reference	Number in sample	Population	% HCV positive	% PCR positive	HIV	HBV core antibody	HBV surface antigen	Assay generation	Year of sample
Victoria	Fairley et al (1990)			61.9						
Victoria, Melbourne	Thomson et al (1998)	95	HAV/HBV +ve	90.4					2	71-75
NZ, Christchurch	Chetwynd et al (1995)	116	MMT	84.2	75.9				2	93
NZ, Wellington	Chetwynd et al (1995)	92	Treatment centre	77.2					2	92-94
NZ, Wellington	Robinson et al (1995)	92	Treatment	77.2						92-94
New Zealand	Kemp et al (1998)	241	Varied	63.9						94
New Zealand	McKenna et al (1994)	19		21.1			30			
New Zealand	Woodfield et al (1993)	110		72.7						
New Zealand	Woodfield et al (1994)			74						
Europe										
Austria	Pont et al (1991)	151	Prison	75.5		18.0	67.5		1	85-90
Belgium, Ghent	Vanderschueren et al (1991)	81		46.9						90
Denmark	Westh et al (1993)	126		97.6						88-89
France, Nice	Quaranta et al (1994)	97	HIV-infected	78.3						
France	Rey et al (1995)		HIV-infected	94						
France	Lucidarme et al (1994)	104		72.1		1.0	32.7	5.8		
France	Ranger et al (1991)			73.5						
Germany, Mainz	Hess et al (1990)			84.5					1	90
Germany, Hamburg	Trubner et al (1991)	282	Deceased IDUs	40.1						88-90
Germany, Hamburg	Gaube et al (1993)			80						
Germany	Batz and Reymann (1997)		Treatment	63			48			96

Region/ country	Reference	Number in sample	Population	% HCV positive	% PCR positive	HIV	HBV core antibody	HBV surface antigen	Assay generation	Year of sample
Germany	Weber et al (1995)			78.9						91-93
Greece	Malliori et al (1998)	375	Prison	80.6		0.3	62.7		2	94-95
Iceland, Reykjavik	Love & Stanzeit (1994)	152		62.5						
Iceland	Love et al (1996)	41		M 76.4 F 33.3						
Ireland, Dublin	Smyth et al (1995)	272	Treatment centres	84.2					2	92-93
Ireland, Dublin	Smyth et al (1998)	735	Treatment	61.8		1.2		1.0	2	92-97
Italy, Cagliari	Coppola et al (1994)	255	Treatment centres		81.2		32.9	7.4	2	91
Italy, Catanzaro	Grob & Joller Jemelka (1990)	41		63.4						
Italy, East Sicily	Cacopardo et al (1992)	175		58.3						
Italy, Naples	Rezza et al (1996)	713	Treatment centres	63.1		1.3			2	91-93
Italy, Padova	Chiaramonte et al (1991)			70						
Italy, Rome	Girardi et al (1990)	80	MMT	67.5		47.5	86.2		1	89
Italy, Rome	Patti et al (1993)	645	10 MMT centres	63.4			71.3	9.3	2	90-91
Italy, Tivoli	Ciuffreda et al (1994)		Hospital	80.9						
Italy, Veneto	Galeazzi et al (1995)	227	Cohort study	75.3			52.0	0.9	2	92
Italy	Corona et al (1991)		STD patients	39.5						
Italy	Salvaggio et al (1993)	151	Female IDUs	74.2						
Italy	Francisci et al (1995)			72			82			

Table 4 continued overleaf

Region/ country	Reference	Number in sample	Population	% HCV positive	% PCR positive	HIV	HBV core antibody	HBV surface antigen	Assay generation	Year of sample
Netherlands, Amsterdam	Van den Hoek et al (1990)	304	Cohort study	73.7					1	85-89
Norway, Oslo	Grinde et al (1997)	144	HAV-infected	81			43			
Norway	Rollag et al (1993)	37		70.3						
Poland, Gdansk	Smiatacz et al (1991)	46		71.7		45.7	78.3			
Poland	Laskus et al (1992b)	100	Unselected	78			69			
Poland	Halota et al (1991)	80		63.8		75	85			
Portugal	Santos et al (1994)			33.3						
Portugal, Lisbon	Gloria et al (1991)	135		83		0.7	81			
Scotland, Glasgow	Goldberg et al (1998)			77						95
Spain, Baleares	Payeras Cifre et al (1992)	110	Patients	86		36	53			
Spain, Galdacamo	de Miguel et al (1994)	45	IDUs	88.9						
Spain, Valencia	Anon et al (1995)		Prison	90 (‘around’)						
Spain, Valencia	Bolumar et al (1996)	1056	Current IDUs	85.5					2	90-92
Spain	Garcia Bengoechea et al (1995)		Hospital patients	85.7						
Spain	Decarvalho et al (1996)	265	Various	75.6		50.2	67.5			90-91
Sweden, Malmo	Widell et al (1991)	172		79.7					1	87-89
Sweden	Sonnerborg et al (1990)			89			83		1	90
Sweden	Krook et al (1997)		Prison, treatment	92			75			94
Switzerland, Geneva	Chamot et al (1990)	262	MMT	64		36	74		1	90
Switzerland, Zurich	Grob & Joller Jemelka (1990)			45						90

Region/ country	Reference	Number in sample	Population	% HCV positive	% PCR positive	HIV	HBV core antibody	HBV surface antigen	Assay generation	Year of sample
Switzerland, Zurich	Chamot et al (1990)	382	Various	48		15	56		1	90
UK, East Anglia	Majid et al (1995)		Rural IDUs	59	44	1.0	22			
UK, North West	Lamden et al (1998)	773	Treatment	67			48			92-96
Middle East										
Israel, Jerusalem	Maayan et al (1994)	51	Drug rehabilitation	54			26			
North America										
Canada, Calgary	Anand et al (1992)			50 (about)						
Canada, Montreal	Roy et al (1997)	200	Street youth	26.5			16.2			96
Canada, Ontario	Stratton et al (1998)	92	Semi-rural	46.7		5.4	23.1			
Canada, Ontario	Lior et al (1998)	94	Prison	52.1		2.2	18.7			97
Canada, Vancouver	Patrick et al (1998)	1080	Field	85		23				96-97
Canada, Vancouver	Strathdee et al (1997)	1006	Field	88.0		23.2				96-97
USA, Baltimore	Fingerhood et al (1993)	687	Treatment centre	63.2		4.2	29.7		1	90-91
USA, Baltimore	Donahue et al (1991)	225	Cohort study	85					1	88
USA, Baltimore	Garfein et al (1996)	312	Cohort study	76.9		20.5	65.7			88-89
USA, Baltimore	Garfein et al (1998)	229	Young IDUs	37.6						94-96
USA, California	Tennant & Moll (1995)	389	Op treatment[C]	93.6			73.6	3.5		
USA, California	Zeldis et al (1992)	585		72		1.0	71.0			
USA, San Francisco	Buchbinder et al (1994)	92	Gay IDUs	25.0					1	83-84
USA, San Francisco	Osmond et al (1993a)			64						
USA, Seattle	Hansen et al (1997)	787	Treatment	88.9		1.2	66.0			94-96

Table 4 continued overleaf

Region/ country	Reference	Number in sample	Population	% HCV positive	% PCR positive	HIV	HBV core antibody	HBV surface antigen	Assay generation	Year of sample
USA, Seattle	Hagan et al (1999)	2462	Treatment +	85.7			68.3		3	94-96
USA	Kelen et al (1992)	175	Inner city A&E[D]	82.9						
South America										
Argentina, Buenos Aires	Fainboim et al (1996)	234	HIV +ve	92.3			72.6	19.2		94-95
Brazil, Santos	Delgado Iribarren et al (1993)	110		75		62	75			

[A]DRCs, Drug Rehabilitation Centre.

[B]MMT, methadone maintenance therapy.

[C]Op, outpatients.

[D]A&E, Accident and Emergency.

Table 13 Hepatitis C virus and haemodialysis: prevalence and associations

Site	Reference	Number			Prevalence (%)			% PCR		No. of transfusions	Duration	Other associations/factors
		Total	HD	CAPD	Total	HD	CAPD	HCV+	HCV-			
Argentina	Curciarello et al (1994)	219			35.6							
Argentina	Fernandez et al (1996)	31			0				12.9			
Argentina	Sartori et al (1993)	48			59					Y		
Brazil	Cendoroglo Neto et al (1995b)	309	185	124		35.1	33.9			Y	Y	HBV
Brazil	Vanderborght et al (1995)	433	398	35	65 (range 47-82)	17						Prevalence 2.9% among dialysis staff
Chile	Castillo et al (1993)	26			54					N	Y	
Chile	Ibarra et al (1995)	56			0							
Croatia	Jankovic et al (1994)	101			38					Y	Y	Prevalence 0% in 75 dialysis staff
Czechoslovakia (the former)	Korcakova (1995)	629 (47 centres)			31 (range 6-60)							
Denmark	Bukh et al (1993b)	340			8.2			96.4	2.6			
Egypt	Abdel Wahab et al (1994)				46.2							
Egypt	el Gohary et al (1995)				70.4							
England	Corcoran et al (1994)	66			13.6					N	Y	
France	Courouce et al (1995)	128			42			98	0			
France	Dussol et al (1995)	984			23.6					Y	Y	Female, kidney grafts, HBV, HD >> CAPD Transfusional and nosocomial risks
France	Simon et al (1994)	217			39.6			82.6				
France	Chauveau et al (1993)	115			54					Y	Y	
Germany	Seelig et al (1994)	1515			23.1			76	4.1			

Table 13 continued overleaf

Site	Reference	Number			Prevalence (%)			% PCR		No. of transfusions	Duration	Other associations/factors
		Total	HD	CAPD	Total	HD	CAPD	HCV+	HCV-			
Germany	Weber et al (1995)				8.1							
Hong Kong	Chan et al (1993)	51			21.6			72.7	2.5			
Indonesia	Hadiwandowo et al (1994)	58			76							
Ireland	Conlon et al (1993)	266			1.7							
Israel	Golan et al (1996)	120	76	44	21.7	30.3	6.8			Y	Y	Ethnicity
Italy	Aucella et al (1995)	80			35			62.5	2			
Italy	Boero et al (1995)	75			40			80	0			
Italy	Castelnovo et al (1995)	127	48	79		52	14		2.2			
Italy	Fabrizi et al (1994)	235			77.9			41				
Italy	Incandela et al (1994)	88			13.6					Y	N	HBV
Italy	Petrosillo et al (1995)	1002			39.4							
Italy	Puoti et al (1995)											
Japan	Fujiyama et al (1995)	548			30.3% overall. 35.4% in transfused 25.7% among non-transfused					Y	Y	Prevalence 2.3% among dialysis staff
Japan	Hayashi et al (1994a)	357			55.5			86.4				
Japan	Hayashi et al (1994b)	310			51.9 Fukuoka							
Japan	Hayashi et al (1994b)	143			9.1 Okinawa			84.5				

Site	Reference	Number			Prevalence (%)			% PCR		No. of transfusions	Duration	Other associations/factors
		Total	HD	CAPD	Total	HD	CAPD	HCV+	HCV-			
Japan	Irie et al (1994)	485 152 w/o trans-fusion			38.6 31.2					Y	Y Y	
Japan	Nakayama et al (1996)	2132			29.9 with transfusion 7.6 w/o transfusion					Y	Y	Duration not assoc in females w/o transfusion
Japan	Tsuyuguchi (1994)	584			22.0			55.9		Y		
Japan	Yamaguchi et al (1994)	1423			22.2					Y	Y	
Lithuania	Ambrozaitis et al (1995)				48.3							Prevalence 7.9% among dialysis staff
Oman	al Dhahry et al (1993)	102			26.5							
Pakistan	Kumar et al (1994)	68			46					Y>4	Y>1y	Females, reused dialyzer
Poland	Polz et al (1995)				57							
Poland	Slizien et al (1995)	67			61.2							HBV
Romania	Boscan et al (1995)	61			79						Y	HBV
Russia	Shakhgil'dian et al (1994a)	269			25						Y	
Russia	Shakhgil'dian et al (1994b)				25							
Saudi Arabia	Huraib et al (1995)	1147 (22 HD centres)			68 (range 14.5-94.7)					Y	Y	Male, ethnicity
Scotland	McIntyre et al (1994)	483			3.9					Y	Y	HD>CAPD
South Africa	Cassidy et al (1995)	103			21					Y	Y	Prevalence 0% in dialysis staff

Table 13 continued overleaf

Site	Reference	Number			Prevalence (%)			% PCR		No. of transfusions	Duration	Other associations/factors
		Total	HD	CAPD	Total	HD	CAPD	HCV+	HCV-			
Spain	Anon. (1995c)											Higher in HD than CAPD Prevalence higher in nurses than in other staff
Spain	Garcia Valdecasas et al (1994)	107			25.2							
Spain	Oliva et al (1995)	43	43		63							
Taiwan	Hou et al (1995)				44							Prevalence 5.4% in family members
Taiwan	Chou et al (1993)	87			44.8							
Thailand	Luengrojanakul et al (1994)	221	55		20	0						
Tunisia	Hmida et al (1995)	235			45.1						Y	
Tunisia	Jemni et al (1994)	63			42					Y	Y	
Turkey	Akpolat et al (1995)											
Turkey	Paydas et al (1994)	56			23.2					Y	Y	
USA	DuBois et al (1994)	208			21			77	0			High levels of viraemia, especially in males
USA	Kuhns et al (1994)	63			25			75	4.3			
USA	Tokars et al (1994)	170,028 (2,170 centres)			8.1							Prevalence 1.6% among dialysis staff
USA	Tokars et al (1994)	(2,304 centres)			9.7							Prevalence 1.6% among dialysis staff
Vietnam	Nakata et al (1994)	28			54							

Table 23 Prevalence of anti-hepatitis C virus in sexual partners of anti-HCV-positive people

Country	Reference	Assay	Risk factor	No. of people	% with antibody	Comments
Canada, Ottawa	Scully et al (1993)	EIA RIBA	Sexual partners of HCV+	29	0	One husband-wife pair were positive, but both were IDU
England	Hallam et al (1993)	EIA2	Sexual partners of HCV+ people with haemophilia	104	2.9	56% of index cases were HIV positive. All those who developed HCV had other risk factors for HCV (1 IDU, 2 had undergone surgery pre HCV screening).
Europe, America, and Australia	Brettler et al (1992)	EIA2, RIBA	Sexual partners of HCV- infected person with haemophilia	106	3	
Finland	Kolho et al (1991)	EIA1	Sexual partners of HCV- infected people with haemophilia	30	3	This one result was indeterminate
France	David et al (1995)	EIA2 RIBA 2	Sexual partners of HCV+	104	10.6	In 8/11, other risk factors were present (3.2% if no other risk). General population levels about 1% in this region.
Germany	Brackmann et al (1993)	EIA1/2	Household contacts of HCV+ people with haemophilia	228	0.4	Only one positive; not clear if this was a sexual contact or not
Germany	Meisel et al (1995)	EIA2/3, RIBA2/3	Husbands of HCV+	94	0	Women were infected by immunoglobulin
Hong Kong	GC Chan et al (1992)	EIA1	Sexual partners of HCV positive	11	0	All heterosexual
Italy, Naples	Coltorti et al (1994)	EIA2 RIBA2	Spouses of HCV+ with chronic hepatitis.	100	27	Only 1.9% of 260 children positive. In spouses, correlated with duration of marriage.
Italy, Bari	Napoli et al (1993)	EIA2 RIBA2	Spouses of HCV infected	108	34	Rate in children was 2%, 14% in siblings, 17% in other cohabitants, 45 family members of 16 negative controls had no HCV
Italy	Gabrielli et al (1994)	EIA, RIBA2	Sexual partners of HCV+ positive IDU	84	29 13 0	In 7 couples where both were HIV+ In 47 couples where index HIV+, exposed HIV- In 30 couples where both HIV-. No effect of condom use.

Table 23 continued overleaf

Country	Reference	Assay	Risk factor	No. of people	% with antibody	Comments
Italy	Marino et al (1994)	EIA2	Sexual contact with HCV+ person (86)	159	18	72/86 anti-HCV-positive patients had unknown risk factors. Rate higher than in other household contacts (3.1%). No mention of IDU.
Japan	Oshita et al (1993)	?	Spouses of HCV+	75	24	Much higher than other family members
Japan	Setoguchi et al (1994)	EIA2, HCV RNA	Sexual partners of those with liver disease due to HCV	83	24	24% is no higher than the background rate in this community
Netherlands	Bresters et al (1993)	EIA2, HCV RNA	Sexual partners of viraemic individuals	50	0	Median duration of sexual partnerships 13 years
Spain, Seville	Lissen et al (1993)	EIA2 RIBA2	Heterosexual partners of HCV+	147	7.4	9.2% if also HIV+, 4.1% if HIV negative
Spain	Diaz et al (1995)	?	Sexual partners of HCV+.	126	1.6	1.6% is no different to the prevalence of HCV in blood donors in this area. Seroconcordant couples had shared toiletry items.
Spain, Seville	Soto et al (1994)	EIA2, RIBA2	Heterosexual partners of HCV+	423	7.1	1.2% in blood donors. Higher if index case coinfected with HIV (9.1%).
Spain	Garcia Bengoechea et al (1994)	?	Sexual partners of patients with chronic HCV	161	4.7	Nonsexual household contacts 2.5%
Sweden	Shev et al (1995a)	EIA2	Sexual partners of HCV+ blood donors	22	23	In seroconcordant partnerships the exposed individual more likely to be HSV2 positive. No difference in syphilis serology.

Country	Reference	Assay	Risk factor	No. of people	% with antibody	Comments
Taiwan	Kao et al (1992)	?	Sexual partners of HCV positive	48	21	Older age and longer duration of marriage were risk factors.
USA	Eyster et al (1991)	EIA1, WB	Sexual partners of HCV+ haemophiliacs	194	2.6	3% in partners of men with HIV+/HCV+, 0% in men with HIV-/HCV+
USA, San Francisco	Osmond et al (1993b)	RIBA2	Sexual partners of HCV+	31	6	2 women with no parenteral risk and with an infected male partner were infected, compared to no women with HCV- partners
USA, Michigan	Gordon et al (1992)	RIBA2	Sexual partners of HCV positive with chronic hepatitis	42	2	90% of partners reported frequent unprotected sex with their partners. Only case of transmission was a woman who reported razor sharing.

Table 24 Rate of mother-to-infant transmission of hepatitis C virus in published studies

Transmission rates refer to numbers of infants, not number of mothers

Country	Reference	Assay	No. of children	Transmission rate (%)	Risk factors
Australia	Latt et al (1994)	EIA2, HCV RNA	25	12	No mothers HIV infected
England	Kudesia et al (1995)	EIA2, HCV RNA	13	0	1 mother coinfected with HIV
France	Roudot Thoraval et al (1993)	EIA2, RIBA2, HCV RNA	18	0	All HIV negative; 8 mothers HCV-RNA-positive
France	Marcellin et al (1993)	EIA2, HCV RNA	10	0	All mothers HIV negative, normal liver transaminases. 5 mothers HCV-RNA positive.
Germany, Berlin	Meisel et al (1995)		231	1.3	Mothers infected by immunoglobulin. No children developed apparent or chronic hepatitis.
Italy, Florence	Resti et al (1992)	EIA, RIBA2, HCV RNA	22	23	All HIV negative. 12/22 mothers HCV-RNA positive. 5/12 babies born to HCV-RNA-positive mothers infected.
Italy, Milan	Paccagnini et al (1995)	EIA2, HCV RNA	70	20	12% if mother HIV negative (17), 23% if positive (53). Rate of vertical transmission higher if vaginal delivery (32%) than by caesarean section (6%). 4 of HCV infants became HIV infected.
Italy, Milan	Zuccotti et al (1995)	EIA, HCV RNA	37	16	31% in 13 mothers who were HCV-RNA positive and had HIV, and 25% of the 8 with HCV RNA alone. 0% in mothers who were HCV-RNA negative. Only infants born to mothers infected with subtype 1b or 3a acquired HCV.
Italy	Novati et al (1992)	EIA1 RIBA, HCV RNA	8	13	All mothers HIV infected
Italy	Giovannini et al (1990)	EIA1	25	44	All mothers infected with HIV. Infection of children defined by persistence of anti-HCV antibody beyond 6 months of age. All 11 children infected with HCV were also infected with HIV.
Italy	Zanetti et al (1995b)	EIA?, RIBA?, HCV RNA	116	7	0/94 cases of transmission in HIV- mothers, but 8/22 (36%) in HIV+ mothers who had higher levels of HCV RNA (transmission was 44% in HIV+ HCV RNA+ mothers). No transmission in 71 breastfed babies of HIV- mothers. No transmission in HCV-RNA- mothers.
Italy	Giacchino et al (1995)	EIA2, HCV RNA	31	6	No mothers infected with HIV. Transmission in HCV-RNA-positive mothers was 10%.

Country	Reference	Assay	No. of children	Transmission rate (%)	Risk factors
Japan	Ohto et al (1994)	EIA2, HCV RNA	54	6	11% transmission in HCV-RNA positive mothers, 0% in HCV-RNA negative mothers.
Japan	Uehara et al (1993)	EIA2, HCV RNA	12	8	Seven mothers HCV-RNA positive. One case of transmission in a HCV-RNA-positive mother. May have been breast milk transmission (initially HCV-RNA negative, later positive).
Japan, Hiroshima,	Moriya et al (1995)		87	2.3	All mothers were HCV-RNA positive but had no evidence of hepatitis.
Scotland	Lam et al (1993)	EIA2, RIBA	66	6	Forty-eight of 56 mothers were coinfected with HIV, and 59% of mothers were HCV-RNA positive. Infection defined by repeated EIA2 positive after 6 months of age. No association between HIV and HCV infection.
Spain	Alvarez (1992)	EIA1 RIBA1	22	4.5	All mothers HIV infected. The one child who was HCV infected was also HIV infected. Mother had advanced stage HIV disease.
Sweden	Wejstal et al (1993)	EIA1/2, RIBA2, HCV RNA	21	5	All mothers were positive for HCV RNA
Taiwan	Lin et al (1994)	EIA2, HCV RNA	15	7	One case of transmission was from a mother with very high levels of HCV RNA (10^{10} copies/mL)
Taiwan	Ni et al (1994b)	EIA2	11	18	No comment on HCV RNA in mothers. All HIV negative.
USA	Thaler et al (1991)	EIA1, RIBA1, HCV RNA	10	80	Five mothers coinfected with HIV. 8 mothers HCV RNA positive, transmission occurred in all.
USA	Reinus et al (1992)	EIA,RIBA, HCV RNA	24	0	Four mothers coinfected with HIV

Table 25 Prevalence of anti-hepatitis C virus in household contacts of anti-HCV-positive people

Country	Reference	Assay	No. and type of index cases	No. of contacts	Prevalence of antibody (%)	Background prevalence, specific risk factors
Germany	Brackmann et al (1993)	EIA1, EIA2, some RIBA2	HCV-infected people with haemophilia	228	0.4	12% of household contacts were anti-HBc positive
Italy, Bra	Napoli et al (1993)	?	HCV infected	108	2-34	Prevalence 0% in family members of negative controls. Rate in children 2%, siblings 14%, other cohabitants 17%, spouses 34%.
Italy, Naples	Vegnente et al (1994)	EIA2 RIBA2	44 children with chronic HCV	77 parents 56 sibs	14 0	No horizontal spread in children
Italy, Naples	Coltorti et al (1994)	EIA2 RIBA2	Chronic HCV hepatitis	100 spouses 260 children	27 1.9	
Italy, Piacenza	Buscarini et al (1993)	EIA2 RIBA2	Chronic HCV disease HCV-infected donors	107 30	14.9 0	Prevalence in blood donors 1.7%. 8 infected children, families had used reusable syringes. Mean age of infected children and sexual partners older than HCV negative.
Italy	Marino et al (1994)	EIA2	HCV infected	159	8.8	Rate higher in those who had sexual relationship with index case (18%) than those who did not (3.1%)
Japan, Fukoaka	Hayashi et al (1995)	EIA2	General population survey	Children Men Women	18 22 in wives 35 in husbands	Community prevalence 20%, ranged from 0 if <19 to 31% if 60-69
Japan, Iki Island	Nakashima et al (1995)	EIA2	General population survey of 1122 people	53 children 51 men 44 women	5.7 33 wives 39 husbands	Community wide prevalence was 14% of 1122. Zero prevalence in 312 people under 20. All positive children of positive mothers were older than 20 and all had undergone surgery.
Japan, Kanazawa	Honda et al (1993)	EIA2	Chronic HCV	88	23	23% (5/22) of positive fathers, 29% (4/14) positive mothers, 30% (3/10) positive siblings, 19% (8/42) spouses
Japan, Osaka	Oshita et al (1993)	EIA2	HCV infected	219	12	Control group rate 2%, volunteer blood donors 1.5%. 24% in spouses, 5% in children, 9% in 34 others. Positivity increased with age. Only 1/33 children aged < 20 positive. No spouses aged < 40 pos.

Country	Reference	Assay	No. and type of index cases	No. of contacts	Prevalence of antibody (%)	Background prevalence, specific risk factors
Japan	Goto et al (1994)	EIA1, EIA2	HCV liver disease	118	12.7	Blood donor prevalence 1.1% (3.1% at age >50). Prevalence 13% father-child pairs (3/24), 18% mother-child pairs (3/17), 25% sibling pairs (2/8), 16% husband-wife (6/38) pairs.
Korea	Kim et al (1994)	EIA2	HCV infected	181	2.2	1% in controls. No evidence of familial clustering. History of acupuncture and transfusion associated with HCV risk.
Spain, Oviedo	Riestra et al (1992)	EIA	120 HCV infected	302	4.3	0.78% in blood donors. Positives were 1 mother, 7 sexual partners, and 5 sons. Positive contacts older, longer 'contact time' (mean of 29 years). Higher risk if index had cirrhosis.
Spain, Oviedo	Riestra Menendez et al (1991)	EIA1	225 HCV infected	530	4.9	0.78% in blood donors. Prevalence increased with age, contact time. No higher if sexual relationship.
Spain	Camarero et al (1993)	EIA2 RIBA?	27 children with HCV infection	80	1	1 brother positive (age 15). No history of drug abuse. There is no mention of whether this brother may have had a blood transfusion.
Spain	Garcia Bengoechea et al (1994)	EIA2 RIBA2	Chronic HCV	401	2.5	Sexual contacts 4.7%, others 2.5%. Of non-sexual contacts, rate was higher in parents (4.2%) than in siblings (2.7%) or offspring (1.1%).
Taiwan	Hou et al (1995)	?	HCV infected haemodialysis patients	186	5.4	Not significantly different from that of age-matched adults
Taiwan	Huang et al (1993)	EIA2	27 HCV RNA+ renal dialysis patients	86	8.1	Spouses 10%, others 7.6%
Taiwan	Kao et al (1992)	?	HCV infected	186	5.4	Higher than background prevalence
Thailand	Pramoolsinsap et al (1992)	EIA1	29 HCV liver disease	20 spouse 72 other	10 4	Prevalence in blood donors 0.4-1.5%. Positive contacts older (all aged >40).

Table 31 Studies of hepatocellular carcinoma in Italy

Reference	Place/test type	Type of study	Definitions	Results	Conclusions
Colombo et al (1989)	Specialist Unit in hospital Stored sera, 1st generation RIA	Descriptive case series	Cases: consecutive cases of HCC=238 diagnosed by histology, sera on 132. Comparison: chronic liver disease patients Chronic hepatitis=139 Posttransfusion=19 Cirrhosis+transfusion=82 Cryptogenic=38	Proportion HCC who were HCV+=0.65 Proportion cirrhosis who were HCV+=0.74 Recorded alcohol consumption, blood transfusion, HBsAg+ had no effect on the proportion of HCC patients who were HCV+ (** actually 70 v. 54%)	HCV common in both the HCC and chronic liver disease groups
Colombo et al (1991b)	Stored sera EIA or RIA ?1st generation	Cases series of HCC and NANBH CLD	HCC=132 Chronic NANBH & cirrhosis=139 Controls=untreated haemophiliacs (11), housestaff (15); miscellaneous liver diseases (11)	HCC: 65% anti-HCV+ (similar frequency if HBsAg+ or -). Chronic hepatitis & cirrhosis: 71/72% anti-HCV+. Miscellaneous disease: 18% anti-HCV+ Healthy control groups 8% anti-HCV+	High prevalence of anti-HCV in patients with HBsAg+ cirrhosis. (53% of all those with HBsAg; 16.7% of all HCC patients had dual infections). Suggests patients infected by both viruses are more likely to develop serious liver disease.
Colombo et al (1991a)	Specialist Unit in hospital Stored sera, 1st generation EIA	Prospective case series of 447 patients with cirrhosis	HCC found in 30 (7%) at baseline and 29 (7% of patients free of tumour at baseline) during follow-up (mean 33 months)	Baseline prevalence of HCC was 7% with yearly incidence of 3% throughout follow-up. The major single cause of HCC was HCV but for many cases there was a multifactorial aetiology.	A viral aetiology for 62% of HCC
Coltorti et al (1994)	Naples, Italy	Case series	Cirrhosis=536 HCC+cirrhosis=122	Cirrhosis: 23.6% HBsAg+; 63.1% anti-HCV HCC+Cirrhosis: 21.3% HBsAg+; 83.2% anti-HCV Age >57 y, male sex, HCV infection and duration of cirrhosis contribute to progression of HCC in cirrhotic patients. Patients with anti-HCV-positive HCC had a significantly longer duration of cirrhosis than anti-HCV-negative ones. Cumulative frequency of HCC was higher in anti-HCV-positive patients, independently of cirrhosis duration.	

Reference	Place/test type	Type of study	Definitions	Results	Conclusions
Curley et al (1995)	1st and 2nd generation EIA	Descriptive case series	Prospective study of 416 patients with chronic hepatitis (340 HCV, 69 HBV, 7 both) screened for HCC	Initial screening identified symptomatic HCC in 33 patients (7.9%);+3 others identified in 1st year of follow-up.	Most HCC found in subset of patients with liver biopsies showing severe CAH, cirrhosis or both.
Farinati et al (1992)	EIA generation not specified, some checked by RIBA (90% concordance)	Cases series	97 patients with histologically proven HCC	Overall presence of anti-HCV was 64%Prevalence was significantly lower in HBsAg+ patients	
Gentilini et al (1994)	Florence 2nd generation EIA, and PCR for HCV RNA	Cases series of HBV or HCV cirrhotic patients	405 patients, followed for up to 15 years	Cumulative occurrence rates (%) for HCC at 5, 10 and 15 y: HCV: 4.6, 24.0, 56.2 HBV: 6.5, 23.4, 31.9 (no significant difference between HBV and HCV) Cumulative occurrence rates were significantly higher in males	Most important predisposing factor for the onset of HCC is cirrhosis. Females may be relatively protected from HCC (by hormonal or immunological factors) that are lacking after the fertile period.
Simonetti et al (1992)	Sicily Referral based hospital EIA, RIBA	Case-control -2 studies	I. Cases: 212 patients with HCC (197 with cirrhosis) Controls: Chronic nonhepatic diseases 2. Cases: 197 patient with HCC+cirrhosis Controls: Pair-matched controls with cirrhosis but not HCC	I. 71% of HCC patients were anti-HCV+ cf. 5% with nonhepatic chronic disease (OR=42; 95% CI 22, 95). Anti-HCV was an independent risk factor for HCC (OR=69; 95% CI 15, 308). HBsAg (OR=8.7, CI, 1.5, 50) and anti-HBc (OR=4.2, CI 1.7, 11) were also risk factors for HCC. No significant interaction was found between anti-HCV and HBV markers 2. 74% of patients with HCC and cirrhosis were anti-HCV+ cf. 62% of those with cirrhosis alone (OR 1.8; 1.1-2.8). Anti-HCV and HBsAg were independent risk factors for HCC	HCV is a risk factor for HCC HCV infection acts independently of HBV infection and of alcohol, age or gender.
Stroffolini et al (1992)	Four hospitals 2nd generation EIA Samples frozen & tested within months of collection	Case control	Cases: Newly diagnosed HCC=65 Controls: Gender & age matched, consecutively admitted to same hospital with nonhepatic chronic diseases	Prevalence of markers (OR compared to no markers) anti-HCV alone: Cases 59%; controls 13%; OR=21.3 (8.8, 51.3) HBsAg+ alone: Cases 17%; controls 6%; OR=13.3 (5.5, 32.2) anti-HCV plus HBsAg Cases 8%; controls 0%; OR=77.0 (3.8, 1421)	

Table 32 Studies of hepatocellular carcinoma in Greece and Turkey

Reference	Place/test type	Type of study	Definitions	Results	Conclusions
Hadziyannis et al (1995)	Athens, 2 hospitals 2nd generation, RIBA confirmed	Case control	Cases: 65 consecutive incident cases of HCC Controls: matched on age and sex 1. 65 metastatic liver disease 2. 65 cases with ENT admissions	HCC: anti-HBs=61.5% HCV=12.3% 1. MLC: anti-HBs=12.3% HCV=4.6% 2. ENT: anti-HBs=6.1% HCV=0% OR HCC v. both controls: HBsAg: 18.8 (95% CI 8.2, 43.2) anti-HCV: 7.7 (95% CI 1.7, 35.1)	Insufficient cases to examine whether there is an interactive effect of HBV and HCV in development of HCC
Kaklamani et al (1991)	Athens Hospitals 1st generation EIA on stored sera	Case control (Record review of patients 1976-84)	Cases: 185 HCC diagnosed by histology (108) or αFP (77) Controls: 1. Accident orthopaedic admissions (432) 2. MLC (35)	Prevalence of HCV (%): HCC=39 MLC=3 Control=7 For HCV: RR for HCC=6.3 (95% CI 3.7, 11.0) For HBsAg+: RR=11.4 (95% CI 6.7, 19.4) For HbsAg+ HCV: RR=20.0 (95% CI 2.5, 157.5)	RR of HCC in hospitalised Greek people with HCV is 6.3. RR is even greater if coinfection with HBV HCV has an interactive role in the origin of HCC
Ozyilkan et al (1994)	Turkey	Case series, prevalence study	Cases: HCC=25 (histology) Also looked at 127 patients with cirrhosis	Prevalence anti-HCV: 1/25=4% Prevalence HBsAg+: 19/25=76%	Low prevalence of HCV in HCC patients may reflect the low carriage of HCV in the Turkish population
Tzonou et al (1991)	Athens Stored sera 1st generation	Case control Patient interview	Cases: HCC=185 Controls: 432 hospital controls	Anti-HCV RR=6.2 (95% CI 3.6, 10.6) Rate ratio is higher in subjects HBsAg+ (RR 20.0 v. 4.4) RR is higher for subjects with pre-existing cirrhosis (11.4 v. 4.4)	The association between presence of HCC and HCV is highly significant
Zavitsanos et al (1992)	Athens hospitals1st & 2nd generation EIA on stored sera, RIBA confirmation	As above	As above	Prevalence of HCV HCC=13.3% MLC=0% Controls=1.4% For HCV: RR for HCC=10.4 (95% CI 4.2, 26.0)	Association between HCC and HCV is increased when a 2nd generation assay is used

Table 33 Studies of hepatocellular carcinoma in Spain

Reference	Place/test type	Type of study	Definitions	Results	Conclusions
Bruix et al (1989)	Hospital Liver and Virus Unit Stored sera, 1st generation EIA	Descriptive case series	Cases: Consecutive cases HCC=96 diagnosed by histology (74); ultrasound/computerised axial tomography/αFP (22) Comparison groups: 1. Cirrhosis without HCC (ultrasound, αFP) 2. Hospital surgical admission not due to liver disease	Proportion HCC who were HCV+=0.75 Proportion cirrhosis who were HCV+=0.556 Proportion surgery unit control who were HCV+=0.073 Recorded alcohol consumption, age, sex, blood transfusion had no effect on the proportion of HCV+	High prevalence of HCV in this group with HCC in Spain
Castells et al (1995)	Barcelona University liver clinic 2nd or 3rd generation EIA, RIBA	Case series of HCC in cirrhosis patients	191 consecutive cases of HCC	HBsAg+ in 14 patients (7%), 8 had dual infection Anti-HCV in 152 patients (79.5%) No significant difference in anti-HCV prevalence by HBsAg+ status (but lower if Ag+, 81.3 v. 57%) 29 patients had a history of blood transfusion before diagnosis of hepatic cirrhosis Mean interval (± s.d.) between date of transfusion and diagnosis of HCC was 29.4±12.6 y in nonalcoholic (*n*=21) cf. 22.7±14.9 y in alcoholics (*n*=8) ('alcoholic' is not defined)	Before anti-HCV testing was available, the aetiology of chronic liver disease was attributed to excessive alcohol in 100/191 patients. Trend to shorter interval between blood transfusion and HCC in alcoholic patients. Prevalence of anti-HCV in patients without a history of previous transfusion was 55.4%.
Ruiz et al (1992)	University liver clinic 2nd generation EIA, nested PCR	Case series	Cases: 70 patients with HCC (cirrhosis 65; CAH 1, normal liver 4) 19 had histories of alcohol abuse (>80 g/day)	HBsAg+ 17%; HBV markers 37% anti-HCV 63% HCV RNA found in 42/68=62% No viral marker 16%	HCVis more prevalent than HBV in HCC patients in Spain. Most HCC patients have a viral marker.

Table 34 Studies of hepatocellular carcinoma in Japan and Korea

Place and reference	Test type	Type of study	Definitions	Results	Conclusions
Chiba, Japan Takano et al (1995)	University Hospital 1st generation EIA, 2nd generation after liver biopsy	Prospective study of chronic hepatitis patients: divided in CPH, CAH2a & CAH2b based on liver biopsy	anti-HCV+:=124 HBsAg+=127 Seven with markers of both excluded	Incidence of HCC in HCV+ patients (13) was 2.6 times that of HBV patients (5). 7.7% of cases in HCV patients *cf*. 40% of cases in HBV patients did not have cirrhosis The prevalence of genotypes in HCC patients was the same as in the total number of followed HCV patients	Despite similar population prevalence of HBV (1.5%) and HCV (1.3%) about 80% of cases of HCC within the institution are HCV-assos'd. Therefore, the authors argue, the incidence of HCC in HCV carriers is higher than in HBV carriers.
Fukuoka, Japan Tanaka et al (1991)	Hospitals 1st or 3rd generation on stored sera, RIBA confirmation	Case control Interview	Cases: 91 HCC diagnosed by histology (30), angiography (58) or ultrasound/CT (3) Controls 1.Cirrhosis, same age, sex (Histo 24; laparoscopy 14; clinical/CT 37) 2. Population (Public health centre) controls, age matched	Prevalence HCV HCC=68% Cirrhosis=64% Controls=7% For HCV: RR for HCC=52.3 (95% CI 23.9, 114.3) For HBsAg+: RR=15.3 (95% CI 2.0, 7.0) If HCV+ and cirrhosis: RR=64.4 (27.4, 151.4) Negative correlation between HCV and HBsAg infection Attributable fraction of HCV for HCC=0.49 (0.39-0.60)	Negative correlation between HBV and HCV is unexplained Heavy alcohol remains a risk but the increase was moderate to slight (RR for HCC=2.2; for cirrhosis=1.4).
Japan Tomimatsu et al (1993)	Surgical unit Stored sera, repeat reactors on 2nd generation EIA	Descriptive case series	Prevalent cases of HCC diagnosed histologically=121 Prevalent cases of CC diagnosed by histology=13 Combined HCC+CC=7	Proportion HCC who were HCV+=0.703 Proportion CC who were HCV+=0.308 Proportion HCC+CC who were HCV+=0.714	HCV is increased in HCC and combined HCC/CC in Japan
Japan Ikeda et al (1993)		Prospective cohort study of cirrhosis	795 consecutive patients with viral or alcoholic cirrhosis, followed for 2-17 y (median 5.8 y). Cumulative appearance rates of HCC were 19.4, 44.3 and 58.2% at 5, 10 & 15 y, respectively.	The appearance rates of HCC in 180 patients with only HBsAg and in 349 patients with only antibodies to HCV were 14.2 and 21.5% at 5 years, 27.2 and 53.2% at 10 years and 27.2 and 75.2% at 15 years, respectively	αFP levels, age and past alcohol consumption were independent predictors in the group of HCV-positive patients

Place and reference	Test type	Type of study	Definitions	Results	Conclusions
Japan Kiyosawa et al (1990)	University hospital Stored sera tested on 1st generation EIA	Retrospective cohort NANBH CLD patients Chart review/interview and family interview	Cases: All HCV+ (nonHBV) patients with biopsy-proved chronic liver disease=205 Comparison: All HCV- patients admitted with biopsy-proven CLD. (excluded CLD other causes)=26	RR HCC of HCV Ab+=6.31 Prevalence of HCV in NANBH=90%; in HBV=19% Prevalence of blood transfusion in NANBH=41%; in HBV=5% Prevalence of HCV in HCC. NANBH=94%; HBV=35% Mean interval (± s.d.) to development of HCC from blood transfusion in those with HCV=29±13.2 y 86% of HCC patients had cirrhosis	Close association between HCC and HCV positivity. High frequency of blood transfusion in this group (other causes had been excluded). Prolonged interval between transfusion and HCC 14-60+ y lag between putative infection and tumour development suggests chronic inflammation &/or hepatic regeneration may play a role in carcinogenesis.
Japan Nishioka et al (1991)	5 hospitals Serum from HCC throughout Japan, 1st generation EIA	Prevalence study, case series	Cases: HCC by histology with available sera, excluding those transfused after HCC diagnosed=180 (HBsAg+=75) Comparison group: Historical data re seroprevalence in blood donors	Proportion HBsAg-ve HCC who were HCV+=0.762 Proportion HBsAg+ve HCC who were HCV+=0.147 Proportion blood donors HCV+=0.012 (HBsAg+ and HBcAb markers same in HCV- & HCV+) Transfusion associated with 39% of HCV+ *cf.* 4.7% HCV-ve.	High prevalence of HCV (76.2%) in this group of patients with HCC. Past alcohol consumption was an independent predictor for the appearance rate of HCC in HCV+ positive but not HBsAg+ patients.
Nagasaki Prefecture, Japan Hamasaki et al (1993)	Stored sera Serial 1st , 2nd generation EIA, then PCR	Marker prevalence study over time, hospital case series	Cases: 253/295 patients with HCC admitted to hospital between 1976 and 1990 (those with stored sera)	More than 90% of patients positive for HBsAg or HCV. Serial changes with HBsAg+ prevalence peaking in 1982-84 and thereafter decreasing; HCV prevalence in cases increasing in last 6 y	Familial clustering found Only 23% of HCV+ patients had received blood transfusions.
Osaka, Japan Pyong et al (1994)	Koreans living in Osaka	Case control	Cases: 90 hospital admissions with newly diagnosed HCC Controls: 249 hospital patients matched for age group	Cases: Prevalence HCV=74.4%; HBsAg+=16.7%; 41.1% of cases were heavy drinkers Controls: Prevalence HCV=8.0%; HBsAg+=3.6% Adj OR: HCV=92.4 (95% CI 33.8, 252); HBsAg+=58.2 (95% CI 15.3, 221)	

Table 34 continued overleaf

Place and reference	Test type	Type of study	Definitions	Results	Conclusions
Osaka, Japan Tsukuma et al (1993)	Stored sera 1st generation EIA	Prospective study of 917 patients with cirrhosis (240) or chronic hepatitis (677)	917 patients with cirrhosis (240) or chronic hepatitis (677)	Follow-up for 35.7± 13.0 months (range 5-52), HCC developed in 52 patients. 3-y cumulative risk of HCC was 12.5% for 240 patients with cirrhosis at enrolment and 3.8% for 677 patients with chronic hepatitis. Risk of HCC increased in patients with HbsAg. Rate ratio 6.92 (95%CI 2.92, 16.39) and 4.09 (1.30, 12.85) in patients with anti-HCV.	Risk of liver cancer in men was 1.33 times that in women. Positive association between risk of liver cancer and age at enrolment. Use of 1st generation assay may underestimate the rate ration for HCC.
Pusan, Korea Park et al (1995)	2nd generation EIA	Prevalence study in CLD and HCC patients		Controls: anti-HCV=1.6%; HBsAg+=5.2% , No HCV/HBV marker=30.3% Chronic hepatitis: anti-HCV=24.3% HBsAg+=63.4%, No HCV/HBV marker=4.2% Cirrhosis: anti-HCV=18.9% HBsAg=47.3%; No HCV /HBV marker=8.0% HCC: anti-HCV=14.3% HBsAg=61.1%, No HCV/HBV marker=3.7%	Current or previous HBV infection is still the major cause of chronic hepatitis, cirrhosis and HCC in Korea.
Tokyo, Japan Shiratori et al (1995)	Hospital series HCV PHA (Dinabbott kit)	Case series, prevalence study	Cases: 205 consecutive patients with HCC	70.7% positive for anti-HCV alone, M:F ratio=3.3:1 12.7% positive for HCV and HBcAb, M:F=5.5:1 11.2% HBsAg+ alone, M:F=7.1 1.0% HCVAb and HBsAg+ 4% no HBV or HCV marker Cirrhosis and severe chronic hepatitis present in 69.3 and 24.8% of HCV Ab cases.	Interval after blood transfusion in HCV+ cases was ~30 y; 35-45 y if transfused before 20 y of age. Less cirrhosis if HBsAg+ (50% cf. >70% in anti-HCV+), patients younger (52 cf .62 y), M:F ratio higher. 3 y survival was higher in HCV related HCC.
Tokyo, Japan Saito et al (1990)	Specialist hospital units Stored sera , 1st generation EIA	Descriptive case series. Record review	Cases: All HCC diagnosed clinically and pathologically=253 Other cancer patients with available sera (including 5 with liver metastases)=148	Proportion HCC who were HCV+=0.545 Proportion HCC who were HBsAg+=0.202 Proportion HCC who were HCV+ and HBsAg +=0.008 Recorded alcohol consumption no effect on the proportion of HCV+	Blood transfusion reported in 35.8% of HCC with HCV. HCV is associated with 55% of HCC, especially high where no HBV markers.
Toyama, Japan Watanabe et al (1994)	Stored sera ?1st generation HCV PCR in those with HCC	Prospective study of patients with chronic hepatitis and cirrhosis	167 patients with anti-HCV+ chronic liver disease: 86 with chronic hepatitis and 81 with cirrhosis Longer follow up in hepatitis patients(mean 53.8 v. 36.6 months)	13/81 (16.0%) hepatitis patients developed HCC 56/86 (65%) patients with cirrhosis developed HCC	A close relationship between oncogenicity and HCV activity. Hepatitis activity index (HAI) score was not demonstrated.

Table 35 Studies of hepatocellular carcinoma in Taiwan

Reference	Place/test type	Type of study	Definitions	Results	Conclusions
Chang et al (1994)	Taiwan, community setting Stored sera, repeat reactors 2nd generation EIA	Nested case control Questionnaire and structured interview	Cases: 38/55 newly diagnosed cases of HCC with sera available Controls: healthy men in community cohort, matched 4:1 by age, date of recruitment and residence	Prevalence of HCV HCC=13.2% Controls=2.6% RR for HCC if HCV+=7.9 (95% CI 1.49, 41.8) RR for HCC if HBsAg+=26.5 (7.9, 88.6) Attributable fraction to HCC. HCV=0.152, HBsAg+=0.636	HCV infection is causally related to HCC in Taiwan although the attributable fraction is less than for HBV
Chang et al (1992)	Taiwan Hospital series 1st generation EIA	Case series	Consecutive hospital admissions with cirrhosis (138) or HCC (306). Cases were those with cirrhosis or HCC who had pre and posttransfusion stored sera, who received >10 transfusions between 1987 and 1990. 30 patients were selected	HCC: HBsAg+=42.9%; Cirrhosis: HBsAg+=57.1%; 5/30 (16.7%) were anti-HCV+ prior to transfusion 7/25 (28%) became anti-HCV+ after transfusion Seroconversions to HCV were much higher in those who were HBsAg- (66.7 cf. 15.8%)	The aetiological role of HCV is not so important in Taiwan as in Western countries. Transfusion might result in an overestimated pathogenic effect of HCV in cirrhotic patients and those with HCV.
Chuang et al (1992)	Hospital & community anti-HCV+ on EIA	Case control	Cases - 128 HCC diagnosed on histology Controls - 384 community participants in gallstone study, matched for age and sex	Prevalence HCV HCC=19.5% Controls=3.3% Relative risk (95% CI) cf. HBsAg-ve, anti-HCV -ve HBsAg+: 68% HCC v. 27.1%, RR=13.96 (7.82, 24.92) HCV+: 10.1% HCC v. 2.1%, RR=27.12 (9.83, 74.83) HBsAg+/anti-HCV+: HCC 9.4% v. 1.3, RR=40.05 (12.57, 127.6)	HBV and HCV were highly associated with HCC. The two viruses contribute independent but synergistic effects to the pathogenesis of HCC.
Lee et al (1992)	Hospital series ?1st generation EIA	Case series	Cases of histologically proven HCC=26 Controls: MLC=35	`	Mean age of patients (± s.d.) with: HBsAg+=55.5 ± 11.9 y anti-HCV=65.1 ± 6.0 y

Table 35 continued overleaf

Reference	Place/test type	Type of study	Definitions	Results	Conclusions
Tsai et al (1994a)	Hospital Stored sera, 2nd generation EIA x2	Case control	Cases: 102 hospital patients with HCC Controls: 1. Age/sex matched, nonhepatic hospital controls=102 2. Age/sex matched healthy community controls=204	Prevalence of HCV HCC=34.3% Nonhepatic disease=10.7%; Healthy control=2.4% Prevalence of HBsAg+ HCC=77.4 Nonhepatic disease=16.6%; Healthy control=19.6 anti-HCV: OR=3.4, 95% CI 2.1, 5.6 HBsAg+: OR=5.6, 95%CI 3.6, 8.5 Dual infection in 18 (17.6%) patients	Calculation of incremental ORs showed no interaction between HBV and HCV - 'they act independently and without interaction'
Tsai et al (1994c)	Hospital series 2nd generation EIA	Case control	Case control HCC=150 Control: community acquired, matched for sex and age	Association with HCC HBsAg+ OR=14.9 (4.2, 39.9) anti-HCV OR=12.8 (7.1, 23.2) Being HBsAg+ and HCV+ had an OR=3.3 cf. HBV+ HCV-ve	Both HBV and HCV infection are independent risk factors for HCC. There was no interaction between HBV and HCV in the development of HCC.
Tsai et al (1994b)	Hospital Stored sera 2nd generation	Case control	Cases: 102 HCC patients with nonalcoholic underlying cirrhosis Controls: 1. 102 age group/sex matched nonalcoholic cirrhotic patients 2. 102 age/sex matched, nonhepatic disease controls	anti-HCV+ prevalence All patients (102): HCC=40/102 cf. 1. 28/102 & 2. 11/102 patients The prevalence of anti-HCV in controls (10.7%) was significantly lower than that in HCC (OR 4.34, 95% CI, 61.7-79.3) or cirrhosis (OR=3.13, 95% CI 1.38, 7.21) HBsAg+ patients (72) anti-HCV+: HCC=20/72 cf. 1. 16/76 and 2. 2/17 patients No difference in prevalence of anti-HCV+ in HBsAg+ patients HBsAg-ve patients: 2. Controls=10.5% (4.6-16.4%) HCC=66.7% (57.5-75.7%) OR=16.88 (5.44, 54.88) Cirrhosis=46.1% (36.5-55.7%) OR=7.23 (2.29, 23.32)	Male sex and increasing age are associated with higher anti-HCV prevalence. HCV is an independent risk factor for HCC. Additive effect modification of HBsAg and anti-HCV as risk factor for HCC &/or liver cirrhosis.

Reference	Place/test type	Type of study	Definitions	Results	Conclusions
Yu et al (1991)	Two major teaching hospitals anti-HCV on EIA	Case control	Cases: Newly diagnosed HCC=127 Controls: Community controls matched for age, gender, ethnicity and residence	Anti-HCV: HCC: 11.0% Controls: 1.6% OR 7.0 (95% CI 1.6, 30.8) HBsAg+/HBeAg-: HCC: 67.7% Controls: 14.2% OR 17.2 (6.8, 43.4) HBsAg+/HBeAg+: HCC: 18.9% Controls: 2.4% OR 28.1 (6.4, 124.1)	Both HBsAg and anti-HCV remained significant risk factor in a multivariate model. Data show a considerably higher prevalence of anti-HCV in HBsAg- (29.4%) than in HBsAg+ (8.2%) HCC patients. Synergistic effect on HCC when both HBsAg+ and anti-HCV were present. Alcohol smoking and peanut consumption frequency interacted as risk factor with anti-HCV.

Table 36 Studies of hepatocellular carcinoma in China

Reference	Place/test type	Type of study	Definitions	Results	Conclusions
Ito et al (1993)	Hospital patients Stored sera, 1st generation EIA	Descriptive seroprevalence study Recorded clinical information	Cases: HCC patients with available sera=16 Comparison: 1. Viral hepatitis Acute=89; chronic=246; cirrhosis=44 2. Blood donors=451	Proportion of HCC patients who were HCV+=0.06 Proportion acute hepatitis patients who were HCV+=0.0 Proportion chronic hepatitis who were HCV+=0.03 Proportion HCC patients who were HBsAg+=0.87 Proportion blood donors HCV+=0.007	HCV accounts for a low proportion of hepatitis and HCC (but small group with HCC)
Jeng & Tsai (1991)	Hospital patients	Descriptive case series	Cases: Prevalent cases HCC diagnosed by histology=129. All HBsAg+ and 12 month of HBsAg+ patients Control: Healthy on physical check-up, no HCC on ultrasound	Proportion HBsAg-ve HCC who were HCV+=0.60 Proportion HBsAg+ve HCC who were HCV=0.24 Proportion HCV+ in healthy controls=0.0 48/129 (37.2%) HCC patients were positive for anti-HCV	HCV may play a role in the immunopathogenesis of HCC
Okuno et al (1994)	Guangxi Province, Southern China, Stored sera 2nd generation EIA	Case series	Cases: 186 patients with HCC diagnosed by histology (25), ultrasound, CT, αFP (161)	Prevalence HCV 10/186=5.4% (9 also HBsAg+, only 1 HBsAg-) Prevalence HBsAg+=70.4% 54 (29.0%) neither HBsAg+ nor anti-HCV	HCV does not play a very important role in the development of HCC in Guangxi
Yuan et al (1995)	Shanghai 2nd generation EIA	Nested case control	Cohort 18,244 men Cases: Incident cases of HCC=76 Controls: Matched for age, time of blood sample collection, residence=410	HBsAg+=48/76 anti-HCV+ 1 case; 1 control; RR 5.0 (0.3-79.0)	

Table 37 Studies of hepatocellular carcinoma in the United States of America

Reference	Place/test type	Type of study	Definitions	Results	Conclusions
Di Bisceglie et al (1991b)	Stored sera, 1st generation EIA	Descriptive case series	Cases: consecutive cases HCC diagnosed by histology=99 Comparison: cancer patients in same institution at some time=98	Prevalence HCV HCC=13.0% Controls=2.0% HCC if HCV+: RR=7.3 (95% CI 1.8, 48.2) HCC if HBsAg+: RR not calculable; estimate=17.3 Attributable fraction of HCV for HCC=0.114 Estimated attributable fraction of HBV for HCC=0.067	
Hasan et al (1990)	Miami Hospital Liver Unit 1st generation EIA anti-HCV positive	Retrospective prevalence study Record Review	Cases - 59 HBsAg-ve HCC diagnosed by histology (51) or ultrasound/CT & αFP (8) Comparison groups 1. HCC with HBsAg+ -28 2. Blood donors - 200 3. Cryptogenic cirrhosis - 76	Prevalence HCV in HBsAg-ve HCC=53% HBsAg+ve: Presence of HCV=14% Blood donors=0.5% Cryptogenic cirrhosis=42%	HCV is prevalent among HCC patients, but causal relationship is unknown. Time relationship of exposure (HCV) and outcome (HCC) is unknown.
Liang et al (1993a)	Miami Hospital Sensitive PCR, three sets of HCV and HBV primers	Cases series Prevalence study	Cases: 91 HBsAg- patients with no other predisposing factors for HCC	29% low levels of HBsAg in serum, liver/tumour tissue 58% HCV infected 13% infected with HBV alone 15% HBV/HCV coinfection 43% HCV markers only 29% no identifiable viral markers	HCV and occult HBV infection accounts for most (71%) of the HCC cases of unknown pathogenesis in the USA
Mangia et al (1994)	Stored sera Immunoblot, PCR for HCV RNA	Case series	Cases: 87 patients with HCC	anti-HCV detected in 16% by EIA; only 57% confirmed by RIBA and an additional 4 -ve on 1st gen were positive. HCV RNA detected in 6 - all +ve on RIBA	HCV plays a less important role in HCC than in Europe and Japan

Table 38 Others studies of hepatocellular carcinoma

Reference	Test type	Type of study	Definitions	Results	Conclusions
France Ducreux et al (1990)	Stored sera tested on 1st generation EIA	Case series comparison without HCC	Cases: 74 cases HCC diagnosed by histology (48), ultrasound/CT & αFP (11) and ultrasound/CT/clinical (15)	Proportion of HCC with HCV Ab=0.28 Proportion of cirrhotic controls with HCV Ab=0.20 Proportion of HCC with HCV+/ HBV+=0.47 Proportion of HCC with HCV+/ HBV-=0.14 Proportion of cirrhotic controls with HCV+/HBV+=0.27 Proportion of cirrhotic controls with HCV+/ HBV-=0.16	No differences in rates of HCV Ab between HCC and cirrhosis cases
France, Paris Ganne Carrie et al (1996)	Hospital Stored sera, 3rd generation EIA	Prospective cohort study of cirrhosis	31/151 patients hospitalised with histological cirrhosis developed HCC	Age ≥ 50 years (P=0.01) Male (P=0.01), Large oesophageal varices (EV) (*P*=0.03) prothrombin activity <70% (*P*=0.04) serum α-FP ≥ 15 ng/L (*P*=0.06) anti-HCV antibodies (*P*=0.08). Liver large cell dysplasia had an additional predictive value in high-risk patients	It is possible to identify by liver biopsy a subgroup at high risk for HCC. May be a basis for intensive screening or preventive measures.
India, New Delhi, Ramesh et al (1992)	Hospital-based 2nd generation EIA	Seroprevalence study	CAH=85 Cirrhosis=44 HCC=53	CAH: HBsAg+=44.7%; anti-HCV=15.3% Cirrhosis: HBsAg+=61.4%; anti-HCV=18.0% HCC: HBsAg+=28.0%; anti-HCV=15.1%	Low prevalence of HCV among patients with HCC and CLD in India cf. Japan and Europe. When HBV cases were excluded, only 14.6% of CLD/HCC cases had HCV.
Rwanda Mets et al (1993)	Stored sera 2nd generation EIA	Case series	Cirrhosis=79 HCC=26 Voluntary blood donors=54	Prevalence of anti-HCV Cirrhosis=48%; HCC=38%; Controls=17% 84% of cirrhosis & 54% of HCC patients were HBsAg+	Prevalence of anti-HCV antibodies was significantly higher for cirrhosis patients who had been in contact with HBV but who had no persistent infection with HBsAg.
Saudi Arabia Al Kawari et al (1992)	Frozen sera 1st generation	Cross-sectional seroprevalence study		Anti-HCV+ Volunteer blood donors=1.5% Antenatal=1.0% Chronic liver disease (HBsAg+)=14.0% Chronic liver disease (HBsAg-)=37.5% HCC (HBsAg+)=12.5% HCC (HBsAg-)=42.3%	Overall seropositivity of 30.4% in 181 liver disease patients is lower than that reported from European countries.

Reference	Test type	Type of study	Definitions	Results	Conclusions
Scotland Haydon et al (1995)	Hospital cases Frozen sera, 3rd generation RIBA	Case series	Cases: 65 patients with HCC	13 patients (20%) had chronic HCV infection, all were negative for HBsAg+ All had histologically confirmed background cirrhosis Genotype 1b in 8 patients, genotype 4 in 2	Study supports the role of specific HCV genotypes, particularly 1b. Strong association between chronic HCV infection, cirrhosis and hepatocarcinogenesis. Time from probable HCV transmission to HCC development ranged from 19 to 49 y (mean± s.d., 38 ± 11).
South Africa Kew et al (1990)	Stored sera tested on 1st generation EIA	Case series with comparison group Recorded data on HBsAg+ and Ab	Cases: 388 histological HCC Comparison: 'healthy', matched for age, gender, rural/urban origin	Proportion of HCC with HCV Ab=0.29 Proportion of controls with HCV Ab=0.007 Proportion of HCC with HB+=0.81 Proportion of controls with HB+=0.55	Prevalence of HCV higher in the group with HCC than in apparently healthy controls. HCV prevalence higher in HBsAg-ve than HBsAg+ patients (34 v. 26%).
Sweden, Goteborg Wejstal et al (1993)	2nd generation EIA, RIBA	Case series	Cases: 5 patients (4 post-transfusion & 1 spontaneous NANBH)	For 4 posttransfusion cases, the mean interval from time of transfusion until diagnosis was 15.8 ± 7.4 y	Chronic hepatitis preceded development of HCC, and cirrhosis was present in all patients when HCC was diagnosed
Switzerland, Zurich, Garson et al (1992)	Hospital Frozen sera, 2nd generation EIA, RIBA confirmation	Case series	Cases: 40 patients with histologically confirmed HCC	Serological evidence of HCV in 14/40 (35%) 12/14 PCR-RNA +ve 7 of the 14 had evidence of previous HBV infection, 2 gave histories of high alcohol consumption	Ongoing viral replication is present in most HCC patients with anti-HCV
Thailand, North East Srivatanakul et al (1991)	?1st generation EIA	Case control	Cases: HCC from 3 hospitals=73 Controls: hospital controls, matched for age, sex & educational level	HBsAg+ OR=12.0 (95% CI 2.9, 50.4) HBV marker OR=5.3 (CI 1.8, 15.2) anti-HCV+ OR=1.3 (CI 0.2, 8.7)	Infection with HCV in Thailand appears to be rare
Vietnam, Hanoi Cordier et al (1993)	EIA ? generation	Case control Hospital	Cases: Male HCC=152 Controls: Hospital, matched for gender, age, hospital and place of residence=241	HBsAg: cases 92.6%, controls 18.3%, OR 61.7 (30, 128) Anti-HCV: cases 2.0%, controls 0.8%, OR 2.0 (0.3, 17.4) If HBsAg- HCV+: cases 3 (27.3%), controls 2 (1.0%) OR=38.1 (2.8-1443)	HBV infection plays the major role in HCC in Vietnam

Table 39 Effect of hepatitis C virus infection on risk of hepatocellular carcinoma

Country	Reference	*n*	HCC			Control			Odds ratio		
			HCV+ve	HCV-ve	%HCV+ve	HCV+ve	HCV-ve	%HCV+ve	If anti-HCV positive	Lower 95% CI	Upper 95% CI
Italy	Stroffolini et al (1992)	164	43	22	66.2	13	86	13.1	12.9	5.59	30.5
Italy	Simonetti et al (1989)	424	151	61	71.2	11	201	5.2	45.2	22.4	97.6
Japan	Pyong et al (1994)	339	66	24	73.3	38	211	15.3	15.3	8.23	28.5
Japan	Tanaka et al (1991)	501	46	45	50.5	12	398	2.9	33.9	16.1	74.8
Taiwan	Chuang et al (1992)	512	25	103	19.5	13	371	3.4	6.93	3.26	15.2
Taiwan	Tsai et al (1994a)	204	40	62	39.2	11	91	10.8	5.34	2.44	12.4
Taiwan	Yu et al (1991)	254	14	113	11.0	2	125	1.6	7.74	1.71	71.22
Taiwan	Tsai et al (1994c)	300	35	115	23.3	3	147	2.0	14.9	4.49	77.1
Taiwan	CC Chang et al (1994)	190	5	33	13.2	4	148	2.6	5.61	1.12	29.5
USA	Di Bisceglie (1994)	197	13	86	13.1	2	96	2.0	7.26	1.56	67.5
Combined Mantel-Haenszel (M-H) Weighed Odds Ratio		3085	438	664	39.7	109	1874	5.5	14.5	12.3	21.1

Table 44 The prevalence of markers of hepatitis C virus infection in clinic populations with different levels of alcoholic liver disease

Population	Reference	Assay	Individuals without a high-alcohol intake (controls)				People with alcoholism				Individuals with noncirrhotic alcoholic liver disease				Individuals with alcoholic liver disease				Individuals with alcoholic cirrhosis				Individuals with hepatocellular carcinoma			
			No. of +ve	No. of -ve	Total	%	No. of +ve	No. of -ve	Total	%	No. of +ve	No. of -ve	Total	%	No. of +ve	No. of -ve	Total	%	No. of +ve	No. of -ve	Total	%	No. of +ve	No. of -ve	Total	%
France	Halimi et al (1991)	EIA																	29	135	164	18				
France, Bobigny	Deny et al (1994)	EIA2 + RIBA2													36	128	164	22								
France, Paris	Pagani et al (1994)	EIA									17	79	96	18					28	50	78	36	32	23	55	58
Germany, Heidelberg	Goeser et al (1994)	HCV RNA(PCR)																					20	61	81	25
Germany, Stuttgart	Bode et al (1995)	EIA2													12	118	130	9								
Italy, Bologna	Brillante et al (1991)	EIA													15	26	41	37								
Italy, Bormio	Marioni et al (1991)	EIA					7	33	40	18																
Italy, Brescia	Nalpas et al (1991)	EIA2													46	59	105	44								
Japan, Fukuoka	Ishii et al (1992)	EIA2					80	146	226	35																
Japan, Matsumoto	Shimizu et al (1992)	EIA + RIBA					5	116	121	4	0	35	35	0					14	25	39	36	14	10	24	58
Japan, Tokyo	Yamauchi et al (1993)	EIA P22+C100													40	23	63	63								

Table 44 continued overleaf

Population	Reference	Assay	Individuals without a high-alcohol intake (controls)				People with alcoholism				Individuals with noncirrhotic alcoholic liver disease				Individuals with alcoholic liver disease				Individuals with alcoholic cirrhosis				Individuals with hepatocellular carcinoma			
			No. of +ve	No. of -ve	Total	%	No. of +ve	No. of -ve	Total	%	No. of +ve	No. of -ve	Total	%	No. of +ve	No. of -ve	Total	%	No. of +ve	No. of -ve	Total	%	No. of +ve	No. of -ve	Total	%
Japan	Ishii et al (1993)	EIA2													46	4	50	92								
Poland, Szczecin	Boron Kaczmarska et al (1994)	EIA2					2	229	231	1																
Poland, Warsaw	Lasku s et al (1992)	EIA					35	109	144	24																
Scotland, Glasgow	Blackmore et al (1992)	EIA2	50	304,962	305,012	0.02									0	60	60	0								
Spain, Barcelona	Pares et al (1990)	EIA + RIBA					1	44	45	2	10	24	34	29					26	35	61	43				
Spain, Santiago de Compostela	Gonzalez Quintela et al (1995)	EIA									1	77	78	1					11	55	66	17				
Sri Lanka	De Silva et al (1994)	EIA2													7	40	47	15								
Sweden, Malmo	Verbaan et al (1993)	EIA2 + RIBA2					45	265	310	15																
Sweden, Stockholm	Bell et al (1992)	EIA2					29	172	201	14																
Taiwan, Tainan	Chang et al (1994a)	EIA2					1	43	44	2					37	86	123	30								

Population	Reference	Assay	Individuals without a high-alcohol intake (controls)				People with alcoholism				Individuals with noncirrhotic alcoholic liver disease				Individuals with alcoholic liver disease				Individuals with alcoholic cirrhosis				Individuals with hepatocellular carcinoma			
			No. of +ve	No. of -ve	Total	%	No. of +ve	No. of -ve	Total	%	No. of +ve	No. of -ve	Total	%	No. of +ve	No. of -ve	Total	%	No. of +ve	No. of -ve	Total	%	No. of +ve	No. of -ve	Total	%
USA, Cincinatti	Mendenhall et al (1993a)	EIA2 + RIBA2													40	256	296	14								
USA, Florida	Coelho Little et al (1995)	EIA2 + RIBA2					6	54	60	10					17	23	40	43								
USA, Los Angeles	McHutchison et al (1992)	EIA + RIBA													18	121	139	13								
USA, Miami	Caldwell et al (1991)	EIA	2	177	179	1.12									11	26	37	30								
USA, Virginia	Caldwell et al (1993)	EIA C100-3					12	36	48	25					10	24	34	29								

Table 48 Prevalence of hepatitis C virus antibody in children

Country	Reference	Year of enrolment	Sample	No. of children	Age at enrolment (years)	Screening assay	HCV antibody (%)	Comments
Australia	Leslie et al (1992)	Jan. 1980-Nov. 1981	Children with haemophilia attending the Royal Children's Hospital in Melbourne	31	mean 9	EIA1	74.2	In Feb 1987 - Jan 1990, HCV prevalence was 68% in children < 10 y old.
Austria	Fink et al (1993)	Not reported	Children surviving malignant disease	203	Not reported	EIA1	20.2	HCV antibody was associated with the number of blood product transfusions and with chronic NANBH
Belgium	Pastore et al (1995)	Mar. 1984-Sept. 1993	Children who had had orthotopic liver transplantation, monitored for hepatitis C infection	249	Not reported	EIA2	6.4	HCV antibody was detected in 11.2% (11/98) and in 3.3% (5/151) of children whose transplantation occurred prior to, or after the introduction, in January 1990, of HCV antibody screening, respectively
Brazil	Martins et al (1995)	Sept. 1990-Dec. 1993	Public day care centres	280	< 9	EIA2	0.0	HCV antibody prevalence increased with age from 0% in children 9-12 y old to 6.9% in children 17-20 y old. Exposure to HCV through blood transfusion, tattooing or IDU accounted for 72% of cases.
			Public primary school students	607	Mean 11.5 s.d. 3.1		0.2	
			Home-based street adolescents	391	-		1.0	
			Homeless adolescents	100	-		3.0	
Cameroon	Ngatchu et al (1992)	Not reported	Students from 6 primary schools in the city of Kumba	696	4-14	EIA1	14.5	HCV antibody prevalence increased with age, from 6.6% in children 4-6 y old to 17.5% in children more than 11 y old
Canada	Blumberg et al (1995)	Mar. 1990-June 1994	People with haemophilia diagnosed and reported to the national registry within 2 y of the study (March - June 1992)	884	Not reported	EIA2	63.3	Prevalence of HCV antibody increased with age, from 2% in children < 5 y old, to 27% in children 5-9 y old and to 74% in people 10 y or older

Country	Reference	Year of enrolment	Sample	No. of children	Age at enrolment (years)	Screening assay	HCV antibody (%)	Comments
Egypt	Khalifa et al (1993)	Nov. 1990-Feb. 1991	Consecutive outpatients with haematological disorders	84	mean 7.0 s.d. 3.7	EIA2	54.8	HCV antibody was associated with the duration of illness, number and volume of transfusions, higher ALT level (after exclusion of cases of acute leukemia), clinical jaundice
			Consecutive hospitalised patients with non-haematological disorders	84	mean 7.4 s.d. 4.0		0.0	
			Consecutive outpatients with acute illnesses	84	mean 6.2 s.d. 3.7		0.0	
France	Dussaix et al (1993)	Mar. 1986-Mar. 1991	Children surviving orthotopic liver transplantation	149	Not reported	EIA1+2	9.4	6 children (4%) had HCV infection prior to liver transplantation and 8 (5.4%) were diagnosed with HCV infection following liver transplantation
Italy	Lai et al (1993)	Jan. 1980-Dec. 1987	Children newly diagnosed with thalassemia major with no history of blood transfusion or of liver disease and no evidence of exposure to HBV followed prospectively	135	mean 2.4 s.d. 1.9	EIA1+2	55.6	HCV antibody was detected in 90% of children with NANBH. Risk of NANBH was associated with the number of units of blood transfused.
Italy	Resti et al (1992)	Not reported	Children with beta-thalassaemia major who had been transfused	78	mean 7.7 s.d. 3.1	EIA1	56.4	HCV antibody prevalence in acute and chronic NANBH was 83.3 and 82.9%, respectively
Italy	Bortolotti et al (1992)	1976-1990	Children with chronic NANBH and without underlying conditions, seen at 4 paediatric centres	33	mean 5.6 s.d. 3.9	EIA1	48.5	HCV antibody was detected in 88% of children with parenteral exposure and in 33% of children without parenteral exposure

Table 48 continued overleaf

Country	Reference	Year of enrolment	Sample	No. of children	Age at enrolment (years)	Screening assay	HCV antibody (%)	Comments
Italy	Romano et al (1994)	May 1987-Nov. 1989	Students in public and private schools in 2 northern cities, 2 southern cities and in Sardinia	2,749	3-19	EIA2	0.36	HCV antibody prevalence was 0.2% in the northeast and 0.6% in Sicily and Sardinia
Italy	Bortolotti et al (1994b)	1991-93	Children with chronic NANBH and without underlying systemic conditions, seen at 7 paediatric centres	43	mean 8.5 s.d. 4.1	EIA2	74.0	HCV antibody detected in 93% of children with parenteral exposure and in 40% of children with unknown exposure
Italy	Iorio et al (1993)	1987-91	Children with chronic NANBH and without underlying systemic conditions	33	mean 3.6	RIBA2	39.4	69% (9/13) of children with HCV antibody were considered to have had parenteral exposure and 23% (3/13) were sporadic cases
Italy	Locasciulli et al (1991)	1969-89	Children with chronic liver disease who had completed chemotherapy for leukemia	50	mean 5.8	EIA1	46.0	Persistent HCV antibody was associated with persistent elevation of serum glutamic pyruvic transaminase
Italy	Arico et al (1994)	1977- 92	Children who had completed chemotherapy for acute lymphoblastic leukemia	102	mean 10.5	EIA-2	29.4	14 children without detectable HCV antibody had HCV RNA, resulting in a prevalence of HCV exposure of 43%
Italy	Dibenedetto et al (1994)	Jan. 1986-Sept. 1992	Children diagnosed with acute lymphoblastic leukemia in first continuous complete remission	90	0-14	EIA2	32.2	Almost all children with HCV antibody (97%) had abnormal liver function test results, 5 (17%) had evidence of chronic liver disease
Japan	Tanaka et al (1992)	1986-1990	Primary and junior high school students in Matsumoto City	1,442	6-15	EIA1	0.0	No cases of elevated serum transaminase
Japan	Matsuoka et al (1994a)	Jan. 1983-June 1992	Children in Tokushima prefecture who received a blood transfusion during open heart surgery	226	2-19	EIA2	9.7	HCV antibody was detected only in children (22/161, 13.7%) who received blood or blood products prior to the introduction, in November 1989, of screening for HCV antibody
Taiwan	Ni et al (1994a)	Oct. 1990-Dec. 1992	Children transfused during open heart surgery, enrolled retrospectively	196	mean 4.9 s.d. 3.1	EIA2	4.1	Of 8 children with persistent HCV antibody, ALT levels returned to normal over 2 y of follow up
			Children transfused during open heart surgery, enrolled prospectively prior to the introduction of HCV-antibody screening	38	mean 5.4 s.d. 4.0		5.3	
			Children transfused during open heart surgery, enrolled prospectively after the introduction, in July 1992, of HCV-antibody screening	56	Not reported		0.0	

Country	Reference	Year of enrolment	Sample	No. of children	Age at enrolment (years)	Screening assay	HCV antibody (%)	Comments
Taiwan	Chang et al (1993)	Not reported	Infants and children with various liver diseases	195	<15	EIA2	1.0	HCV antibody prevalence was 4.4% (1/23) in children with HCC and 16.7% (1/6) in children with NANBH
			Apparently healthy infants and children	748	<1-15		0.1	
Taiwan	Hsu et al (1991)	July 1979-June 1989	Children with chronic NANBH	27	median 5.4	EIA1	36.4	A higher proportion of cases with a history of transfusion and with chronic NANBH had HCV antibody
United Kingdom	Myers et al (1995)	1976-91	Children from Nottingham and Sheffield with haematological malignancy transfused at a single transfusion centre	98	mean 10.5	EIA2	1.0	At 9 y posttransfusion, the only case of HCV antibody was positive for HCV RNA and had elevated transaminases. Liver biopsy indicated mild hepatitis
USA	Nowicki et al (1994)	Not reported	Children surviving orthotopic liver transplantation for at least 6 months	62	mean 5.3	EIA2	5.1	At a median of 3 y following transplantation, HCV RNA was detected in 6.2% of children
USA	Jonas et al (1992)	Not reported	Patients undergoing either haemodialysis or peritoneal dialysis at the Jackson Memorial Medical Centre, Miami	27	mean 20.9	EIA1	18.5	HCV antibody was detected only in patients who had been transfused. HCV antibody was associated with older age (25.9 vs 19.7), longer duration of haemodialysis and number of units of blood transfused

Table 49 Natural history of hepatitis C virus infection in children

Country	Reference	Year of enrolment	Sample	Number of children	Age at enrolment (years)	Number of months of follow up	Outcome
Italy	Bortolotti et al (1993)	1983-93	Children with chronic HCV infection and without underlying systemic diseases	37	Not reported	mean 40.8 s.d. 38.4	10% were symptomatic, 3% had ALT normalisation, 0% developed liver failure
Italy and Spain	Bortolotti et al (1994a)	1978-82	Children with chronic HCV infection and without underlying systemic conditions, identified incidentally on routine screening	77	mean 4.4 s.d. 2.9	Posttransfusion mean 81.6 s.d. 37.2 Sporadic mean 73.2 s.d. 46.8	Most children remained asymptomatic during follow-up. Liver histology was consistent with inactive liver disease in > 60%. Severe active hepatitis and cirrhosis were infrequently associated with chronic HCV infection.
Italy	Lai et al (1993)	Jan 1980-Dec 1987	Children newly diagnosed with thalassaemia major with no history of blood transfusion or of liver disease and no evidence of HBV, followed prospectively	135	mean 2.4 s.d. 1.9	mean 69.6 s.d. 24.0	Of 83 children with NANBH, 57 developed chronic NANBH. HCV infection was documented in 53 of these children.
Italy	Resti et al (1992)	Not reported	Children with beta-thalassaemia who had been transfused (35 followed from birth, 43 presented at mean age 7.7 y)	78	mean 7.7 s.d. 3.1	mean 158 s.d. 36	No difference was found between cases of chronic NANBH with respect to HCV infection status. 30% of children had cirrhosis
Japan	Inui et al (1994)	Not reported	Children with HCV infection and without other causes of liver disease	25	mean 9.1	mean 44.2	17 children with malignant disease or aplastic anaemia had a higher grade of histological activity in the liver compared with 8 children without malignant disease. However, all children with malignant disease had been treated with multiple transfusions and cytotoxic and immunosuppressive agents.
Japan	Matsuoka et al (1994a)	From 1991	Children transfused in open heart surgery	29	mean 10.2 s.d. 4.4	mean 85.2 s.d. 33.6	13 children had chronic HCV infection (elevated ALT for > 6 months following surgery and elevated ALT within the last 2 y of follow-up) and 6 had CAH, 6 had CPH

Country	Reference	Year of enrolment	Sample	Number of children	Age at enrolment (years)	Number of months of follow up	Outcome
Taiwan	M.-H. Chang et al (1994)	Prior to July 1992	Children at risk of HCV infection due to blood transfusion for congenital haemolytic anaemia, blood transfusion for open heart surgery or children of women with chronic HCV infection	88	< 18	36	During follow-up, 10 children acquired HCV infection (5 with haemolytic anaemia, 2 with open heart surgery and 3 children of HCV-infected mothers) and 5 had an episode of acute hepatitis. 6 children progressed to chronic HCV infection.

Table 50 Effect of interferon treatment in children with chronic infection with hepatitis C virus

Country	Reference	Year of enrolment	Sample	No. of children	Age at enrolment (y)	Treatment	Outcome
Italy	Bortolotti et al (1995)	Apr 1991-Jun 1992	Children with chronic HCV infection without underlying systemic diseases, metabolic liver disorders, HBV or HIV infection and without a history of immuno-suppressive or antiviral therapy	27	2-14	Random assignment to treatment (5 MU/m^2 recombinant IFN-α2b 3 times weekly for 12 months) or no treatment	10 children completed therapy. By the end of therapy, all had normal ALT and 9 had undetectable HCV RNA. Of 9 children followed for 12 months after therapy, 5 maintained normal ALT and undetectable HCV RNA. Of 13 untreated children, 1 had ALT normalisation and none were HCV-RNA negative.
Japan	Komatsu et al (1996)	Not reported	Children with chronic HCV infection who had completed treatment for acute leukaemia	13	5-17	Natural IFN-α (0.1 MU/kg) daily for 2 weeks, then 3 times per week for an additional 22 weeks	Complete response (normalisation of ALT and undetectable HCV RNA within 6 months of cessation of therapy, with ALT remaining normal for at least 6 months thereafter) in 38% (5/13), partial response (ALT normalisation with detectable HCV RNA) in 1 case and no response (persistence of abnormal ALT values for at least 12 months after cessation of therapy) in 54% (7/13)
Spain	Ruiz-Moreno et al (1992)	Not reported	Children with chronic HCV infection and without metabolic liver disorders, HBV or HIV infection. Source of HCV infection was unknown in 83%.	12	1.5-15	3 MU/m^2 recombinant IFN-α 3 times per week for 6 months	11 children completed therapy. At the end of therapy, 36% (4/11) had normal ALT levels and 8 had undetectable HCV RNA. At 24 months, 45% (5/11) had normal ALT levels.

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