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Completed hepatitis C lookback in Northern Ireland

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SUMMARY. Hepatitis C virus screening of blood donors was introduced in September 1991 using a second-generation enzyme-linked immunoassay (ELISA) and subsequent confirmatory testing with immunoblot (RIBA) and polymerase chain reaction (PCR). In April 1995 a lookback exercise was announced by the Department of Health, the purpose of which was to trace, counsel, investigate and, if necessary, treat individuals who may have been infected with HCV through blood and blood products prior to screening. A total of 231 321 donations have been screened, of which 553 were found to be reactive. Subsequent confirmatory tests identified 24 HCV-positive donors; 13 were repeat donors who had given a total of 164 units. Ninety-three units were traced and 117 components were identified as having been issued to hospitals. Twenty-five recipients requiring follow-up were identified, of which three were assessed by their GPs as not requiring counselling. Of 22 recipients of potentially infectious units 12 showed no evidence of exposure to HCV. We discuss these results in detail.

Key words: hepatitis C transmission, lookback.

The procedures for HCV Lookback (Health Service Guidelines, 1995) were announced in April 1995. The fate of all previous blood donations from donors confirmed positive for HCV infection since the introduction of screening was to be traced and where possible recipients of these potentially infectious units identified and offered counselling, testing and treatment if appropriate. In the original pilot HCV lookback study (Ayob *et al.*, 1994) archive samples were retrieved and tested and the date of seroconversion identified. This was not adopted in the national HCV lookback procedures (Health Service Guidelines, 1995), one reason being that archive material was not equally securely laid down in all UK regions.

It was anticipated that there would be problems with this exercise associated with documentation failures in Regional Transfusion Centres (RTCs), hospital blood banks and in patients' clinical notes. In some cases potentially infectious units were transfused some 30 years previously. Further, the issues of interpretation of test results in recipients, counselling and treatment were not completely resolved.

Screening and supplemental tests that are used are serological tests to detect antibody and are not exclusive for HCV. A positive result may indicate past infection or active current infection (Barbara & Contreras, 1991a). The latest generation of tests which make use of synthetic peptides and recombinant proteins from both the core and nonstructural regions of the HCV genome show improved performance. (Dow *et al.*, 1993). The recipients identified for lookback have been tested using these latest generation of tests and a positive reaction is likely to indicate a true infection.

Polymerase chain reaction (PCR) confirms viral replication but there are problems due to lack of standardization between reference laboratories (Dow *et al.*, 1993) and false negative results caused by variant strains and high mutation rate of HCV (Garson *et al.*, 1990a; Barbara & Contreras, 1991a, b). While a positive PCR result is thought to indicate an adverse prognosis (Alberti *et al.*, 1992) and greater infectivity (Garson *et al.*, 1990a; Farci *et al.*, 1991), a negative result does not indicate absence of HCV infection (Barbara & Contreras, 1991a). The natural history of post-transfusion HCV infection is far from certain and there is a lack of longitudinal follow-up studies (Wood *et al.*, 1989; Alberti *et al.*, 1992; Seef *et al.*, 1992). The true value of specific antiviral therapy with interferons is unproven (Yano, 1992; Seymour, 1994; Terrault & Wright, 1995).

The Northern Ireland Blood Transfusion Service (NIBTS) has effectively completed the lookback exercise and this is the first such report from Transfusion Services in the UK. The anticipated failure to trace recipients is confirmed and an important additional finding is that 12 of 22 recipients of potentially infectious units showed no evidence of HCV transmission.

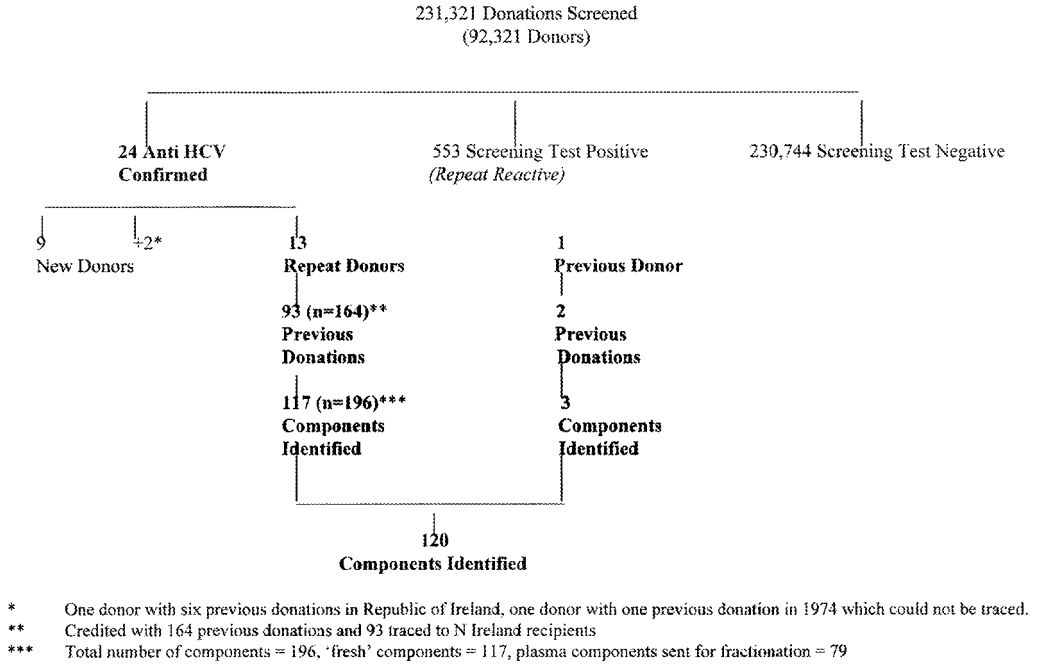

Fig. 1. Fate of all previous donations from donors now confirmed HCV positive.

MATERIALS AND METHODS

Routine screening of blood donors for HCV was introduced in the NIBTS in September 1991 using a second-generation enzyme immunoassay (Abbott 2 ELISA). This was superseded by the third-generation Abbott 3 ELISA in January 1994. Repeat reactive screening test results are confirmed at the Scottish National Blood Transfusion Service Microbiology Reference Unit (SNBTS MRU) at Ruchhill Hospital, Glasgow, using a recombinant immunoblot assay Ortho RIBA-2 superseded in January 1994 by Ortho RIBA-3. Positive and indeterminate results undergo PCR testing (method described by Chan *et al.*, 1992) at the University of Edinburgh Medical School Microbiology Department.

Donors who are RIBA positive irrespective of PCR result and the small number of donors who are RIBA indeterminate with a positive PCR result are placed permanently off service and counselled as part of the NIBTS donor care programme. The lookback exercise

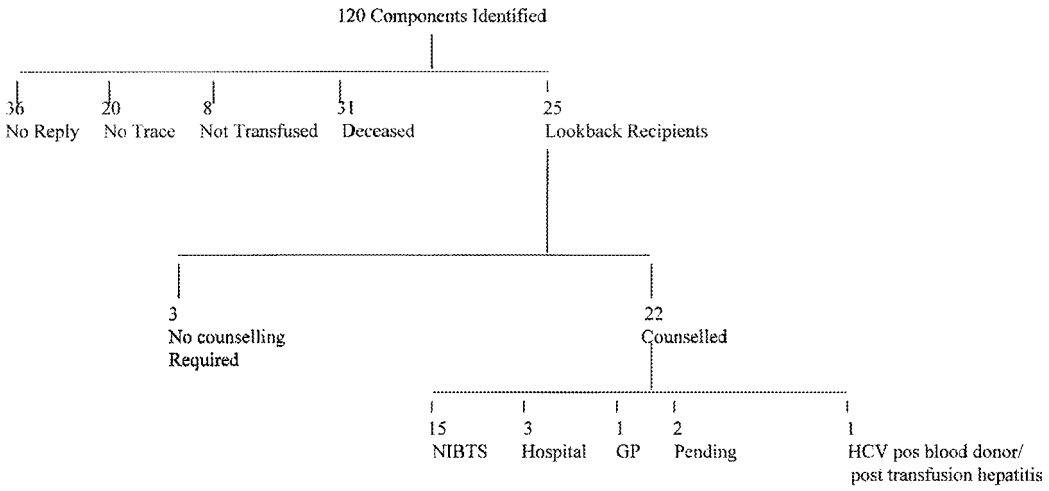

Fig. 2. Recipients of components identified in lookback.

Table 1. PCR-positive donors with no matching recipients

Donors				
HC no.	RIBA-2*	PCR	Risk exposure	Recipients
047	4+ 2+ 2+ 4+	Pos	No	No matching recipients identified
119	4+ 4+ 4+ 4+	Pos	DNA†	No matching recipients identified
169	4+ 4+ 4+ 4+	Pos	IVDA‡, London 1970s Tattoos, Dublin 1980s	No matching recipients identified

*5-1-1/c100/c33/c22. †Did not attend. ‡Intravenous drug use.

initiated by the UK Departments of Health specifically excludes archive testing. All donors are questioned as to risk exposure for HCV and this provides indirect data regarding the date of probable seroconversion. It is this group of donors whose donations were indexed for lookback. Blood components made from these donations were identified and recipients traced. Clinicians were notified and recipients offered counselling, testing and, if appropriate, treatment in accordance with HCV lookback procedures. Recipients were tested at the Regional Virus Laboratory, Royal Group of Hospitals, Belfast, using two third-generation ELISAs (Abbott, Sanofi-Pasteur) which provided an important independent source of confirmation. Samples were also sent to SNBTS MRU for confirmatory Ortho RIBA-3 and to University of Edinburgh Medical School for PCR testing.

Table 2. PCR-positive donors and matching recipients

Donors				Recipients			
HC no.	RIBA-2*	PCR	Risk exposure	Lookback no.	RIBA-3†	PCR	Transformation history
023	− 3+ 4+ 4+	Pos	IVDA, London 1971 'Blood brothers', London 1973 Blood Tx London 1976	LB001	− − 4+ 2+	Neg	Platelets 8/86
				LB003	− 4+ 4+ 4+	Pos	RBCs 4/86
				LB011	− 1+ 4+ −	Neg→Pos	Paediatric FFP 7/90
				LB016	4+ 4+ 4+ 1+	Pos	RBCs 7/87
044	4+ 3+ 3+ 4+	Pos	Blood Tx 1976	LB004	− 2+ 2+ − DK	Neg (No counselling required)	RBCs 12/85
054	2+ 1+ 4+ 4+	Pos	Blood Tx 1978	LB006	4+ 4+ 4+ −	Neg	RBCs 3/89
				LB008	− − − −	Neg	RBCs 6/85
				LB013	4+ 4+ 4+ 4+	Pos	RBCs 4/91
102	− 2+ 4+ 4+	Pos	IVDA, NI 1980s	LB005	− − − −	Neg	RBCs 1/80
105	4+ 4+ 4+ 4+	Pos	Blood Tx 1961	LB014	4+ 4+ 4+ 4+	Pos	RBCs 4/81
413	4+ 4+ 4+ −	Pos	IVDA, USA 1960 Ears pierced, USA 1962 Acupuncture, NI 1988	LB023/ HC552	− 2+ 2+ −	Neg→Pos	RBCs 6/85 IVIgG 6/90
Previous donor				LB019	4+ 4+ 4+ −	Pos	RBCs 12/88

*5-1-1/c100/c33/c22. †c100/c33/c22/NS5.

RESULTS

Trace fate of all blood donations from donors now confirmed HCV positive (see Fig. 1)

In the first 3 years of screening 231 321 donations were tested. This represents 92 362 donors, which is effectively the entire NIBTS active donor panel.

Anti-HCV antibody was confirmed in 24 donors. Nine were first-time donors, one donor was 'new here' in that she had given six previous donations in another jurisdiction and one donor had given once in 1974 and the donation could not be traced. These 11 donors are not considered further.

It is noteworthy that of 13 repeat donors who had evidence of past exposure to HCV, 11 were identified in the first 6 months of testing and all 13 were identified within 18 months of introduction of screening. Since March 1993 we have confirmed exposure to HCV only in new donors with the exception of a 'lapsed donor' with a 17-year interval since her previous donation.

The 13 repeat donors in whom we performed lookback were credited with 164 previous donations. Ninety-three donations were traced, 36 donations had been given elsewhere in the UK and 35 donations given prior to 1980 could not be traced because production and issue records were not available at NIBTS. One hundred and seventeen fresh blood components were made. A further 79 plasma components were sent for fractionation and details were passed to the Protein Fractionation Centre, Edinburgh, in accordance with HCV lookback procedures (Health Service Guidelines, 1995). Additionally we were informed of one previous donor who was found to have HCV antibody coincidentally at a hospital clinic. His donation record was reviewed and the three components made from his two previous donations included in the final total of 120 requiring lookback.

Identify recipients and offer counselling, testing and where appropriate treatment (see Fig. 2)

Fifty-six components could not be accounted for; 20 could not be traced by the hospital blood bank and in a further 36 cases we have had no reply from hospital clinicians. It is unlikely that we will obtain any further information at this stage. These cases reflect incompleteness of documentation in the clinical notes or indicate that patient records could not be obtained by the clinician. There are several examples of blood components issued from the hospital blood bank where it is not possible to confirm that the units have in fact been

Table 3. PCR-negative donors and matching recipients

Donors				Recipients			
HC no.	RIBA-2*	PCR	Risk exposure	Lookback no.	RIBA-3†	PCR	Transfusion history
033	3+ 2+ – –	Neg	No	LB010	– – – –	Neg	Platelets 7/87
				LB017	– – – –	Neg	RBCs 4/82
				SMcC	(No counselling required)		
048	– – – 4+	Neg	DNA	LB009	– – – –	Neg	RBCs 11/85
	Repeat†						
	4+ – 4+ –	(Neg)					
				LB020	– – – –	Neg	Platelets 6/89
				LB021	– – – –	Neg	Platelets 6/90
089	1+ – 1+ 4+	Neg	Oral hallucinogenic drugs	LB002	– – – –	Neg	RBCs 7/87
			?? IVDA				
				LB022	– – – –	Neg	RBCs 1/88
183	– 1+ 1+ 2+	Neg	Ears pierced 1985	LB007	– – – –	Neg	RBCs 12/82
	Repeat†		Electrolysis 1990s				
	1+ 1+ 3+ –	(Neg)	TOP‡ London 1986 (? anti-D injection)				
				LB012	– – – –	Neg	RBCs 7/86
				SH	(No counselling required)		
				LB018	– – – –	Neg	RBCs 9/91

*5-1-1/c100/c33/c22. †c100/c33/c22/NS5. ‡Termination of pregnancy.

transfused. This has highlighted a failure in institutional blood transfusion practice and documentation procedures which is being addressed through the Hospital Transfusion Committees.

This is perhaps the single most important finding from the NIBTS HCV lookback exercise and it will be interesting to see if it is reproduced elsewhere.

Sixty-four components can be accounted for, eight were not transfused (this was documented) and 31 recipients are deceased. It is likely that there are more deceased recipients among those for whom we have not received a reply though this remains unconfirmed. Twenty-five recipients of potentially infectious units were identified; three were not considered suitable for counselling by their GPs. HCV-positive blood donors are divided into three groups; PCR positive with no matching recipients, PCR positive with matching recipients and PCR negative with matching recipients. Risk exposures for donors and transfusion histories for recipients for these three groups are presented in Tables 1–3. The clinical follow-up details of the two groups of recipients are presented in Tables 4 and 5.

DISCUSSION

This is the first report of clinical follow-up of HCV lookback recipients in the UK. An important finding is the failure of HCV transmission in the majority of cases. Ayob *et al.* found all recipients of confirmed HCV-positive donors to be HCV positive while others have found 81% and 60% of recipients to be HCV positive (Vrielink *et al.*, 1995, Koerner *et al.*, 1995). NIBTS has effectively completed its HCV lookback exercise. Twelve recipients are HCV antibody negative and a further three who are RIBA positive and PCR negative have probably eliminated the virus (Barbara & Contreras, 1991a). Seven recipients are RIBA positive and PCR positive, six of whom have been referred to a hepatologist. There are other risk factors for acquisition of HCV infection in two cases – tattoo in LB001 and

Table 4. Clinical follow-up details of recipients of PCR-positive donors

Lookback no.	Sex	Age	LFTs	Comments	Referral to hepatologist	Liver biopsy	Interferon
001	M	46	AST = 52 u L^{-1}* ALT = 56 u L^{-1}	Tattoo C_2H_5OH = 30 u w^{-1}	No	No	No
003	F	57	Normal	Monitor LFTs every 6/52	Yes	No	No
011	M	06	Normal	Attends Paed OPD 'Nephrotic syndrome'	No	No	No
016	F	46	Normal	Acupuncture 3/93	Yes	No	No
004	M	65	Normal	C_2H_5OH = 20 u w^{-1}	No	No	No
006	M	39	Normal	C_2H_5OH = 14 u w^{-1}	Yes	No	No
008	F	43	Normal	Reassured, discharged	N/A	N/A	N/A
013	M	23	Initial LFTs normal LFTs at 6 months AST = 50 u L^{-1}* ALT = 106 u L^{-1}*	C_2H_5OH = 10 u w^{-1}	Yes	Pending	No
005	F	56	Normal	Reassured, discharged Blood donor-tested HCV ab neg × 6	N/A	N/A	N/A
014	M	41	GGT = 118 u L^{-1}*	C_2H_5OH = 21 u w^{-1}	Yes	Pending	No
023/HC 552	F	34	Normal	Confirmed HCV positive 'lapsed' blood donor	Yes	†	No
019	F	75	AST = 189 u L^{-1}* ALT = 55 u L^{-1}* GGT = 223 u L^{-1}*	Counselling pending			

*Normal range: BR = 2–20 μmol L^{-1}. AlkP = 90–280 u L^{-1}. AST = 2–35 u L^{-1}. ALT = 2–42 u L^{-1}. GGT = 5–60 u L^{-1}. Alb = 36–53 g L^{-1}.
† Normal architecture. No evidence of necrosis or inflammation. Collection of chronic inflamatory cells seen in one periportal area only.

Table 5. Clinical follow-up results of recipients of PCR-negative donors

Lookback no.	Sex	Age	LFTs	Comments	Referral to hepatologist	Liver biopsy	Interferon
010	F	30	AST = 50 u L^{-1}*	Reassured, discharged	N/A	N/A	N/A
017	F	50	GGT = 69 u L^{-1}*	Reassured, discharged C_2H_5OH = 4 uw^{-1}	N/A	N/A	N/A
021	F	58	Not done	Counselling pending			
009	M	29	Normal	Reassured, discharged	N/A	N/A	N/A
020	M	13	Normal	Reassured, discharged	N/A	N/A	N/A
002	F	51	Normal	Reassured, discharged	N/A	N/A	N/A
022	M	76	Normal	Reassured, discharged	N/A	N/A	N/A
007	M	42	Normal	Reassured, discharged	N/A	N/A	N/A
012	M	55	BR = 36 μmol L^{-1}* ALK P = 301 u L^{-1}* AST = 83 u L^{-1}* GGT = 126 u L^{-1}* Alb = 24 g L^{-1}*	Attends MOPD 'Alcoholic liver disease'	N/A	N/A	N/A
018	M	70	Normal	Reassured, discharged	N/A	N/A	N/A

Normal range: ALT = 2–42 u L^{-1}. GGT = 5–60 u L^{-1}*. Alb = 36–53 g L^{-1}. BR = 2–20 μmol L^{-1}. Alk P = 90–280 u L^{-1}. AST = 2–35 u L^{-1}.

acupuncture from an unregistered practitioner in LB016. Only three out of seven have abnormal liver function tests and alcohol is a strong confounding variable in two of these three cases.

There were three PCR-positive recipients for whom no matching recipients were identified. Fortunately, however, this group accounted for only eight blood components, two of which were not transfused and one was transfused to a recipient who is now deceased. PCR-positive donors with matching recipients accounted for 56 components. Twelve recipients were identified in lookback; a further 27 components are not accounted for.

LB011 illustrates some of the problems with PCR. Initially this recipient was tested and found to be PCR negative. The result was a little surprising as we and others have found a strong correlation between a single c22 band and the combination of c22 and c33c bands in RIBA with PCR positivity (Follet *et al.*, 1991). LB011 had been investigated for nephrotic syndrome independently at a hospital paediatric clinic and was found to be anti-HCV positive and PCR positive. The discrepancy in PCR results was resolved when he was retested by the Reference Laboratory and confirmed PCR positive. The discrepant results are not inconsistent with transient viraemic episodes which are recognized to be part of the natural history of HCV infection in some individuals (Garson *et al.*, 1990b)

There is strong circumstantial evidence that LB006 and LB013 were infected by transfusions from donor HC054. LB008 has not acquired HCV infection however, and it is significant that her transfusion pre-dates the other two. It would be reasonable to assume she was transfused before the donor acquired HCV infection though we do not have archive material to confirm this hypothesis. The only history of risk exposure for this donor is a blood transfusion in 1978 which pre-dates all three donations.

LB005 is the second example of failure of transmission of HCV from a PCR-positive blood donor. The risk exposure in this case occurred some 3 years after the relevant blood donation.

LB023/HC552 was confirmed HCV positive when she presented as a blood donor after a 17-year interval. Her PCR status has also changed over time. Her only risk factor was a previous blood transfusion and she was confirmed to have post-transfusion hepatitis when she was identified independently as a lookback recipient.

PCR-negative donors have a different profile in that they have lower grades of reaction in RIBA with smaller numbers of bands and lower intensity staining of bands. Significantly there is no strong history of risk exposure for any of these donors. Perhaps not surprisingly these donors failed to transmit HCV – 12 recipients were identified all of whom were HCV antibody negative. This is an important negative finding and represents new information. All serologically confirmed anti-HCV antibody-positive donors had previously been thought to transmit HCV following blood transfusion (Ayob *et al.*,

1994). PCR-negative donors accounted for 56 components, 24 of which cannot be traced and we can take some reassurance from the apparent failure of transmission of HCV.

Donor HC033 has two bands in RIBA 2-c100 and 5-1-1. This pattern of results would now score as indeterminate in RIBA-3. Likewise donor HC048 has a single band in RIBA-2 albeit a c22 band. Subsequent testing with RIBA-3 confirmed HCV antibody showing c22 and c100 bands. The decision to look back was based on the original pattern of results even though they do not confirm HCV infection in this donor. These are only two of five examples where implicated components failed to transmit the virus and this finding is important to note in the light of the decision to extend lookback to HCV indeterminate donors. Donors HC089 and HC183 failed to transmit HCV and while they gave lower intensity bands in RIBA the most important characteristic which they share with the other two donors in this group is their PCR negativity. PCR-negative material is less likely to transmit HCV (Garson *et al.*, 1990a).

The net result of this exercise is that seven lookback recipients have been identified with active current infection, liver biopsy has been indicated in three cases and none has been considered to require treatment with alpha-interferon at present.

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REFERENCES

Alberti, A., Morsica, G., Chemello, L., Cavalletto, D., Noventa, F., Pontisso, P. & Ruol, A. (1992) Hepatitis C viraemia and liver disease in symptom-free individuals with anti-HCV. *Lancet,* **340,** 697–698.

Ayob, Y., Davidson, J.I., Baxter, A., Jordan, A., Yap, P.L. & Gillon, J. (1994) Risk of hepatitis C in patients who received blood from donors subsequently shown to be carriers of hepatitis C virus. *Transfusion Medicine,* **4,** 269–272.

Barbara, J. & Contreras, M. (1991a) Non A, non-B hepatitis and the anti-HCV assay. *Vox Sanguinis,* **60,** 1–7.

Barbara, J.A.J. & Contreras, M. (1991b) Post transfusion NANBH in the light of a test for anti-HCV. *Blood Reviews,* **3,** 234–239.

Chan, S.W., McOmish, F., Holmes, E.C., Dow, B., Peutherer, J.F. & Follett, E. (1992) Analysis of a new hepatitis C virus type and its phylogenetic relationship to existing variants. *Journal of General Virology,* **73,** 1131–1141.

Dow, B.C., Coote, I., Munro, H., McOmish, F., Yap, P.L., Simmonds, P. & Follett, E.A.C. (1993) Confirmation of Hepatitis C virus antibody in blood donors. *Journal of Medical Virology,* **41,** 215–220.

Farci, P., Alter, H.J., Wong, D., Miller, R.H., Shih, J.W., Jett, B. & Purcell, R.H. (1991) A long term study of hepatitis C virus replication in non-A non-B hepatitis. *New England Journal of Medicine,* **325,** 98–104.

Follet, E.A.C., Dow, B.C., McOmish, F., Yap, P.L., Hughes, W., Mitchell, R. & Simmonds, P. (1991) HCV confirmatory testing of blood donors (letter). *Lancet,* **338,** 1024.

Garson, J.A., Tedder, R.S., Briggs, M., Tuke, P., Glazebrook, J., Trute, A., Parker, D., Barbara, J.A.J., Contreras, M. & Aloysius, S. (1990a) Detection of hepatitis C viral sequences in blood donations by 'nested' polymerase chain reaction and prediction of infectivity. *Lancet,* **335,** 1419–1422.

Garson, J.A., Tuke, R.W., Makris, M., Briggs, M., Machim, S.J., Preston, F.E. & Tedder, R.S. (1990b) Demonstration of viraemic patterns in haemophiliacs treated with hepatitis C virus contaminated factor VIII concentrates. *Lancet,* **336,** 1022–1025.

Health Service Guidelines *NHS Executive HSG.* (1995) *Hepatitis and Blood Transfusion Look Back.*

Koerner, K., da Silva Cardoso, M., Dengler, T., Kerowgan, M. & Kubanek, B. (1995) Look back on hepatitis C-virus infections of HCV-RIBA-2 positive blood donors and their respective recipients. *Vox Sanguinis,* **69,** 78–79.

Seef, L.B., Buskell-Bales, Z., Wright, E.C., Durako, S.J., Alter, H.J., Iber, F.L., Hollinger, F.B., Gitnick, G., Knodell, R.G., Perrillo, R.P., Stevens, C.E., Hollingsworth, C.G. & the National Heart, Lung and Blood Institute Study Group. (1992) Long-term mortality after transfusion-associated non-A and non-B hepatitis. *New England Journal of Medicine,* **327,** 1906–1911.

Seymour, C. (1994) Asymptomatic infection with hepatitis C virus. *British Medical Journal,* **308,** 670–671.

Terrault, N. & Wright, T. (1995) Interferon and Hepatitis C. *New England Journal of Medicine,* **332,** 1509–1511.

Vrielink, H., van der Poel, C.L., Reesink, H.W., Zaaijer, H.L., Scholten, E., Kremer, L.C.M., Cuypers, H.T.M., Lelie, P.N. & van Oers, M.H.J. (1995) Look-back study of infectivity of anti-HCV ELISA-positive blood components. *Lancet,* **345,** 95–96.

Wood, G.M., Levy, L.J., Losowsky, M.S., Cooke, D.I., Read, A.E., Hambling, M.H., Clarke, S.K.R., Waight, P. & Polakoff, S. (1989) Chronic liver disease. A case control study of the effect of previous blood transfusion. *Public Health,* **103,** 105–112.

Yano, M. (1992) Advances in hepatitis: sero-epidemiology and antiviral therapy. *Journal of Gastroenterology and Hepatology,* **7,** 549–555.