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JB/mm

31 August 1994

Dear Dr Bird

Many thanks for very kindly sending me the information we discussed on the telephone. Since you have been in contact with Pat Hewitt and Verge James, I have taken the liberty of copying your papers to them, in relation to their donor-selection working group. Naturally, they will maintain confidentiality as you have requested.

The data is certainly striking and I imagine that Dr. James or Dr. Hewitt may wish to comment further when they have read the papers.

Certainly, prior to the introduction of HBsAg screening of donors in 1971, the prison population represented an attractive source of donors - a truly 'captive' audience - but in North London we noted HBsAg detection rates up to tenfold higher in donor sessions at prisons, compared with rates elsewhere. At the time we thought that this might be due to increased levels of homosexuality: however, in the light of HCV epidemiology (see enclosed reprint), a considerable proportion of the HBV infections may have been drug associated. You may indeed quote the above. Certainly, the difference in rates was sufficiently obvious to prompt the cessation of blood collection from prisoners in North London in 1973 (see enclosed memorandum and a summary of some of our observations).

With best wishes.

Yours sincerely

GRO-C

Dr John Barbara
Head of Microbiology and
Microbiology consultant to the NBA

P.S. I note from my file records that a Mr. Moore raised a question in parliament regarding HBsAg rates in prisons in March 1986.

c.c. Dr Hewitt
Dr James - Sheffield RTC

HBsAg prevalence in Prisons, Borstals etc (NLBTC)

(NB: screening was performed using immunodiffusion ('1st generation') assays, considerably less sensitive than currently available tests, although the *ratios* of prevalence in prisons vs the total population would be similar, regardless of the sensitivity of the test used.

	Jan 1971 to Dec 1971	**Jan 1972 to June 1972**
HBsAg rate in donors overall	89 in 155,448 (1 in 1745)	40 in 77,843 (1 in 1946)
HBsAg rate in prisons/borstals etc	11 in 1,016 (1 in 92) (i.e. 19 times higher)	1 in 339 (i.e. 5.7 times higher)

Dr John Barbara

28 August 1994

JB/mm/31aug94
Micro/misc/HBs-pris

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A study of anti-hepatitis C positive blood donors: the first year of screening

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SUMMARY. In the U.K., blood donations have been routinely screened for anti-HCV since September 1991. In order to get the most epidemiological benefit from these extensive screening data, the histories obtained at counselling from donors confirmed to be anti-HCV positive, 'indeterminate' and falsely positive have been analysed in detail. In addition, the associations with potential risk factors have been investigated by comparing these groups of donors with a control group of 771 routine donors bled on one day during the study, at North London Blood Transfusion Centre. This paper documents the prevalence and demography of HCV infection in asymptomatic blood donors, to assess various possible sources of infection and the association between liver function test results and alcohol consumption in donors. One in 1400 previously untested donors was confirmed positive for anti-HCV. Age (the group 30–49 years being highest), tattooing and intravenous drug use in both sexes, ear-piercing in males and blood transfusion in females were all significantly associated with an increased risk of HCV infection. Intravenous drug use proved to be the factor most strongly associated with risk. Liver function tests (alanine aminotransferase) were elevated in a significant number of donors confirmed to be anti-HCV positive but no clear correlation between alanine aminotransferase level and either time since infection or alcohol consumption was found. Alcohol consumption was significantly higher in donors confirmed to be anti-HCV positive and was particularly marked in those admitting to previous intravenous drug use. Although donors confirmed to be anti-HCV positive had a 5–10 times greater chance of non-Caucasian ethnic origin compared with controls, the association with ethnic origin was not as marked as it was for HBsAg positive donors.

Key words: hepatitis C virus, anti-HCV, counselling, epidemiology, risk factors, intravenous drug use, tattooing, alcohol consumption, ear-piercing, transfusion, liver function test.

On 2 September 1991 the U.K. Blood Transfusion Service commenced routine screening of all blood donations for antibody to hepatitis C virus (anti-HCV). In a preliminary analysis of the results of the first 2 months of this testing, we reported a prevalence of 0·06% donors confirmed as positive and 0·12% classified as 'indeterminate' (MacLennan *et al.*, 1992). At counselling, 46% of confirmed anti-HCV positive donors in that study admitted a past history of intravenous drug use. Similar results were subsequently reported in other regions (Crawford *et al.*, 1992; Gesinde *et al.*, 1992; Goodrick *et al.*, 1992).

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Correspondence Dr J. A. J. Barbara.

In this paper, we have extended the study of these almost exclusively well and asymptomtic HCV seropositive donors to cover the first year of screening at the North London Blood Transfusion Centre, from September 1991 to August 1992.

Although the overall cost-effectiveness of the screening programme has been a matter of some debate (Barbara & Contreras, 1991; Brown *et al.*, 1991), the screening of a large number of donors (approximately 2·5 million per annum in the U.K.) for this newly defined virus provides an unrivalled opportunity to assess the prevalence and distribution of HCV infection in the 'healthy' population of the U.K. Blood donors are not representative of the whole population but they are the only group of individuals not under medical care who are screened *en masse* for anti-HCV.

MATERIALS AND METHODS

Anti-HCV screening and confirmation

All donations were screened using the second-generation Ortho anti-HCV assay (ELISA-2). Reactive sera were retested in duplicate using the same assay. Repeatably reactive donations were referred to Professor R. S. Tedder at the virology department of the University College London Medical School for Ortho second-generation recombinant immunoblot assay (RIBA-2). When two or more antigens were reactive on RIBA-2 the samples were deemed 'confirmed positive'. When only one antigen was reactive the result was deemed 'indeterminate'. If all viral antigens were negative the reaction was described as 'false-positive'.

Counselling

When one 'positive' donation or two 'indeterminate' donations from the same donor were confirmed as such, donors were informed and invited for counselling. Donors whose screening tests proved false-positive on at least two occasions were also informed as current U.K. policy excludes the transfusion of such donations.*

At the counselling sessions trained staff explained the meaning of the HCV test result, and provided information both about the virus and about likely implications for the donor and his/her future health. Advice on how to minimize any possibility of spread to others was given, as far as current understanding allowed. During the interview the counsellor also administered a questionnaire, enquiring into any history of blood transfusion, drug use of scarification (ear-piercing, tattooing, acupuncture or electrolysis). Details of past sexual contact, in particular with partners who were haemophiliac, intravenous drug users or prostitutes, were sought. Ethnic origin and the timing of relevant events were recorded as accurately as possible. Weekly alcohol consumption was noted. A random proportion of donors with false-positive results also completed a questionnaire to act as a control group for the study.

Counsellors tried to interview donors alone for at least part of the interview, but when requested they also spoke to partners and discussed testing of family members.

Donors confirmed to be positive were advised to visit their general practitioner (GP) to discuss specialist referral. A list of specialists was sent to the GP, together with an explanatory letter, after obtaining the donor's written consent for this contact. Follow-up information about events subsequent to our counselling was obtained by sending questionnaires to both donors and GPs, and this is reported in a separate paper (Ryan *et al.*, 1993).

* Subsequent to this study a protocol for readmission of 'false-positive' donors has been approved in the U.K.

All donors confirmed as anti-HCV positive, indeterminate or false-positive were removed from the donor panel, and their donations were not used. As only 4% of the population of England and Wales are blood donors and are undergoing testing for evidence of infection with other agents, their demography cannot be assumed to reflect the total population. To assess the significance of demographic characteristics of HCV seropositive donors, a second control group, consisting of all blood donors attending on one day (29 September 1992), was asked to complete an anonymous questionnaire about blood transfusion history, scarification and occupations with a potential for exposure to blood or needles (e.g. ambulance staff, nurses). However, it was felt that in the context of an anonymous and voluntary questionnaire it would be inappropriate to ask about drug use or past sexual history. Nevertheless, donors reacting falsely positive for anti-HCV were able to provide some measure of control for these aspects of history. On the day in question, the sessions reflected an increased proportion of male manual workers compared with the overall donor panel. Statistical analysis was performed with the aim of identifying potential risk factors which might be associated with hepatitis C infection.

The effect of each risk factor was assessed by obtaining odds ratios after performing logistic regression analyses to model the number positive for each outcome using bionomial error structure and a logit link. To evaluate statistical significance, 95% confidence intervals were obtained for these estimates. Single variable analyses were performed to obtain unadjusted odds ratios and 95% confidence intervals for each risk factor. Multivariable analyses were performed to obtain adjusted odds ratios and 95% confidence intervals for each risk factor after controlling for the effects of other risk factors and interactions.

Anti-HCV positive donors were compared with those reacting indeterminate or false-positive combined, to obtain P values for each risk factor, using single and multivariable analysis. Those confirmed as anti-HCV positive were then compared with controls, for each risk factor for which control data were available.

RESULTS

Prevalence of anti-HCV

During the year September 1991 to August 1992, 241 831 anti-HCV tests were performed on donations

Table 1. Age/sex distribution of the total donor population for September 1991 to August 1992, plus control group, and confirmed anti-HCV positive, indeterminate and false-positive donors given as numbers (and percentage) of total donors in that age and sex band. Only those anti-HCV reactive donors that took part in the study are included in this analysis and reactivity rates are not therefore those of the overall donor population

Age group (years)	Total donors for year		Confirmed positive		Indeterminate		False-positive		Controls	
	M	F	M	F	M	F	M	F	M	F
<20	1788	2648	0 (0·0%)	1 (0·038%)	0 (0·0%)	0 (0·0%)	0 (0·0%)	0 (0·0%)	18 (1·007%)	8 (0·302%)
20–29	20250	28327	10 (0·049%)	6 (0·021%)	5 (0·025%)	8 (0·028%)	2 (0·010%)	3 (0·011%)	126 (0·622%)	89 (0·314%)
30–39	20371	19675	31 (0·152%)	21 (0·107%)	8 (0·039%)	8 (0·041%)	4 (0·020%)	2 (0·010%)	127 (0·623%)	71 (0·360%)
40–49	16386	17182	25 (0·153%)	19 (0·111%)	9 (0·055%)	5 (0·029%)	9 (0·055%)	0 (0·0%)	103 (0·629%)	92 (0·535%)
50–59	8638	8166	2 (0·023%)	2 (0·024%)	4 (0·046%)	6 (0·073%)	5 (0·058%)	1 (0·012%)	77 (0·891%)	28 (0·342%)
>60	2974	1929	0 (0·0%)	0 (0·0%)	1 (0·034%)	2 (0·103%)	3 (0·101%)	1 (0·052%)	24 (0·807%)	8 (0·414%)
Total	70407 (47%)	77927 (53%)							475 (62%)	296 (38%)
	148334								771	

Table 2. Potential risk factors in donors reactive for anti-HCV, and in control donors

	Confirmatory anti-HCV result											
	Positive			Indeterminate			False-positive			Controls		
	T	M	F	T	M	F	T	M	F	T	M	F
Number of donors	100	53	47	48	21	27	14	9	5	771	475	296
Intravenous drug use (IVDU)	37 (37%)	23 (43%)	14 (30%)	4 (8%)	3 (14%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)		not asked	
Sexual contacts of IVDU	26 (26%)	8 (15%)	18 (38%)	4 (8%)	3 (14%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)		not asked	
Blood transfusion	31 (31%)	13 (25%)	18 (38%)	7 (15%)	1 (5%)	6 (22%)	0 (0%)	0 (0%)	0 (0%)	191 (25%)	124 (26%)	67 (23%)
Ear-piercing	76 (76%)	33 (62%)	43 (91%)	28 (58%)	4 (19%)	2 (89%)	5 (36%)	1 (11%)	4 (80%)	318 (41%)	75 (16%)	243 (82%)
Tattoos	30 (30%)	21 (40%)	9 (19%)	3 (6%)	3 (14%)	0 (0%)	1 (7%)	1 (11%)	0 (0%)	43 (6%)	37 (8%)	6 (2%)
At risk sexual behaviour, e.g. sex with prostitutes	15 (15%)	10 (19%)	5 (11%)	2 (4%)	1 (5%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)		not asked	
Potential occupational exposure	13 (13%)	5 (9%)	8 (17%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	1 (11%)	0 (0%)	79 (10%)	33 (7%)	46 (16%)
Acupuncture	9 (9%)	6 (11%)	3 (6%)	7 (15%)	4 (19%)	3 (11%)	2 (14%)	2 (22%)	0 (0%)	32 (4%)	16 (3%)	16 (5%)
Electrolysis	6 (6%)	0 (0%)	6 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	20 (3%)	2 (<1%)	18 (6%)
No risk factor identified	5 (5%)	5 (9%)	0 (0%)	11 (23%)	10 (48%)	1 (4%)	7 (50%)	6 (67%)	1 (20%)	286 (37%)	257 (54%)	29 (10%)

* T, total; M, males; F, females.

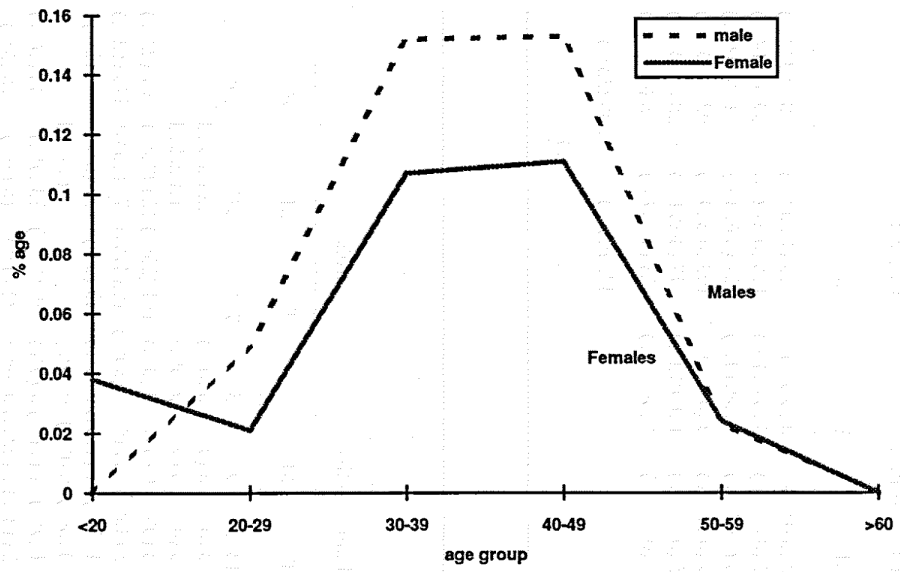

Fig. 1. Confirmed positive donor as a percentage of the total donor population by age and sex.

from 161 937 donors; 1490 (0·62%) tests were initially reactive and 968 (0·4%) were repeatably reactive. One hundred and seventeen donors were subsequently confirmed positive by RIBA-2 (0·071% or 1 in 1400). Two hundred and thirty donors (0·14%) had indeterminate RIBA-2 results, 56 of whom had two such results during the year and were therefore invited for counselling. Thirty donors had false-positive reactions on more than one occasion and were also contacted.

The 'control group' questionnaire was answered by 771 donors. On the day of distribution, 952 screening tests were performed, three of which were repeatably reactive and one of which was confirmed anti-HCV positive. We were unable to identify the questionnaire responses relating to this donor as the questionnaire was anonymous.

Table 1 shows age/sex distributions for the total donor population of the year, the control group, and for those donors confirmed anti-HCV positive, 'indeterminate' and false-positive that were included in the study. Figure 1 shows how the prevalence of anti-HCV varies with age and sex—the highest prevalence is in the 30–49 age groups for both sexes; the majority of routine blood donors are below 40 years of age. The multivariable analysis confirmed that being in the age group 30–49 was significantly associated with an increased rate of hepatitis C infection for both men and women.

Donor counselling

Some donors could not be counselled either because we were unable to establish contact or because they declined to attend. One hundred of 117 confirmed as positive, 48 of 56 indeterminate and 14 of 30 false-positive donors attended for counselling. We were then able to explore possible routes of infection and in many cases to estimate intervals from the probable date of infection elicited from their histories.

Source of infection

Table 2 shows a comparison of the proportions of donors who admitted to the various 'risk behaviours' in each group: confirmed positive, indeterminate, false-positive and controls.

Preliminary analysis compared the proportions exposed to each potential risk factor over the three test result groups (positives, indeterminates and false-positives), and found that the proportions amongst confirmed positives were significantly higher than amongst indeterminates for each risk factor. Amongst the false-positives the proportions were lower but this group was too small to show a significant difference from the indeterminate group. On the basis of this analysis, indeterminates and false-positives were combined in subsequent analysis.

Single variable analysis showed a significant ($P = < 0{\cdot}01$) increase in risk of hepatitis C infection associated with intravenous drug use (IVDU; $P = < 0{\cdot}001$), blood transfusion, ear-piercing, tattooing, 'at risk' sexual behaviour, sexual contact with IVD users, and occupational exposure. After adjustment was made for confounding effects, blood transfusion ($P = 0{\cdot}01$), occupational exposure ($P = 0{\cdot}02$), ear-piercing ($P = 0{\cdot}05$) and tattooing ($P = 0{\cdot}05$) remained

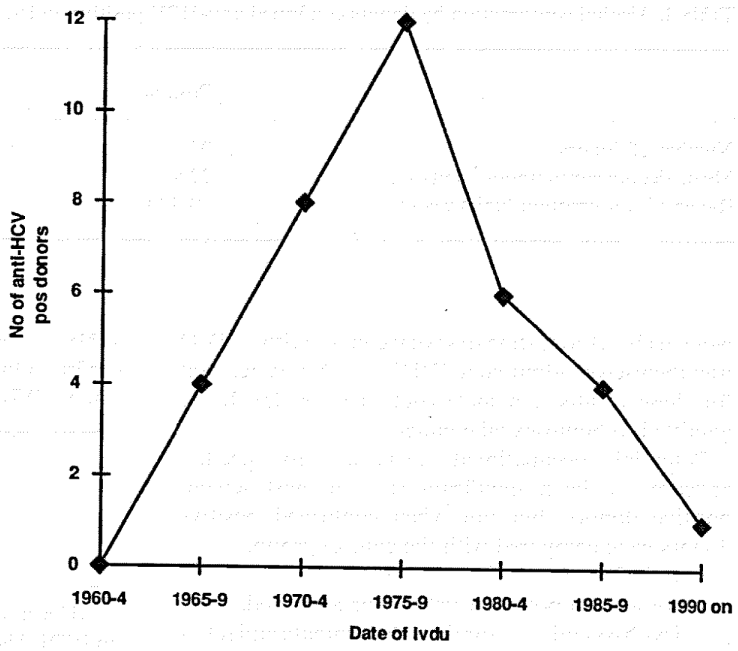

Fig. 2. Estimated date of IVDU in donors confirmed anti-HCV positive.

significant. IVDU showed evidence of an increased risk of infection, with $P=0{\cdot}06$. As well as the marked increase in IVDU among the confirmed positive donors, there was a slight increase in this risk behaviour in indeterminate donors compared with those reacting false-positive. The grouping of the four indeterminate donors who admitted to IVDU with the false-positives for the purpose of analysis may account for the unexpectedly high P value of 0·06.

Analysis was performed comparing donors confirmed anti-HCV positive with the control group, for those factors for which the data were available. On single variable analysis both sexes combined showed a significantly increased risk of hepatitis C infection associated with age group 30–49, ear-piercing, tattooing and acupuncture. On multivariable analysis, age group 30–49 ($P=<0{\cdot}01$), ear-piercing ($P=<0{\cdot}01$) and tattooing ($P=<0{\cdot}01$) and, less strikingly, blood transfusion ($P=0{\cdot}04$) were of significance in females.

There appears, therefore, to be reasonably strong evidence of an association between hepatitis C infection and age group 30–49 and tattooing in both sexes, with ear-piercing in males and blood transfusion in females being additional significant risk factors. The control group percentage rates for blood transfusion (26 and 23%, respectively, for males and females) were at first sight surprisingly high, but this may reflect the increased motivation amongst recipients of blood transfusion to donate.

'At risk' sexual behaviour and sexual contact with IVD users were significant risk factors on single variable, but not multivariable, analysis. Ten out of 18

Table 3. ALT levels in donors confirmed anti-HCV positive, indeterminate and false-positive

	Positive ($n=100$)	Indeterminate ($n=56$)	False-positive ($n=30$)
Donors with increased ALT*	60 (60%)	3 (5·4%)	0
Mean ALT levels (iu/l)	68	21	21
Range of ALT (iu/l)	5–448	5–80	9–42

* >45 iu/l males, >30 iu/l females.

Table 4. Alcohol consumption by donors confirmed anti-HCV positive, indeterminate and false-positive

	Positive	Indeterminate	False-positive
Number of donors	97	47	15
Mean alcohol consumption (units/week)	22·8	10·5	6·8
Range of consumption (units/week)	0–140	0–56	0–22

women (56%) admitting to sexual contact with an IVD user themselves admitted to IVDU which may account for these results. No male (but one female) donor admitted to homosexual contact.

Potential occupational exposure to needles appeared to be a significant risk amongst screen-positive donors, but not when confirmed positive donors were compared with the control group.

In only 9% of male donors confirmed as anti-HCV positive was no potential risk factor identified, compared with 48 and 67% for the indeterminate and false-positive groups, respectively. Because of the high rate of ear-piercing in women a potential risk factor was rarely absent, although in most cases the actual risk posed was probably negligible. When ear-piercing was removed as a risk factor in female donors, similar results to males were obtained; no potential risk factor was identified in 5/47 (11%) of confirmed positive, 13/27 (48%) of indeterminate and 5/5 (100%) of false-positive donors.

Alanine amino transferase (ALT) levels and alcohol consumption

ALT levels were determined for all anti-HCV positive donations. Table 3 compares ALT levels in donors confirmed anti-HCV positive, indeterminate and false-positive. An elevated ALT level was significantly associated with the risk of hepatitis C infection ($P = < 0{\cdot}001$).

Possible factors for elevated ALT levels other than anti-HCV reactivity were investigated in these donors. Table 4 shows average alcohol consumption of those donors for whom this information was available. Increased alcohol consumption amongst confirmed positive donors was significant on single variable ($P = < 0{\cdot}01$) but not multivariable analysis ($P = 0{\cdot}17$).

These data suggest that alcohol consumption by donors infected with HCV is greater than for those who are not infected, but there was no obvious correlation between ALT levels and extent of reported alcohol consumption. Several donors, however, who reported a marked decrease in their alcohol intake following counselling were found to have lower ALT levels when samples taken at a later date were tested.

Table 5. Average alcohol consumption by donors confirmed to be HCV positive, comparing those with and without IVDU history

	Average alcohol consumption (units/week)		
	T	M	F
IVDU history	31 ($n=36$)	40 ($n=23$)	16 ($n=13$)
no IVDU history	19 ($n=61$)	30 ($n=29$)	9 ($n=32$)

Using the data obtained at counselling, an estimate of the likely date of infection could be made for the majority of donors. We found no correlation between ALT levels and either likely time interval since infection, or alcohol consumption.

Within the group of donors confirmed to be anti-HCV positive, alcohol consumption by those admitting to a past history of IVDU was compared with the consumption by donors denying this history. Results are given in Table 5, which shows higher average consumption by the IVDU group in both male and female donors.

Ethnic analysis

The ethnic origin of most of the donors was recorded. Table 6 shows the ethnic distribution within each HCV category and compares the data with a control group of routine donors donating on one day (22 February 1993) and also with donors found positive for HBsAg but negative for anti-HCV at this Centre during 1992. The vast majority of anti-HCV positive donors are from the U.K./North European/Australasian group. However, Table 7 compares the proportions of donors from non-Caucasian ethnic groups in each category.

Table 6. Ethnic origin of donors confirmed anti-HCV positive indeterminate and false-positive, compared with a group of 1008 consecutive routine donors and 28 consecutive HBsAg positive donors

	Anti-HCV positive	Anti-HCV indeterminate	Anti-HCV false-positive	Routine donors	HBsAg positive
Number in group	117	56	30	1008	28
U.K./North European/Australasian	103 (89%)	51 (93%)	25 (89%)	987 (99%)	13 (46%)
Mediterranean	5 (4%)	2 (4%)	0	0	0
African	0	0	1 (4%)	11 (1%)	2 (7%)
Afro-Caribbean	1 (<1%)	0	0	0	1 (4%)
Asian	4 (3%)	2 (4%)	1 (4%)	2 (<1%)	12 (43%)
South American	0	0	0	2 (<1%)	0
Arabic	3 (3%)	0	1 (4%)	0	0
Not known	1	1	2	6	0
Total non U.K./North European/Australasian	13 (11%)	4 (7%)	3 (10%)	15 (1·5%)	15 (54%)

Table 7. Percentage of donors from non-Caucasian groups, comparing donors confirmed anti-HCV positive, indeterminate and false-positive, with routine anti-HCV negative control donors and HBsAg positive donors

Anti-HCV	
confirmed positive	12·8
indeterminate	7·3
false-positive	10·7
Controls (anti-HCV negative)	1·5
HBsAg positive	53·6

The anti-HCV positive rate is approximately 5–10 times greater than control donors who tested negative for anti-HCV (including indeterminates and false-positives), but the incremental factor is less than that for HBsAg positive donors.

DISCUSSION

Screening of blood donations for HCV antibody has led to the identification of a previously undefined group of donors who are seropositive for this virus and who have not been identified through self-exclusion questionnaires or screening for evidence of infection with other microbiological agents. Although, prior to donation, north London donors are asked to reply to a confidential questionnaire which includes a query about past IVDU, most of those seropositive donors who later admitted to this said that they thought it 'too long ago' to be relevant.

A history of previous IVDU was given by 43% of seropositive males and 30% of females. For most of these, this experience occurred about 15 years ago when they were teenagers, or in young adult life (see Fig. 2). From analysis of possible risk factors for exposure to the virus and by comparison with seronegative controls, this appears to be the most important potential source of infection; ear-piercing in males and tattooing in both sexes may be contributory factors *or* may reflect a pattern of behaviour rather than a specific risk factor; interestingly, the prevalence of histories of ear-piercing and tattooing is higher, suggesting they may carry their own independent risk. Indeed, many donors reported multiple risk factors. For example, 17/23 males admitting to IVDU had pierced ears and eight of these were also tattooed. The donors infected with HCV through IVDU had generally used drugs before 1980—it is not clear whether this is because people indulging in this practice since that time are not donating or whether they have used safer practices while using drugs. The timing at which drug use occurred, however, could certainly account for the increased infection rates in older (30–40 years) donors; the majority of routine donors are in the 20–30 age group.

The introduction of screening has wide implications, not least for the donors themselves. They present for donation as 'normal, healthy' people, almost all of whom had no idea that they might be infected with

HCV. For many it was a shock to receive this information, and for some it has caused problems with marriage partners and at work (unpublished observations). There may, however, be some benefits for donors knowing their HCV status in that prophylactic treatment, e.g. reduction in alcohol intake (and interferon therapy, which Makris *et al.* (1991) showed to have a beneficial effect in at least 50% of haemophiliacs infected with HCV) can be instituted early. As yet the extent of secondary transmission of HCV is still unclear; the potential benefits of awareness of HCV infection in this respect cannot therefore be estimated.

The transfusion service must bear the considerable expense of screening (£5m annually for test kits alone) and of counselling seropositive donors, adding to the cost of treatment for patients requiring blood transfusion. Cost implications for the National Health Service are considerable since seropositive donors will be referred for specialist assessment, possibly including admission for liver biopsy and commencement of interferon treatment (Ryan *et al.*, 1993). Furthermore, the transfusion service must then recruit donors to replace those who are no longer acceptable because of positive anti-HCV screening tests, including those who test false-positive. The elimination of seropositive donations will undoubtedly decrease the risk of transmitting HCV infection, but our results confirm that there is only a minimal gain since the HCV seropositivity rate is 0·07%. As anti-HCV reactive donors are eliminated from the established donor panel the numbers of newly detected anti-HCV positive donors will fall; seroconversion in previously tested donors is rare (unpublished data); the cost of detecting each new HCV-infected donor will consequently increase accordingly.

In-depth interviews with HCV seropositive donors have revealed that donor selection procedures are not always effective. Although donors may understand the information given, they will not always behave in the manner expected of them, especially in the case of past history of IVDU. Clearly, this issue must be addressed.

The introduction of mass screening has provided an opportunity to study the natural history of HCV infection, about which little was previously known in asymptomatic individuals. Post-transfusion hepatitis (PTH) has been extensively studied and it is reported that as many as 50–62% of patients with PTH (Realdi *et al.*, 1992) or acute hepatitis due to HCV (Alter *et al.*, 1992) will progress to chronic liver disease (CLD), but it is not known what proportion of people exposed to the virus, not all of whom will develop acute hepatitis, will go on to suffer later sequelae such as chronic hepatitis or hepatocellular carcinoma. Indeed, our data suggest that many of these donors remain perfectly healthy with normal liver function tests (LFTs) many years after exposure. If HCV infection consistently leads to CLD we might have expected a trend towards raised LFTs with increasing time from exposure, which was not found. Identification of individuals who are positive for anti-HCV through screening will enable a more accurate assessment of risk from HCV infection to be made, but this may take as long as another 20 years to accrue as present cohorts of donors are followed up. This has been clearly indicated by the study of Seeff *et al.* (1992) where no increased mortality and little extra morbidity was seen in 500 PTH patients, compared with controls, after follow-up at 18–20 years.

The significance of LFTs in anti-HCV positive individuals is not clear. We found no correlation between ALT levels and either level of alcohol consumption or interval since probable date of infection, although raised ALT levels were significantly associated with risk of infection with hepatitis C. Alberti *et al.* (1992) found that ALT levels did not correlate with either PCR positivity or liver disease as shown at biopsy, but all patients with chronic hepatitis were PCR positive and those with normal histology were PCR negative. Coexistent exposure to hepatitis B is, however, associated with an increased likelihood of elevated ALT levels (Aloysius *et al.*, 1992; Gesinde *et al.*, 1992). It is possible that a more accurate measure of infectivity and predisposition to late sequelae of infection in anti-HCV positive donors would be gained from PCR studies, but to perform this routinely would greatly increase the costs to the transfusion service. Interestingly, at counselling, a history of jaundice was obtained in 8% of donors confirmed to be anti-HCV positive although this had usually not been recorded during donation. Furthermore, 57% of the anti-HCV positive donors who had a history of jaundice were also anti-HBc positive. In other studies at the NLBTC only 2 of 690 (0·3%) donors with a history of jaundice (a history reported by 0·6% of our donors) were found to be confirmed anti-HCV positive (unpublished data).

Seeff *et al.* (1992) comment that HCV infection is common among alcoholics and our data support this as we found average alcohol consumption to be higher among donors confirmed to be HCV antibody positive compared with those found to be indeterminate and false-positive. Within the confirmed positive group, alcohol consumption appeared to be higher amongst those admitting to IVDU in the past. This may reflect the different lifestyle of some individuals, several aspects of which may predispose them to infections such as HCV, e.g. IVDU or tattooing, rather than suggesting that the alcohol itself has a causative role.

'Anti-HCV indeterminate' donors pose the biggest

questions. It is of interest that in those areas of 'risk behaviour', more common in confirmed positive donors compared with false-positive and control donors (e.g. IVDU and ear-piercing in males), the 'indeterminate' group had intermediate prevalence of such behaviour, suggesting that some members of this group possess the same history and therefore risks: the likelihood of actual infection with HCV in such individuals may thus be greater. Follett *et al.* (1992) found 5·4% of Scottish donors reacting as RIBA-2 indeterminate to be viraemic when tested by PCR for HCV RNA, and Kohlo *et al.* (1992) reported transfusion-transmission of HCV by 3 of 52 first-generation RIBA 'indeterminate' donations (5·8%), confirming that some of these donors are truly infected.

This study has extended our previous short report (MacLennan *et al.*, 1992) and explored some aspects of the demography of HCV-infected donors in fuller detail. However, even this current study can be no more than suggestive in certain aspects because of the relatively small number of donors studied and serves mainly to identify some tantalizing possibilities for enhancing our understanding of the natural history of HCV infection. IVDU stands out as a clear risk factor, but to define unequivocally the extent of sexual and materno-fetal transmission, more studies are needed. Because of the apparently low rate of transmission by the latter routes, a much larger data base is required and this might best be served by a multicentre approach to accruing statistically significant data. In the meantime, some questions asked by HCV-infected individuals cannot be answered definitively and fuller funding is vital for the elucidation of the remaining gaps in our knowledge of the natural history of HCV infection.

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