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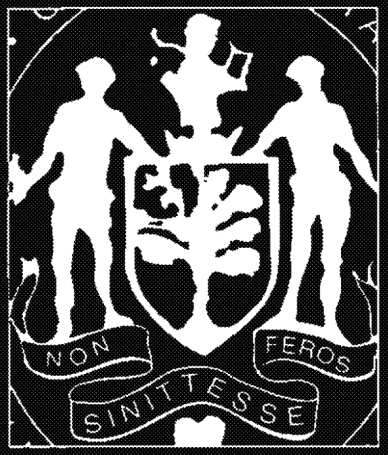


Hepatitis C

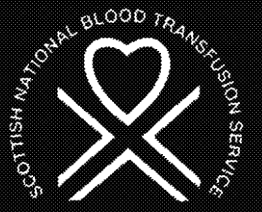
A Report produced by a working party of the Royal College of Physicians of Edinburgh

IN THE CONTEXT OF BLOOD TRANSFUSION SERVICE

Lookback STUDIES &

SIMILAR CIRCUMSTANCES (SCOTLAND)

Designed & Printed by Metro Press, Edinburgh



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Scottish National Blood Transfusion Service

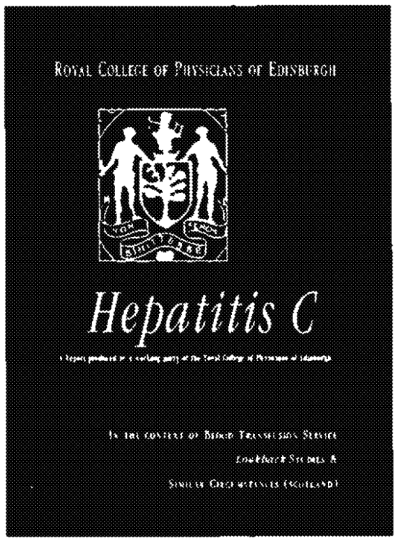
Scheuer P J Classification of chronic virus hepatitis: a need for reassessment -J Hepatol (1991)13: 372-374.

Seeff L B et al. Longterm mortality after transfusion associated nonA-nonB hepatitis - New Engl J Med (1992)327: 1906-1911.

Simmonds P. Significance of sequence variability of hepatitis C virus -Proc. Roy. Coll. Phys. Edin. (1995) 25: 598-603.

Tong M. et al. Clinical outcomes after transfusion-associated hepatitis - New Engl. J Med (1995) 332: 1463-1466.

Vrielink H et al. Lookback study of infectivity of anti-HCV ELISA-positive blood components - Lancet (1995)345: 95-96.



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Dusheiko G M. Rolling review - the pathogenesis, diagnosis and management of viral hepatitis
- Aliment Pharmacol Ther (1994)8: 229-253.

Dusheiko G, The management of chronic hepatitis C
-Proc. Roy. Coll. Phys. Edin. (1995) 25: 604-610.

Dusheiko G., Roberts J., Treatment of chronic Type B and C hepatitis with interferon-alfa - an economic appraisal
- Hepatology (1995) 22: 1863-1873.

Hoofnagle J H et al. Antiviral therapy of hepatitis C - present and future
- J Hepatol (1993)17(Suppl 3): s130-136.

Kasahara A et al. Ability of prolonged interferon treatment to suppress relapse after cessation of therapy in patients with chronic hepatitis C - a multicentre randomised controlled trial
- Hepatology (1995)21: 289-297.

Kobayashi Y et al. Detection of hepatitis C virus RNA by nested polymerase chain reaction in sera of patients with chronic nonA-nonB hepatitis treated with interferon
- J Hepatol (1992)16: 135-144.

Koff R. S., Seeff L. B., Economic modelling of treatment in chronic hepatitis B and chronic hepatitis C: Promises and limitations
- Hepatolgy (1995) 22: 1880-1882.

Lau J Y N, Davis G L. Managing chronic hepatitis c virus infection
- Brit Med J (1993)306: 469-470.

Marcellin P, Benhamou J P. Treatment of chronic viral hepatitis
- Ballieres Clinical Gastroenterology (1994)8, No 2: 233-253.

Rolti L et al. Break-through during recombinant IFN alpha therapy in patients with chronic hepatitis C virus infection - prevalence, etiology and management
- Hepatology (1995)21: 645-649.

APPENDIX - F

References

Allander T et al. Frequent patient-to-patient transmission of hepatitis C virus in a haematology ward
- Lancet (1995)345: 603-606

Alter M et al. The natural history of community acquired hepatitis C in the USA
- New England Journal of Medicine (1992)327: 1899-1905.

Ayob Y et al. Risk of hepatitis C in patients who received blood from donors subsequently shown to be carriers of hepatitis C virus
- Transfusion Medicine (1994)4: 269-273.

Booth J et al. The management of chronic hepatitis C virus infection.
- Gut (1995) 37: 449-454

Chemello L et al. Predictor of sustained response, relapse and no response in patients with chronic hepatitis C with interferon-alpha
-J Viral Hepatitis (1995)2: 91-96.

Davis G L. Prediction of response to interferon treatment of chronic hepatitis C
-J Hepatol (1994)21: 1-3.

Davis G L. Interferon treatment of cirrhotic patients with chronic hepatitis C: a logical intervention
- Am J Gastroenterol (1994)89: 658-660.

Desmet VJ et al. Classification of chronic Hepatitis diagnosis, grading and staging
- Hepatology (1994) 19: 1513- 1520.

Di Bisceglie A et al. Long term clinical and histopathological-follow-up of chronic post-transfusion hepatitis
- Hepatology (1991)14: 969-974.

1. Background

1.1 Hepatitis C virus (HCV) is now established as the main causative agent in Non A Non B post-transfusion (and parenteral) hepatitis. It is a major cause of chronic liver disease worldwide. Since the onset of blood donor screening in the UK about 3,000 HCV infected donors have been identified. The great majority of donors found to be sero-positive by 2nd and 3rd generation confirmatory tests (RIBA) have evidence of viral RNA in the blood (positive polymerase chain reaction) and histological evidence of chronic liver disease. An unknown proportion of these will ultimately develop end-stage liver disease (cirrhosis and/or hepatoma) but the disease process is in the majority certainly very protracted (Di Bisceglie et al, 1991, Alter et al, 1992, Seeff et al, 1992, Tong et al, 1995).

1.2 Recently the Edinburgh and South East Scotland Blood Transfusion service made a preliminary retrospective (*lookback*) study of donors found to be HCV positive in the early stages of the introduction of the national screening programme (Ayob et al, 1994).

Previously established donors had made 70 donations prior to the onset of screening in 1991 and 9 living recipients of these donations (many had subsequently died) were identified, traced, and found to be positive. Probably some 300 such recipients would be traceable in Scotland (2,000 - 3,000 in the UK as a whole). A recent Dutch study (Vrielink et al, 1995) suggested that 81% of recipients of PCR (virus RNA) positive blood components were HCV infected. It should be noted that only those recipients of potentially infected blood from donors who return to donate after September 1991 will be identified by *look back* studies.

1.3 These findings suggested that an integrated and co-ordinated programme of *lookback* was urgently necessary. Now that interferon is licensed for treatment of HCV hepatitis (and other treatments are actively under trial) with at least moderate success there are strong medical and ethical reasons for undertaking such a programme.

1.4 Persons identified as being potentially HCV positive must be told. There is a duty to provide care and support for these patients to the highest clinical standards.

1.5 In order to facilitate the clinical component of the HCV *lookback* a group of interested clinicians met to discuss operational issues from January 1995, at the instigation of the Medical Director of the Scottish Blood Transfusion Service and under the aegis of the Royal College of Physicians of Edinburgh.

This brief report attempts to set out a plan for action and broad guidelines for management in the light of current knowledge without wishing to dictate or to constrain clinical judgment in individual situations. It also makes an urgent plea for the setting up of a Scottish HCV interest group.

APPENDIX - E

Membership of Working Party

Dr P W Brunt (Chairman)	Consultant Physician/Gastroenterologist, Aberdeen
Dr N D C Finlayson	Consultant Physician/Gastroenterologist, Edinburgh
Dr J Gillon	Consultant, Scottish Blood Transfusion Service, Edinburgh
Dr Ian Kerr	General Practitioner, Currie
Dr P Mills	Consultant Physician/Gastroenterologist, Glasgow
Dr P Hayes	Senior Lecturer in Medicine/Hepatologist, Edinburgh

In attendance: Dr Aileen Keel
Senior Medical Officer
Scottish Office

APPENDIX -D

Local Centres in Scotland offering clinical advice, counselling and treatment for Hepatitis C (contact clinician in each Group)

WEST SCOTLAND	Department of Gastroenterology, Western Infirmary, GLASGOW (Dr P Mills).
SOUTH EAST SCOTLAND	Centre for Digestive and Liver Disease, Edinburgh Royal Infirmary, EDINBURGH (Dr N D C Finlayson, Dr P Hayes).
EAST SCOTLAND	Gastrointestinal Unit, Ninewells Hospital, DUNDEE (Dr J Dillon).
NORTH EAST SCOTLAND	Gastrointestinal and Liver Service. Aberdeen Royal Infirmary, ABERDEEN (Dr P W Brunt).
NORTH SCOTLAND	Raigmore Hospital, INVERNESS (Dr P Zentler-Munro).

Local advice may also be obtained at many Departments of Gastroenterology, Infectious Disease Units and Departments of Microbiology (Virology) throughout Scotland and at the Regional Blood Transfusion Centres.

2. *Introduction*

2.1 The *lookback* survey expected to identify some 300 patients nationwide (Scotland) who are at risk and efforts are being made to trace each one of these.

2.2 (a) The Regional Transfusion Centre (RTC) will send details of the incriminated components to hospital blood bank haematologists where appropriate, who will in turn identify the recipients from blood bank and/or hospital records.

(b) The haematologists will then contact the clinician responsible for the transfusion, using a standard letter, offering the clinician the opportunity to undertake the counselling and testing if the patient is still under his/her care.

(c) If the patient is no longer attending the clinician responsible for the transfusion or, if the clinician declines to become involved, the GP will be offered the opportunity to contact the patient.

(d) Every effort is made to ensure that the patient is known to be alive before an attempt is made to establish contact.

(e) A pack of background information and details on blood samples and testing arrangements have been made available for GPs and clinicians undertaking the counselling and testing.

(f) If both the clinician and the GP decline to become further involved, the RTC clinician responsible for the *lookback* will contact the patient and undertake counselling and testing.

(g) A comprehensive system for recording data from each stage of the exercise will be made available. The documentation will be held centrally in the Regional Transfusion Centres.

2.3 Discussion with general practitioners and including the Chairman of the Scottish CGMS suggests that most general practitioners would be happy for direct referral to a specialist medical clinic by the BTS. (It is recognised, however, that there may be cost implications for fund-holding practitioners and close discussion with the patient's general practitioner will be essential).

2.4 Specialist clinicians (gastroenterologists/hepatologists) have been identified in the major Scottish centres (Appendix D). It is expected that most or all patients will be dealt with through these contacts in order to maintain some uniformity of approach and give opportunities for data collection, audit and research. This does not, of course, in any way preclude involvement of other clinicians in individual instances.

2.5 Patients will undergo a general medical assessment and examination as many may have complex existing medical disorders. It may be necessary to obtain medical records from the hospital the patient is/was attending. Details of the patient's transfusion record should be available to the clinician and other potential sources of HCV infection sought.

The patient's previous and current health, drug and alcohol history, evidence of liver disease and other serious pathology will be recorded.

2.6 Most patients will be anxious about their condition and require considerable reassurance. An explanation of the nature of the infection, the source of infection and the natural history of the illness as far as is known will be required. Patients will be given an information sheet and encouraged to call back with further questions. A clinical nurse specialist in each centre may have an important role in this counselling. Several visits may be required for each patient. The physician will explain what investigations are to be conducted, the plan for follow-up and possible treatment options. Patients will be invited to attend for regular follow-up.

2.7 Recipients found to be SERO-NEGATIVE will be invited to be seen, examined and counselled and their data recorded as control data for comparison - either by the hospital clinician concerned, if appropriate, or by the Blood Transfusion Service consultant.

Length of Follow-up

Hepatitis C is only slowly progressive in most patients. Therefore these patients must be followed for a 10-20 year period to judge the ultimate success of any treatment programme. It is suggested that patients are seen every three months before and during alpha interferon therapy and for one year after therapy. Thereafter they could be seen annually. Liver biopsy should ideally be repeated at five year intervals unless the liver histology had previously returned to normal.

These patients form an ideal cohort to follow long-term as a research project as their precise date of infection and infecting genotype is known. This will allow a better understanding of the epidemiology of this disease and this mode of infection. Alternative therapy will almost certainly become available in the future and fully documented patients attending such a clinic are well placed to take advantage of such advances.

paracetamol. With continuing therapy anorexia, hair loss, fatigue and weight loss are occasionally seen. Depression may occur. All patients will show some degree of marrow suppression. Other complications include seizures, bacterial infections, thyroid disease, cardiomyopathy, rashes, aggravation of diabetes, autoimmune reactions, retinal changes and interstitial lung diseases.

Assessment of Response to Therapy With Alpha Interferon

Response to alpha interferon has hitherto been judged by serum alanine transaminase (ALT) alone as defined below:-

Complete: normal serum ALT usually within two months.
Partial: > 50% reduction in serum ALT to a level of < 1.5 times upper limit of normal.
None: no effect on ALT.
Sustained: normal ALT for six months after therapy.

However, since serum ALT Levels can be normal in the presence of chronic hepatitis, evidence of active viral replication (serum HCV-RNA) and liver histology are rather more important criteria to judge success of therapy (Kobayashi et al 1992). It is suggested that serum HCV-RNA is monitored every three months before during and after therapy. Liver biopsy maybe repeated at 1 and 2 years after the start of interferon.

The degree of necro-inflammatory activity and fibrosis in the liver biopsy can be recorded on a 0-4 scale (Scheuer 1991 Desmet et al. 1994).

Treatment Failures with Alpha Interferon

Patients who fail to have a sustained response at 6 months after cessation of therapy are defined as treatment failures. Break through may occur during apparently successful treatment (Rolti et al 1995). Patients with no response, or a partial response only probably do not warrant any further treatment but should be kept under observation. Patients with a complete response who relapse after cessation of therapy may justify a resumption of therapy for a further 6 or 12 month period.The clinician must judge each case individually.

The significance of HCV variants in determining response to treatment is being increasingly recognised. (Simmonds, 1995)

3. Medicolegal Implications

3.1 In a number of countries the possibility of compensation and legal action against Blood Transfusion Services is an important current issue. In Britain the Government has made it clear that compensation will not be paid for people infected with Hepatitis C virus through blood transfusion (prior to 1991). It is likely that the Haemophilia Society and other groups of patients will continue to press for compensation.

3.2 Government statistics suggest that in Britain 6000 people may have been infected with HCV -of whom 3000 are haemophiliacs.

3.3 In France a recipient of HCV blood won his lawsuit against Marseilles Blood Transfusion Service on appeal. Other countries have active on-going lawsuits.

3.4 Clearly all patients being tested must be informed why they are being tested and offered the option of refusing tests. Counselling and specialist referral must be available.

3.5 All patients (subjects) who have been exposed, however remotely, to HCV infection in the context of transfusion treatment should be identified and offered tests. Authorities who do not now take steps to identify and inform patients may be at serious risk of successful civil action.

4. The Sero-Positive Recipient

4.1 Following referral to the specialist centre that consultant will assume clinical responsibility for the patient - subject to the approval of the general practitioner and any other clinician directly involved.

4.2 An investigation and management programme will be tailored to the individual's needs on the general lines outlined in Appendix C. Variation from these guidelines is at the discretion of the individual hepatologist.

4.3 Sero-positive patients will be invited to attend the hepatology clinic at three-monthly intervals (or more frequently initially as required). Liver function tests and serum PCR for HCV-RNA will be monitored. If patients are still infected or have abnormal liver function tests they will be invited to undergo a liver biopsy to assess the aetiology of their chronic liver disease and the severity of the chronic hepatitis. Pathologists will be asked to record the severity of both inflammation and fibrosis preferably using the Scheuer histological activity index (Scheuer, 1991).

At this stage patients with histological evidence of chronic hepatitis C and active viral infection (serum HCV-RNA positive) may be considered for treatment.

4.4 Patients regarded as not requiring treatment will remain under regular follow-up. It is anticipated that this would be for a minimum of ten years.

4.5 The specialist clinics should remain in close co-operation with the Scottish Blood Transfusion Service. The database should be maintained within and between agencies to monitor progress, outcomes, cost implications, etc. and to determine future policies (see 7.1).

Group (a) will be treated as below and groups (b) and (c) followed in the clinic to observe the natural history of the disease, to watch for complications and await new guidelines and developments in this area.

Alpha Interferon Regimens (Dusheiko, 1995)

Two commercial products (Roferon-A, Viraferon) are now licensed for the treatment of chronic hepatitis C. They are recombinant alpha-2 interferon, are equally effective, and have similar cost. Competitive quotations for supplies should be sought.

It is recommended to use alpha interferon 3 or 6 MU injected subcutaneously three times a week for 3 months initially. If there is no response at 3 months therapy should cease. Responders then continue with 3 MU as before for a further nine months completing a one year course in total. Patients with risk factors for a poor response should start with the higher dose regimen. Patients are taught to administer the subcutaneous injections themselves.

Side-effects or toxicity with alpha interferon may necessitate a reduction in dose or cessation of therapy at any stage.

Monitoring of therapy

It is recommended that patients are seen at 1, 2 and 4 weeks and thereafter monthly until 6 months and then at 9 and 12 months during therapy. A clinical nurse specialist with experience in this area could fulfil this role provided there is readily available medical support. Monitoring should include support and encouragement for the patient observation for any side effects or complications and blood tests including full blood count renal function and liver function tests. Marrow suppression may require a reduction in dosage. Serum PCR for HCV-RNA should be checked every 3 months and thyroid function tests every 6 months.

Frozen serum should be stored in triplicate at -20°C for all patients every three months. This will allow retrospective testing for Hepatitis C as newer and more accurate assays are developed in the future.

Side Effects of Alpha Interferon

Almost all patients experience malaise, fever, shivering and influenza-like symptoms within hours of the first few injections. They should be warned of this response and advised to take prophylactic

The following are suggested inclusion and exclusion criteria for selection of patients for alpha interferon therapy :-

Inclusion criteria:

a Age 70 years or less.
b. Either sex.
c. Serum PCR positive for HCV-RNA.
d. Six months of active infection or abnormal liver function tests.
e. Liver biopsy evidence of chronic Hepatitis C (not absolute). Patients with moderate and severe hepatitis should be treated. Patients with mild changes only should probably be reassessed after an interval.

Exclusion criteria:

a. Marked obesity (body mass index > 35).
b. HIV positive or patients who are immunosuppressed.
c. Patients with cirrhosis together with features of liver failure (consider for liver transplantation).
d. Evidence of primary hepatocellular carcinoma.
e. Patients with evidence for another cause for chronic hepatitis such as alcohol excess or auto-immune liver disease (smooth muscle antibody positive, high IgG).
f. Patients with significant co-morbidity due to neoplasia or cardiac, respiratory and renal disease.
g. Patients unable or unwilling to co-operate with subcutaneous injections or follow-up at the clinic.
h. Pregnancy, breast-feeding mother, or pre-menopausal female not using effective contraception.
i. Patients with contraindication to use of interferon such as depressive illness, epilepsy or compromised CNS function, psoriasis or known hypersensitivity to interferon products.

Patients with mixed hepatitis infections (i.e. hepatitis B, C and D) require individual consideration. Patients with compensated cirrhosis may be considered but the response to treatment is likely to be poor.

Therefore patients will fall into one of four categories:

a. Suitable and agreeable to treatment with interferon.
b. Suitable but not agreeable to treatment with interferon.
c. Not suitable for interferon treatment.
d. Mixed hepatitis infections.

5. Cost Implications

5.1 Although primarily outwith the remit of this Working Party, cost considerations do nevertheless have major implications for implementing a management policy.

5.2 *Staff costs:*

Patients will be attending clinics regularly and take up considerable medical, nursing, secretarial and clerical staff time. Some regional specialist hepatology clinics might employ a clinical nurse specialist to co-ordinate the running of the programme and record the necessary data.

5.3 *Laboratory costs:*

Monitoring of these patients will require costs for haematology, biochemistry, virology, x-ray and histopathology. This laboratory cost of PCR (qualitative/quantitative) and genotyping is approximately £60-70.

5.4 *Drug costs:*

Only alpha-interferon is licensed for use in chronic Hepatitis C. Current basic cost for 3 million units is approximately £15 plus VAT, i.e. £17.50. Hence a six month course of 3 million units three times weekly would cost in the region of £1,400, and a course consisting of 6 million units three times weekly for 3 months followed by 3 million units three times weekly for 9 months would cost approximately £3,370.

5.5 There is currently no general agreement as to who should meet the drugs cost, general practitioner or hospital. There is a growing tendency in Scottish regions to set up special drug lists and "prescribing interface" meetings to establish local policies. In general, the clinician carrying the responsibility for prescribing (and its safety) would be expected to be the "cost bearer".

5.6 In the smaller regions of Scotland the additional numbers generated by a *lookback* survey are relatively modest and may be largely absorbable into existing budgets. In the west of Scotland, in particular, the additional costs are likely to be substantial.

5.7 The recommendation of the appointment of a Hepatitis Counselling and Support Nurse in larger centres needs consideration. This might be a part-time appointment in smaller centres but full-time in larger centres.

6. Research Possibilities

6.1 *Background*

The opportunities for collaborative research based on the HCV *lookback* are potentially great. These proposals have been designed to take particular advantage of:

(a) The unique features of *lookback* studies: namely that donor and recipient are identified and date of infection known.

(b) Close existing collaboration among clinicians, with centralised facilities for follow-up and treatment.

(c) The established excellence of the University of Edinburgh Department of Medical Microbiology and the MRC Institute of Virology in Glasgow in this field of research.

6.2 *Proposals*

(a) Epidemiology

- HCV genotype in donor and recipient, and relation to risk factors in donor.
- Detailed sequence comparisons of variable regions of genome for evidence of sequence clustering (refs 1,2,3).

(b) Virology

- Rate of change of HCV sequence in response to selection pressures.
- Investigation of the possibility of immune escape as the basis for persistent infection (ref 4).
- Significance of evolutionary drift vs emergence of "unseen variants" (cf HIV, ref 5).
- Use of stored samples to examine predictive factors for infectivity (especially virus load and possibility of infection by PCR negative donors).

(c) Natural History

- Relationship between virus type and sequence variation and disease progression.
- Disease progression as a function of duration of infection.
- Use of novel markers of liver damage (eg hyaluronic acid) as measures of disease severity and progression.

(d) Response to Treatment

- Significance of virus type
- Significance of route of transmission and duration of infection.

Available Therapy for Hepatitis C (Davis G., 1994. Hoofnagle, J. et al, 1993. Lau, J. et al, 1993. Marcellin, Percel, 1994)

The only agent with proven efficacy for the treatment of Hepatitis C is alpha interferon. Response rates are currently defined by normalisation of serum transaminases but ultimately loss of serum HCV-RNA and recovery of liver histology are better criteria of success. Overall initial response rates are 45-89%, depending on patient selection, dose and duration of therapy. A response to initial therapy is nearly always seen within three months such that therapy may be stopped in nonresponders at this stage. After 6-12 months of continuing therapy in responders about 50% of patients will show a relapse of infection within a few months of ceasing therapy as indicated by a rise in serum transaminases and return of serum HCV-RNA. Only approximately 25-30 % of patients will achieve a sustained response with serum transaminases remaining normal six months after cessation of therapy. Data on long-term follow-up are not yet available. Patients who relapse may respond to further therapy and the dose and duration to produce a sustained response is still being evaluated.

Nucleoside analogues are being used experimentally in Hepatitis C virus infection. Ribavirin will produce a reduction in circulating serum HCV-RNA levels but rebound usually occurs on cessation of therapy. Recently the combination of alpha interferon and ribavirin in patients who were refractory to or had relapsed after previous alpha interferon therapy was more successful in producing a sustained response.

Selection of Patients for Alpha Interferon Therapy (Booth J., et al. 1995)

In general, alpha interferon is most successful in the young patient with mild liver disease and a low viral load. In view of the long natural history of Hepatitis C infection it would seem sensible to limit therapy to patients aged 70 years or younger, other than in exceptional circumstances. Other factors associated with a poor response to interferon include marked obesity, high levels of circulating HCV-RNA, HCV genotype 1b, associated HIV infection or immunosuppression, inherited coagulation disorders, iron overload and cholestatic liver function tests. Patients in Scotland usually have HCV genotypes 1, 2 and 3. While genotypes 2 and 3 may respond more readily than 1 (Kasahara A. et al, 1995), the latter group warrant a trial of therapy. Similarly patients with compensated cirrhosis may not respond as well as precirrhotic patients but they also have potentially more to gain and thus warrant consideration. About 80% of haemophiliacs and other patients with inherited coagulation disorders are infected with the HCV. They do not respond as well as other patients, but there is a strong need to include them in a treatment programme.

APPENDIX - C
Management Protocol

Investigations

The following investigations may be indicated in all patients who wish assessment:-

- Full blood count
- Coagulation screen
- Serum liver function tests
- Serum creatinine
- Serum ferritin
- Serum immunoglobulins, thyroid function tests
- Serum HBsAg
- PCR for HCV RNA. (Quantitative PCR and HCV genotyping are now becoming available.)
- Serum alpha-1-antitrypsin, alpha-fetoprotein, caeruloplasmin if < 40 years)
- Serum auto-antibodies: antinuclear factor, smooth muscle antibody and mitochondrial antibody
- Serum anti-HIV (if not already done by transfusion service) - if considered appropriate
- Ultrasound examination of the liver

Other investigations may be ordered at the first visit to clarify non-hepatic conditions.

MANAGEMENT

Natural history of Hepatitis C Infection (Tong et al. 1995)

Hepatitis C was first identified in 1989 and the natural history has yet to be established. However, it is known that 50-70% of patients infected with the virus became chronic carriers and that the majority of carriers will show evidence of mild chronic hepatitis. It is estimated that approximately 0.2-0.4% of the UK population are chronic carriers. The infection is usually very indolent and only gradually progresses over a period of many years. However, older patients and those who are immunosuppressed may run a more rapid course. Patients who have been infected by blood transfusion will have received a large viral load and may be at risk of more severe liver disease. It is currently estimated that 20-50% of patients with chronic hepatitis may progress to cirrhosis over 10-20 years. About 25% of patients with cirrhosis will eventually develop liver failure and 10-20% develop primary hepatocellular carcinoma.

6.3 ***References***

1. Power, J.P., et al (1995) Lancet 345:1211-1213
2. Healey, C.J., et al (1995) Gut 36:148-150
3. Rice, P.S.. et al (1993) Lancet 342:1052-1053
4. Weiner, A.J., et al (1991) Virology 180:842-848
5. Simmonds, P., et al (1991) J. Virology 65:6266-6276

7. Recommendations for ongoing developments

7.1 It is suggested that in order to monitor progress, outcome and continuing cost implications a Monitoring Group should be set up. This might be called 'The Scottish HCV Monitoring Group'.

7.2 In addition to monitoring clinical progress this Group could oversee collaboration in research. This should involve the Scottish Blood Transfusion Service and the Scottish Centre for Infection and Environmental Health.

7.3 The remit of the Monitoring Group should be enlarged to encompass all HCV positive patients identified through blood transfusion and, in particular, those haemophiliacs and other recipients of HCV positive blood components and also blood donors found to be positive on screening.

7.4 Representatives of other groups with interest in HCV infection (eg in drug addiction and sexually transmitted disease clinics) and in public health medicine should be included in addition to hospital clinicians, general practitioners, virologist and pathologists.

7.5 Setting up of this Group, which could have advisory as well as co-ordinating functions should be regarded as a matter of urgency.

8. Conclusions

Chronic hepatitis C infection is a major world problem. Transmission through the administration of blood and blood components raises special issues which demand clear and coherent policies. Unfortunately, the astonishing rapidity of the expansion of knowledge and the still many unanswered questions make the formulation and maintenance of those policies especially difficult. (Koff R.S., Seeff L.B., 1995). Furthermore, currently available treatment is far from ideal. The cost benefits are not clear and the cost implications of the widespread introduction of interferon therapy for chronic hepatitis C are difficult to assess but certainly potentially enormous (Dusheiko G., Roberts J., 1995). The clinician faced with the advising and treatment of such patients can only do the best with the limited knowledge (when guidance may be out of date when it is published) and the restricted treatment available.

February 1996

Epidemiology - modes of transmission

The commonest route of transmission is by sharing needles or equipment during intravenous drug use. Transfusion of blood or fresh components (platelets, fresh frozen plasma or cryoprecipitate) prior to the introduction of routine screening on 1 September 1991, or of clotting factor concentrate prior to the use of virus inactivation procedures in 1984, also carried a risk of infection. Other parenteral routes include tattooing, and, theoretically, electrolysis, ear-piercing and acupuncture. Sexual transmission occurs, but the frequency is uncertain - most studies indicate infection rates of under 5% in sexual partners. Vertical transmission (mother to baby) appears to be rare. The risk of nosocomial infection, eg following a needlestick injury (involving HCV infected blood), is around 10%, ie intermediate between HIV and Hepatitis B. Transmission in other medical settings from patient to patient has recently been described (Allander T, et al, 1995).

Avoiding infecting others

1. Anti-HCV positive individuals should not donate blood, tissue or semen, and should not carry an organ donor card.

2. Toothbrushes and razors should not be shared, and cuts or skin lesions should be covered with waterproof dressings.

3. When seeking medical or dental care, patients should be advised to inform those responsible for their care of their anti-HCV status.

4. Existing sexual partners should be offered testing. At present there is insufficient evidence to recommend changes to current sexual practices with a steady partner, though the possibility of infection must be discussed. Patients should be advised to practise safe sex with new partners.

5. There is no evidence to support advising against pregnancy, though the very small potential for transmission should be discussed.

Further assessment and follow-up

All anti-HCV positive patients should be referred to a specialist with an interest in the condition for further assessment. This will usually involve a period of observation, and, in most cases, a liver biopsy. Patients considered to be at risk of progressive liver disease may be offered treatment with interferon.

APPENDIX - B

Transfusion- Transmitted Hepatitis C - Guidelines for Counselling Patients

These guidelines are intended for use in counselling patients found to have Hepatitis C as a result of a previous blood transfusion. Recipients of blood or blood components from donors now known to be carriers of the virus are being traced with a view to providing counselling, testing and specialist referral as appropriate.

Transfusion services in the UK began screening for antibodies to HCV on 1 September 1991. Patients transfused subsequent to that date have a negligible risk of having been infected by the transfusion. Not all of those transfused with potentially infectious blood prior to the commencement of testing will, however, be identified by the *lookback* procedure; the donors of the transfused materials may not have returned since September 1991. Thus, even in cases where the *lookback* has not implicated an individual patient, it may only be possible to provide full reassurance by offering to test the patient for antibodies to HCV.

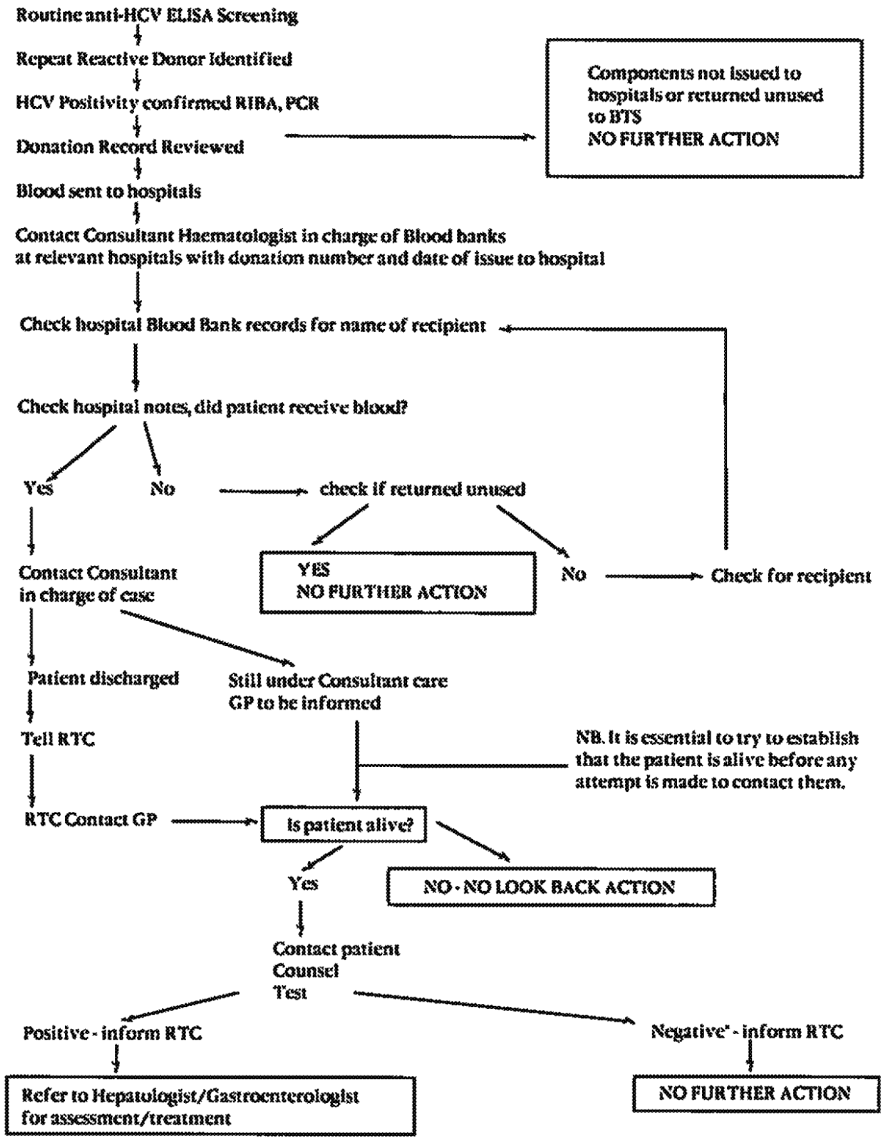
Patients confirmed to be anti-HCV positive should be counselled on the implications of the test result, and referred for a specialist opinion. It should be borne in mind that the infection may have been contracted as a result of risk behaviours other than the incriminated transfusion, and since this and the duration of infection, may have some bearing on the prognosis and on the outcome of treatment, the patient should be questioned about such risk behaviours.

Implications of a positive test - prognosis

Patients are described as anti-HCV positive when a screening test for the antibody is repeatedly positive and the result has been confirmed by a recombinant immunoblot assay (RIBA). Most such patients will also be positive for HCV RNA using the polymerase chain reaction (PCR). PCR positive patients commonly have raised transaminases (especially ALT), though this may be intermittent and unimpressive. It has been shown that virtually all of these patients have some abnormality, on liver biopsy and at least 20% will go on to cirrhosis with an attendant increased risk of hepatocellular carcinoma. PCR negative patients usually have normal liver function and appear to have a good prognosis.

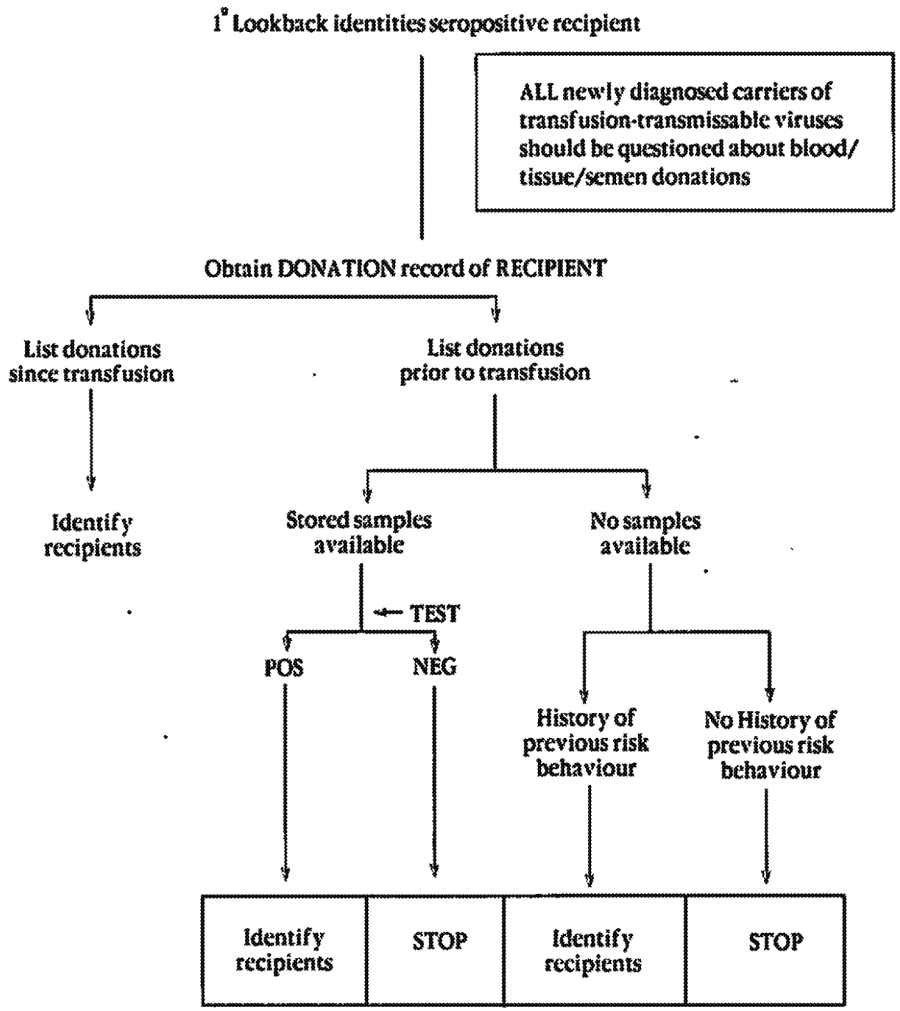
APPENDIX A (1)

Algorithm for Lookback for HCV



*If patient is immunocompromised, ELISA may give a false negative result and PCR may be required.

APPENDIX A (2)
"Secondary" Lookback Procedure



APPENDIX A (3)
"Tertiary" Lookback Procedure