FURTHER REPORT FOR THE PENROSE INQUIRY

ANTI HCV TESTING

Screening for hepatitis C virus (HCV) antibody was introduced in September 1991 through virology laboratories working within Public Health (largely). This was performed with a 'first generation' ELISA. This assay proved to be both insensitive and non-specific and a great deal of skill was required to ensure that tests were interpreted appropriately. The false positive rate was between 50 and 70% when low risk blood donors were screened particularly in the presence of hyperglobulinaemia. Most of us who were using the test at that time were aware of these difficulties; prior to the formal introduction there had been considerable experience gained with that test over the previous nine months, testing patients from both high risk groups and patients with liver diseases known not to be related to HCV so that we had a feel for the quality of the testing performed. Within 18 months or so these tests were replaced by second generation ELISAs. At this point because of the previous concerns about reliability it was agreed generally that a second RIBA test (recombinant immuno blot assay) should be performed before telling patients that they were positive for HCV. The principle of a second test needing to be performed before informing patients they are positive holds true today. Around 1993 and 1994 the majority of centres with a particular interest in HCV infection had introduced PCR techniques, often in house, to identify the presence of HCV RNA in blood and tissue. These were of variable quality and not available to all.

It is hard to be critical of these early tests. These were major breakthroughs in the management of HCV infection. What was important at this point was to ensure that the results were interpreted in the appropriate context. Our own practice for example and for some years thereafter, was to follow up patients with equivocal test results until third generation tests were introduced at which point almost all of the patients that we were following with equivocal tests (nearly 200 at one stage) were discharged from the service. It was important to note that of the patients who had equivocal positive tests very, very few carried a risk factor for HCV infection, emphasising the importance of placing test results in context.

In answer to the specific questions you ask, HCV testing was introduced formally in September 1991. The test was an ELISA. The tests were carried out usually by departments of virology through the public health service (now the HPA). The tests would have been available to all of those involved in the field of liver disease, liver transplantation and virology and also to general physicians. In most centres patients with positive results would have been managed by hepatologists or gastroenterologists with an interest in hepatology. The correct approach to using the first generation tests was circumspection and careful review.

HEPATITIS C VIRUS LOOK BACK

The HCV look back was a pragmatic approach to the recognition that for many years patients had been at risk of exposure to HCV infection with the transfusion of blood or blood products. A look back exercise in the field of HIV was carried out in the mid 1980s and on the basis of the success of that venture, it was proposed by transfusion services (probably in 1992) that an HCV look back should be commenced after the development of testing for hepatitis C virus antibody. There are a number of important points to make when discussing the success or the likely success of an HCV look back exercise:

- HIV and HCV are not comparable.

- When first introduced HCV antibody testing in 1991 was not reliable. The high rate of false positive results was a concern and in particular the knowledge that testing low risk groups was more likely to be associated with a false positive test than testing high risk groups for obvious reasons.

- The Transfusion Service was keen to implement a look back despite the concerns about the quality of the testing but a look back programme did not begin until April 1995 because that was the point at which the Government decided to fund the study. It was felt in 1995 that testing was now appropriate to make the approach more focussed and not to cause concern by identifying a large number of potential donors and recipients who were actually HCV negative although the tests were positive.

- Samples from blood donors were only stored for three years in the English Blood Transfusion Service although stored for much longer in the Scottish Transfusion Service.

- The English back log of samples from donors that were could have been tested totalled more than six million at that point.

- Matching an HCV infected donor sample with the correct recipient was more difficult than one might imagine. Hospital records were not maintained long term in 1991 through 1995. There was no effective computerised system matching recipients and donors. Bar code techniques hadn't been introduced at that point.

- The logistics of testing six million retrospective stored donor samples for HCV in England alone, while continuing to run a blood transfusion service were enormous and would have been very expensive.

- Perhaps the main issue in the early 1990s was that we weren't fully aware of the natural history of the disease. The number of patients who later proved to have benign disease and near normal liver function tests with chronic HCV infection was not appreciated at that point.

- The number of patients with chronic HCV infection who had injected drugs in the distant past had not been appreciated. Nor had it been recognised at that stage that many of the blood donors who came forward and proved to be HCV positive had a very short history of injecting drug use often many, many years before, that they themselves discounted as irrelevant.

- The difficulties for blood donation in the work setting had not been fully appreciated at that point. Specific questions about distant injecting drug use could not be addressed easily in that context for potential blood donors.

The points above really determined how the look back exercise was undertaken. Thus donors were tested prospectively. As a consequence donors who were HCV positive who didn't attend after 1991 have not been identified and obviously, neither have the corresponding recipients.

If after 1991 a donor was found to be positive for HCV the donor was informed by the transfusion service and a recommendation was made to the general practitioner that the patient should be followed up by a hepatologist or a gastroenterologist with an interest in hepatology; for almost all transfusion centres in the UK at that time there was a list of named hepatologists who could be contacted.

Once a donor had been found to be HCV positive there was an attempt to contact all possible recipients of that donor's blood or blood products at any stage in the preceding years, which in some cases represented a large number of recipients over many years. This was done by contacting the hospital where the transfusion had taken place. This was an enormous undertaking. In many cases the hospitals had inadequate records to match donor and recipient. In some cases the hospital records were no longer present. In some cases the hospitals had closed even when a possible recipient had been identified. Sometimes that

recipient might have moved home and there might not have been a clear record of the general practitioner.

Where a recipient was identified of a blood donor who was found to be HCV positive a letter was then sent to their general practitioner. There was a lot of discussion about who should be the point of contact for identifying positive recipients and it was felt that the general practitioner would be best placed to determine whether to take things further. It was recognised that HCV might also be a new concept to the GP and letters to the GPs were framed in such a way as to encourage referral and often provided a local contact for further information. The important point to make here is that patients are usually (but not always) transfused for serious underlying disease. It was felt that the general practitioner would be best placed to determine whether any follow up of the likely infection with HCV should be undertaken or not. There was a view that pursuing the issue of HCV infection might not be helpful in those who were elderly or infirm or had life shortening disease. This is in fact supported by the data that show that the patients who were transfused with blood that was infected with HCV have a similar life expectancy to those who were transfused with blood that was not infected with HCV albeit that the causes of death do differ between the two groups and that liver related mortality is greater in those who were transfused with HCV infected blood.

It was then the responsibility of the general practitioner to make the referral to a hepatologist or a gastroenterologist with an interest in hepatology.

The question arises of whether this was an appropriate screening strategy to identify patients who had been transfused with HCV infected blood. By and large the majority of countries around the world have followed a similar programme and I am aware of only one country (France) that has made a more determined search to identifying all HCV positive donors retrospectively. This was an option that was open to the Scottish Transfusion Service because they kept donor samples long term in contrast to the rest of the UK, but a national policy was implemented.

Having recognised that there was perhaps only one realistic viable option for identifying positive donors there have been campaigns to inform people who have been transfused that they might have been at risk of HCV infection and to encourage such patients to come forward. Similar programmes have been targeted at injecting drug users. In addition over many years there have been numerous opportunities to discuss the risk factors for HCV infection with groups of general practitioners and it is unusual for example, now to see a patient in clinic with abnormal liver tests in whom the GP has not considered HCV infection. As a consequence of introduction of screening policy targeting high risk groups in 1995 perhaps a third of the patients who were seen in the new patient clinics at that stage in

Cambridge certainly, had been identified by the Transfusion Service as either a positive donor or a recipient of HCV infected blood.

My involvement in the look back exercise was as Chairman of the Hepatitis C virus steering group. This was a body set up to ensure that the look back strategy was managed efficiently and effectively and in line with ethical standards. It was also to encourage the use of the database that was developed over time for research purposes both by those involved directly with the steering group but particularly to be available to the UK as a whole should they have bright ideas about how to use the database. Defining the natural history of HCV infection from a known date of infection was seen as invaluable and there are only three similar cohorts elsewhere in the world.

In terms of understanding the disease the exercise has been successful. As a strategy to find all the patients with transfusion related HCV infection retrospectively it has been much less successful. For those individuals found to be positive it has had real benefit. It has allowed those individuals to be processed appropriately and in many circumstances treated effectively. It allowed a large number of them to be compensated financially for developing disease as a consequence of the transfusion.

However the logistics of the whole exercise probably explain that only a tiny minority of those who were exposed to hepatitis C have been identified during the programme. Soldan et al. in 2002 estimated that just 5% of the total number of HCV infections over the 11 year period to September 1991 have been identified, which represented a higher proportion (13%) of those who were alive in 1995 who had received infected blood.

In retrospect and with hindsight one could argue that it would have been more effective to screen all plasma samples that were available from donors (a backlog of three years for the English and longer for the Scottish). However testing this large number of samples could have crippled the transfusion service from doing its normal every day job.

The delay in screening tests being introduced in 1991 and the introduction of a look back programme in 1995 can be explained by a number of factors. There had to be a willingness to fund such a study which wasn't expressed until 1995 based on pragmatic reasons such as the quality of the test, the problems of identifying the wrong group of patients, missing those who had got HCV and perhaps in retrospect the look book could have started a few months earlier but I don't think would have been effective in 1991 and could have caused a lot of problems.

COMMUNICATION OF RESULTS AND IMPLICATIONS OF DIAGNOSIS

In the early 1990s patients found to be positive for HCV were warned that we didn't understand fully the implications of the test and as a consequence patients underwent regular testing for HCV and in our own centre all the patients were offered the opportunity of a liver biopsy. Many patients underwent liver biopsy that we would not now offer routinely. Where there was evidence of liver injury patients were offered close follow up and regular liver biopsy perhaps as often as every two or three years where there was concern. At this point of course there was no available therapy for such patients. The patients that we were seeing in clinic were aware that we were learning from our clinical practice at that point.

The introduction of testing for HCV RNA was a major step forward allowing us to separate patients into those who had probably cleared infection from those with ongoing infection. There was doubt about the quality of that elimination and its duration based on concerns about the tests themselves and our lack of knowledge of the natural history.

The other major factor that changed the way we managed patients was the introduction of effective anti viral therapy, but that came much later.

In 1974 and in 1985 non-A, non-B hepatitis was recognised only in the context of abnormal liver tests following a transfusion of blood or blood products. I am not sure that this happened but patients should have been warned that they were likely to have had a virus infection that could not be explained readily at that time and in whom the natural history was uncertain but that the natural history could include progression to more serious liver disease. Management at that point was most often based on liver function tests and it is not unusual to find that such patients had been discharged when liver function tests settled on the assumption that the disease itself had resolved. Other centres would have performed liver biopsies to assess status and in some of those 'treatments' were offered. A small number of donors were aware that their blood had transmitted infection and were managed in much the same way.

Many of the patients who were affected by post transfusion hepatitis had been transfused for serious underlying disease and the non-A, non-B hepatitis was seen as a less important component of that illness.

In 1991 patients should have been informed that they were likely to have a virus infection of the liver but that testing was unreliable. At that point we did not understand the transmission routes of HCV as well as we do now. For example sexual transmission is rare and vertical transmission occurs in about 6% of pregnancies. In 1991 we did not know if sexual transmission occurred or not and we did not know what the risk of vertical transmission was. In fact when I got up in a meeting to explain that we had seen an example of vertical

transmission I was told that it was unlikely by a number of eminent virologists. So that the advice that I was giving in 1991 and I suspect many others in a similar position was very cautious with an emphasis on the fact that the physicians were learning as they went along. It was not possible to transpose the information we gained from non-A, non-B hepatitis epidemiology studies to HCV infection because introduction of testing had identified a far greater spread and number of patients than we had imagined prior to 1991. The notion that a patient who was completely healthy might have acquired HCV infection from transfusion or drug addiction three decades or more previously was quite a surprise I think to almost all of us in the field. From 1995 onwards issues such as the natural history were still being resolved but studies of vertical transmission and sexual transmission were allowing us to fine tune the information given to patients. Natural history studies from 1997 and 1998 onwards guided the information that we provide for patients currently except in those unusual circumstances such as transplantation or the immune suppressed where the numbers were then very small.

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