Penrose Inquiry

The introduction of screening for Hepatitis C

Statement (5) by Professor Juhani Leikola

1. A specific test for hepatitis C virus (HCV) was developed by an application of recombinant gene technology without isolation of the virus itself. It was published in 1989 (Choo et al., Science 244:359-361, 1989).

2. I was approached by Ortho in spring 1989 and was asked to arrange for a study on this new test together with Sweden and Denmark. I contacted my colleagues in Gothenburg and Copenhagen. We decided to divide the study so that Denmark would investigate stored donor samples, Sweden patient specimens and we in Finland the material we had from Dr. Ebeling's research. The test kits were received in the beginning of June 1989.

3. The prospective study by Dr. Ebeling on transfusion-transmitted NANBH was done in 1987-1989 and published in final form in 1991 (Dissertation, Helsinki 1991; F. Ebeling, R. Naukkarinen, R. Hanhela, J. Jalonen, L. Kaukinen, M. Salmenperä, M. Suistomaa and J. Leikola: Post-transfusion hepatitis after open-heart surgery in Finland – A prospective study. Transfusion Medicine 1; 103-108, 1991). Over 15,000 samples were tested.

4. An independent clinical evaluation team determined that eleven patients had NANBH. The majority was symptomless and no case was severe. Six out of these eleven patients (55%) were positive with the new test. Five of these six patients could be linked with an anti-HCV positive donor.

5. I wrote a memorandum, dated 10 October 1989 (presumably intended for internal discussions and for the National Board of Health). In this paper I concluded (unofficially translated): *Since a specific test now exists that may reduce the blood inventory by as little as less than one per cent, a general screening test has to be introduced in our country to safeguard transfusion safety.* However, I pointed out that one of the greatest weaknesses was that there was no confirmatory test. Nevertheless, the reproducibility was good and the screening should not be delayed because of lack of confirmatory test.

6. I noted that technically the screening could commence during the first quarter of 1990 if the manufacturer could provide the tests. I then presented some financial calculations on the testing, and mentioned that *one has to add the value of discarded blood (0.7 %), information to the donors, delay in testing the blood units, etc.* The end conclusion of my memorandum reads: *Despite the costs and other difficulties anti-HCV screening has to be started at the FRC BTS as soon as it is technically possible.*

7. We received information from Ortho either in late November or early December that FDA had given export permit to the new test. According to my diary, we had a meeting on 11 December 1989 with the Director General and the medical officer responsible for blood transfusion-related matters at the National Board of Health. After having read my memorandum and seen the results of Dr. Ebeling's study the health authorities endorsed our policy aims and agreed that the costs incurred could be added to the charges of products.

8. Routine testing commenced in the beginning of February 1990 and was extended to all blood donations in Finland as of first of April.

9. We felt that we had to explain to our clinical colleagues why this testing was started, what were the first results and was it worth the increased charges to the hospitals. In the latter part of 1990 we wrote an article in Suomen Lääkärilehti (*Journal of Finnish Medical Association*; 45:3103-3105, 1990). I wrote an editorial in the same issue.

10. I wrote in my book (Pieni vaiva – hyvä mieli. Suomen Punaisen Ristin Veripalvelun ja sen edeltäjien historiikki. *Written in Finnish, unofficially translated: Little effort – Good feeling. History of FRC BTS and its predecessors. Helsinki, pp. 1-336, 2004)* that our philosophy was, as expressed by my deputy, Professor Myllylä, *if a new test seems to be inevitable, it pays off to start it as soon as possible, and then with flags waving.*

11. We published the preliminary results of Dr. Ebeling in Lancet (April 21 1990). Likewise, our study on haemophilia patients, NANBH and HCV was published in the same year (Annals of Medicine 22:393-396, 1990). Thus, the Finnish experiences should have been known to the UK colleagues in 1990. I have discussed the question of confirmatory tests for anti-HCV in my review article (J. Leikola: Viral risks of blood transfusion. Reviews in Microbiology, 4:32-39, 1993).

12. Comments on specific questions:

    1. On the basis of what is known now, was it reasonable for the UK to wait until September 1991 before screening donors for hepatitis C?

       It is interesting to read the Preliminary Report and the chronology of UK studies into surrogate testing for NANBH from autumn 1989 until September 1991. It appears that Ortho with the new anti-HCV test had approached the UK at about the same time as it contacted several other countries. The results of the preliminary trials in various countries were presented and discussed in Rome in September 1989. Thereafter, pondering over the question of whether or not to introduce anti-HCV screening went on in the UK for more than a year.

       It seems to me that there were two camps in these discussions: The "academic scientists" and the "practical transfusionists". From the scientific point of view, there were many reservations as to routine screening with the new test: lack of confirmatory test (the most serious one), lack of understanding the virus itself, deficient specificity in identifying the putative virus, assumption that the situation in the UK may differ from the US where most of the information was gathered.

       On the other hand, some people involved in these discussions understood better the issues in public health policies. They had seen and felt the HIV tragedy and learnt that pure scientific reasoning may not be enough when dealing with transfusion safety. The note of Dr. Perry (SNF.001.1711), dated 30 April 1990, illustrates the dilemma: "Despite ill defined science of test, high false positive results, lack of correlation of test positivity and confirmatory test there is good evi-

dence in the US that testing prevents 50% of P. T. H. NANB - compelling reason to introduce test."

After noting correctly that testing had commenced in France, Belgium, Luxembourg, Finland and Australia, Dr. Perry concludes: "H. G. [Harold Gunson] and R. J. P. [R. J. Perry] felt that there was sufficient data to justify testing now (based on US data suggesting 50% reduction in PTH) but the majority [of ACVSB] and D. O. H. preferred more cautious approach."

An important argument was that FDA had not approved the test to be used in the US even if it had given the export permit. This obstacle was removed on 2nd May when FDA licensed the Ortho anti-HCV test. Screening started in the US immediately thereafter. At about the same time the first confirmatory test (RIBA-1) became available. In Dr. Skidmore's words, published in June 1990 (Preliminary Report, para 9.208): "While supplies of the test were limited, she was of the view that the RIBA test might be just the test needed to confirm a positive Ortho anti-HCV ELISA result." We noted in our paper in Lancet (April 21, 1990) "The RIBA may offer help in differentiating infective from non-infective blood donors."

It seems to me that on the basis of this development and regarding the practice in other countries, the UK ought to have decided earlier to start screening of blood donors. Admittedly, it would have interfered with the planned and on-going studies on the incidence of transfusion-transmitted NANBH. Eventually, the study by Contreras et al. was too small for meaningful conclusions as to the policy of general donor screening.

2. On the basis of what is known now, ought screening for hepatitis C to have been introduced earlier in the UK?

It seems to me that the delay in introduction of anti-HCV screening was due to three factors: Lack of a proper prospective study on the incidence of transfusion-transmitted NANBH; pressure from the scientifically oriented members of ACVSB and ACTTD to get more precise information on the usefulness of the test; and reluctance of some blood centres to introduce a new screening of questionable value involving discarding appreciable amount of blood products, counselling of donors etc.

Those decision-makers preferring a cautious view were waiting for better tests to come to the market since information was flowing in that such tests would be available in due course. However, it should have been clear at the time that starting routine with a test does not preclude switching it into a better one once this becomes possible.

On the basis of what we know now, I believe that a decision to introduce anti-HCV screening could have been made in June or July 1990. From reading the Preliminary Report I got the impression that there

was no clear mechanism for making a definitive decision concerning the whole UK. The time needed for practical arrangements in the blood centres could have been a maximum of four to five months, so the screening could have been in place in late 1990, possibly in October-November 1990.

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