IN CONFIDENCE

NOTE OF MEETING AT NBTS HQ, MANCHESTER, MONDAY DECEMBER 18th 1989, TO DISCUSS PROVISIONAL RESULTS OBTAINED FROM EVALUATION OF ORTHO HCV KIT AT N. E. THAMES, BIRMINGHAM AND SHEFFIELD BLOOD TRANSFUSION CENTRES

In attendance:

Dr H Gunson, National Director, BTS

Dr R Mitchell, West of Scotland BTS

Mr J Francis, Deputy, Scottish BTS

Dr V James, Director, Sheffield BTS

Mr P Savage, Mr A Follett, Ortho Diagnostic Systems (UK) Ltd.

Mr R Davis, Johnson & Johnson (US Parent of Ortho)

Mr M Fuller, MHS Procurement Directorate

Apologies: Mr P Ballantyne, Mr J Canavan

The meeting proceeded according to the agreed agenda (Ref letter 8 Dec. to Dr H H Gunson), and covered all 12 items. The following notes the results and views obtained from the meeting, and suggests requirements for future progress. Notes are numbered as per agenda item.

1. Sheffield BTS:

Tested 4480 samples in 5 days of operation (including a weekend) - 14 samples positive (0.3%), retested gave 0.18% positive, without equivocation.

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Birmingham BTS:

3300 tests done (to date) - 8 repeat positive = 0.24%

Brentwood BTS:

To date 0.85% of tests performed positive.

Sheffield BTS also looked at samples "expected" to be positive, and achieved higher (presumbly undefined, figures in report) positively rates for HIV Ab positive homosexual and haemophiliac groups, as well as patients with various liver pathologies.

The experienced higher positivity rate from Brentwood was as expected, they have the highest population incidence of HIV positives also.

2. These figures obtained on fresh, unselected samples reflect those found previously by Bristol, Manchester and North London transfusion centres when testing frozen serum samples. Results:

Bristol: 3015 tests, 17 positive (0.56%)

Manchester: 3690 tests, 22 positive (0.59%)

N. London: 3036 tests, 26 positive (0.86%)

If these figures reflect the "healthy" population, then the incidence of positivity for this antibody may be 1 in 200. What this actually means in the population connot be considered with confidence at this stage.

3. "Surrogate testing" does not provide any increased sensitivity if used in conjunction with the HCV test. The most commonly cited alternative is measurement of serum alanine aminotransferase (ALT), a liver enzyme raised in liver disorders (as well as liver activation due to, eg, alcohol abuse). The previous stored samples (referred to in (2)) gave raised (> 100 IU/ml) ALT

levels as:- Bristol 4.5%, Manchester 1.99%, N. London 3.06%. If antibodies to Hepatitis B Core Antigen (HBc Ag) were sought in these samples as well, incidence of positivity was seen as:-

Bristol 0.87%, Manchester 2.04% and N. London 3.23%.

This testing schedule targets individuals who may be a higher risk of liver disorder, within which a smaller group may be those having antibody to HCV. The identification of various, potential liver disease, groups was out-with the remit of this study, and will require a vast amount of further data, with clinical information and follow-up, long term, to have any meaning.

4. Other, larger, studies published to date have shown a regional division in incidence of positivity, with Socio - economic groupings appearing to be a factor (ie N-South variation). Again, with a small study such as this, data will be inevitably biased.

Figures from: France gave range of 0.52 - 1.78% positive
Germany give range of 0.24 - 0.74% positive
Italy - Milan 1.4%, Brindisi 5% positive.

5. No publication of the survey result is advocated until a decision on future policy has been made and published.

6. Screening implications are manifold, and difficult to resolve at this stage (ie no comfirmatory testing, no counselling policy, no treatment available and no clinical evidence of predictive outcome). Some large assumptions have to be made, viz:

a. 0.5% of blood product donations may by positive, and possibly

transmitting an infective agent.

b. this agent has the potential to trigger liver disease in a previously well person at a rate of one per cent per year for ten years (ie 1 in 10 may get liver disease within 10 years)

c. Up to 50% of patients receiving transfusions (non-therapeutic maintainence) will have succumbed to the original condition necessitating transfusion, within 2 years.

d. Blood usage is around 2.5 million units/year, involving 1.25 m donors, each donating twice yearly. Therefore, 6250 donors, nationally, may be positive for this antibody. These will require confirmation, counselling (by appropriately briefed, clinical gasteroenterlogists) and monitored at appropriate levels, within the first year of instigation of a screening programme, and subsequently on a 0.5% diminshing scale, if and when these donors are replaced in the pool. Compare this with the current cost of monitoring a group of similar size who have predictable clinical course and outcome, positive conformatory testing and clinical provision.

The 12500 positive donations will require replacement. Recipients (presumably having been recipients for the previous 50 years of transfusion history), at 1% positive per year for 10 years, assumming one single donation per patient NB, with half-life of 2 years, will possibly give 62 patients after 2 years showing clinical signs of liver disease. (Worst case, 6250 patients positive, per year, surviving 2 years post-transfusion)

Note - all HIV positive heamophiliacs treated with blood products prior to 1984 have been shown to be positive for this marker. Blood products heat treated (dry heat, 80^{o}, 3 days) from pools, tested positive prior to treatment, are negative subsequently. This is obviously an Ab denaturation, as there is no "Viral Antigen" test. — SBTS data only.

A question which will need addressing is "How to screen recripients of therapeutic blood products, multiply transfused over many years?" (A panel of these patients should be tested for HCV Antibody positivity.)

At this stage, the group were joined by representatives from Ortho(UK) and the parent company - Johnson and Johnson.

7. Other countries who have organised blood transfusion services have elected to use the Ortho (currently only available) HCV kit for screening of donations, currently: France, Japan, Canada, as the best predictor of the presence of Non-A, Non-B hepatitis virus (HCV) in donors.

8. "Conformatory" test protocol is currently under active development in USA. A testing format was expected Mid December ('89), with field evaluation commencing January 1990. The test is called Recombinant Immunoblot Assay (RIBA), and does <u>not</u> contain any antigenic epitopes that are not present in the original screen, linked to the putative HCV genome.

The antigenic determinants comprised of: The original recombant (HCV) antigen, Yeast antigen (the "cloning" of antigen is done in yeasts), Superoxide desmutase antigen, and two immunogloblins - to remove any anti-species activity to the immunoglobulins utilised in the original ELISA.

The validation of further antigenic epitopes of HCV is progressing, without any projected timescales as yet.

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Transfusion centres generally do not have facilities for immunoblotting of this type, and therefore the costs and consequences of requiring this service will fall to the PHLS. Philip Mortimer, John Parry and Eddie Follett (Glasgow) have apparently been approached in this regard.

The cost of this test is undecided at present. I would be suprised to see it below £25.00 per sample.

9. Dr James confirmed that there were no technical or logistical difficulties involved in performing the test. She explained that it could be readily fitted into the work schedule employed at Sheffield, and this included weekend working. "Emergency" testing per se did not occur, due to planning provisions. There was confirmation from Ortho representatives of John Francis' experience that new equipment was not necessary and that the test may be performed using any common ELISA system. To this end, Ortho had linked with Sanguin - software Manufacturers - to provide an IBM compatible programme, which would be available in the new year.

The Scotish BTS are self-sufficient on equipment, as should be most regional centres. However, with a possible additional workload, extra capacity should be provided for, especially as back-up, should the front line system malfunction.

Note: the projected Abbott system may fit into some centres better (bead-assay) than piggy-backing a plate ELISA.

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10. Ortho are keen to negotiate an all-in package nationally - which could include instrumentation where required (Dr Gunson has agreed to coordinate enquiries about further equipment provisioning as applicable). A package must involve PHLS in "confirmatory" testing provision- the projected workload of possibly 10K tests/year will certainly have staffing consequences for PHLS. In Regional Centres the staff requirement may be greater than any (?) slack available to accommodate, although no mention of how centres involved in the trial coped with the extra work was made. The current cost of testing is a sticking point, with Ortho declaring a pan-European strategy of supply to all at a Cost-price (dependant on $ exchange rate) of between £2.00 and £2.40. (The French contract at 4 million test per year is claimed to be at a list price of Fr22 per test). This, therefore, gives the revenue cost of between £6M and £7.2M, plus an expected £.25M for conformatory testing.

Equipment would be almost certainly "thrown-in", if such an expression is pertinent to these prices! (cf ~ £2M for current HIV and HBS Ag Antibody testing, annually, - these for conditions which do have lethal outcomes, in real time).

There were no problems anticipated with supply of "training" kits. Equipment would require early ordering, as any cost would be accrued to the fiscal year (Ortho's = Dec/Dec) in which the outlay was required, and would be adsorbed by "adjustment" to the kit price.

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11. Ortho are unable to carry stock of this test other than that which is required to service orders and provide an emergency back up of replacement supply for orders placed. They are obviously incrementing their production facilities stepwise with each (very large) order that they receive. The current lifespan of the kit is 5 months from manufacture, and this will be expected to be 6-9 months in the near future, when stability-trial data are validated to enable the shelf-life to be extended. Ortho are expecting to manufacture for any particular order in bimonthly slots, which will mean shelf-life of 3 months on delivery currently, probable maximum of 6 months in future.

A 90 day lead-time is required by Ortho for the first delivery, therefore any decision made early in the new year (Feb/March) will not be provisioned until June. Delivery will invaribly be constituted from more than one batch.

12. In the absence of Peter Ballantyne, this point was not explored in depth. However, if such issues as National contracting are required, involvement of the Scottish BTS would be considered essential. A meeting of any group to discuss such will therefore require: Ortho, PHLS (John Smith/D. McCabe?), NBTS - Roger Moore, SBTS - John Francis and NHS PD - including Peter Ballantyne, to attend.

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The meeting conveyed the concern of the BTS that a decision should be made as soon as possible, with the Advisory Committee for Virological Safety for Blood meeting on 17 January. Obviously in the forefront of minds are liability implications. However, at the current revenue expectations (see 10 above), and without knowledge of Chiron's licencing fee, the impending arrival of the Abbott format, (and possibly Fujeribio?), a monopoly - based supply decision would be precipitous at this stage. I feel that J&J are attempting to recover R&D and licencing costs, as well as making monoply (supernormal) profits out of this situation.

GRO-C

MARK FULLER

STD PG1C

December 1989

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