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Post-transfusion hepatitis in North London in 1981; a review, including a case of hepatitis A

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At the hepatitis workshop held in Scotland last year we presented a review of post-transfusion hepatitis (PTH) in North London during the previous ten years[1]. The present report provides details of our 1981 PTH enquiries.

Two of the 16 PTH reports received in 1981 were thought to be of non-viral origin and we have excluded them. This still left us with 14, twice as many as 1980. The increase was probably due to an improvement in hospital reporting of PTH which is still far from perfect. We were reminded of this when enquiring into the fate of a patient transfused with blood from a donor who developed jaundice 18 days after donating. Though the recipient of the donation became jaundiced, the hospital failed to report the case. In the end we notified them, not they us.

A breakdown of the 14 PTH cases is shown on Slide 1. Whenever possible serum samples were obtained from the recipient and donors involved. RIA tests were done for all the appropriate hepatitis A and B markers and serum transaminase estimations were also carried out.

Post-transfusion hepatitis B (summarised in SLIDE 2)

Case No. 1 All 8 donors involved were negative for all hepatitis B markers, therefore this was not a case of post-transfusion hepatitis. Infection might have occurred at operation or as a result of hospital treatment or it might have been co-incidental.

Case No. 2 The incubation period was 6 months which is longer than usual. 71 donors from NLBTC were involved; 57 have been tested so far and all are negative for all HBV markers. The patient was also transfused with blood in Spain 7 months before the onset of his hepatitis B. The long incubation period could have been due to him receiving an anti-HBs positive donation from a Spanish or British donor who we did not test. We concluded that the patient was probably infected in Spain where hepatitis B is much more common, but we could not prove this.

Case No. 3 One of the 2 donors involved had been infected with HBV in the past. He had anti-HBc and a low level of anti-HBs (0.01 IU/ml). These markers were stable and anti-HBc IgM antibody was not present. The donor could have been suffering from an inapparent infection at the time he donated or he could be a long-term HBV carrier with anti-HBc and a low level of anti-HBs, but no detectable HBsAg, of the type described by Dr. Dike at last year's conference.[4] We know of a few other similar cases. When a donor like this is found associated with PTHB he should be removed from the panel.

Case No. 4 7 donors were involved; 6 were negative for all markers but the other donor was positive for anti-HBc only. He had suffered from acute hepatitis B in 1976 when he had donated during the incubation period, and we had found his donation to be HBsAg positive. The sub-type of his antigen was ad which was the same as we found for the recipient of his later donation. Our records are not at the moment organised to alert us at the time of donation to a donor who has previously been found to be positive. He did not mention it himself, though he had been told not to donate again. Presumably computerized records could eventually guard against this happening.

Cases No. 3 and 4 are examples of HBsAg negative donors who probably transmitted hepatitis B. Similar cases have been reported by other We recognise three types of potentially infectious HBsAg negative, anti-HBc positive donors (Slide 3). The first type has just recovered from an acute infection, HBsAg is no longer detectable and anti-HBs has yet to appear; anti-HBc, some of which may be IgM, is the only evidence of the recent HB infection. In the second type anti-HBc is again the only marker of a previous HBV infection, but as with our Case No. 4 this state of affairs is not temporary and may go on for years. The third type of donor has anti-HBc and low titre anti-HBs. The best evidence for the existence of this type of infectious donor could come from the Centres which keep an aliquot

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of every donation tested.

Screening for anti-HBc in the UK would undoubtedly prevent a dozen or two cases of PTHB each year. If all anti-HBc positive donors were removed from the panel we would lose approximately 2% of our donors. 5 We could reduce this by testing positives for anti-HBs and retaining donors who had high or moderate titres of this antibody. At the present time we doubt whether total anti-HBc screening would be cost-effective.

Case No. 5 This patient was a young haemophiliac boy who had received various blood products. The timing of his infection suggests NHS Factor VIII as the source. He was tested for HBsAg because his transaminases were raised. This was due to non-A, non-B hepatitis but he did جلل turn out to be incubating hepatitis B. When first tested he had 0.5 ng/ml HBsAg; this rose to 20 ng/ml over the next few weeks and his transaminases became normal. Then, quite suddenly he lost his HBsAg and developed good levels of anti-HBs and also anti-HBc. This aborted infection was a demonstration of the most satisfactory way of dealing with hepatitis B virus! We have followed similar aborted acute infections in two donors found to be HBsAg positive on routine screening.

Post-transfusion non-A, non-B hepatitis

Eight cases which fell into this category were reported to the Centre. Case No. 13 was of particular

slide 4a.

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interest (Slide 4b). Two donors were involved and one had slightly raised transaminases. His next donation 6 months later was given to a patient who developed an icteric hepatitis after 4 months. ~~3 other donors were involved in this case, but all had normal enzymes.~~ The donor who was associated with these cases had chronically elevated SGOT and SGPT and said that he had been feeling slightly unwell for some months. We think there is little doubt that he caused the two cases of non-A, non-B hepatitis.

Several authors[6] have reported an association between donors having anti-HBc only and an increased likelihood of transmitting non-A, non-B hepatitis. It is not yet clear whether this reflects a specific association or is due to the people who get hepatitis B being more likely than other people to get non-A, non-B hepatitis. Our donor who we think caused two cases of non-A, non-B hepatitis was anti-HBc and anti-HBs positive.

This incident led us to formulate a provisional policy for our Centre when dealing with cases of presumed post-transfusion non-A, non-B hepatitis (Slide 5). The last recommendation that any donor involved in more than one episode should be removed from the panel will remind old transfusion hands of how they dealt with hepatitis B carriers before the introduction of HBsAg screening. We do not expect the measures outlined to have much impact on post-transfusion hepatitis but they are a beginning.

Post-transfusion hepatitis A

PTH due to hepatitis A virus is rare because of the natural history of the virus but it has been reported occasionally[7,8]. One of our 14 PTH cases in 1981 provides a further example[2]. The recipient became jaundiced 3 weeks after receiving 4 units of blood. When investigated later she was negative for all hepatitis B markers, but positive for anti-HAV IgM. One of the 4 donors became jaundiced 18 days after giving blood. She was found to be negative for all hepatitis B markers, but positive for anti-HAV IgM. The other three donors involved were negative for all HBV and HAV markers. If one of them had been immune to hepatitis A there might have been nothing to report, since the infectious donation might have been neutralized!

Conclusion

Our enquiries into PTH during 1981 illustrate the diversity and complexity of this work. The small number of PTHB cases which we still see are no longer due to straightforward HBsAg carriers as in the past. Instead we find cases caused by donors in the early HBsAg negative stage of incubating the disease or by carriers who are HBsAg negative, but nevertheless carry enough virus in their blood to transmit hepatitis B with the help of the Transfusion Service.

We are trying to encourage the hospitals we supply to report <u>all</u> PTH in the hope that we can get more information about non-A, non-B as a cause of PTH in the UK.

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We do what we can in the way of testing the donors involved, but we cannot make much more progress without a specific test for non-A, non-B virus.

The case of PTHA we found ~~does little more than~~ shows that it can happen, and that we must always exclude hepatitis A before designating non-B PTH as non-A, non-B.

It may be of interest to conclude with an American analysis prepared by Paul Holland (see slide 6).

[redacted] in Press:- [redacted]

References

1. Barbara, J.A.J. and Briggs, M. Hepatitis of the non-A, non-B type following blood transfusion in the North London region. Med. Lab. Sci. (1981), 38, 423-426.

2. Barbara, J.A.J., Howell, D.R., Briggs, M. and Parry, J.V. Post-transfusion hepatitis A. Lancet (1982), i, 738

3. Katchaki, J.N., Siem, T.H. and Brouwer, R. Chronic 'low-level' hepatitis B virus carrier with probable infectivity. Lancet (1982), i, 853.

4. Dike, A.E. Post-transfusion hepatitis B transmitted by HBsAg negative blood containing anti-HBc. Med. Lab. Sci. (1981), 38, 415-417.

5. Tedder, R.S., Cameron, C.H., Wilson-Croome, R., Howell, D.R., Colgrove, A. and Barbara, J.A.J. Contrasting patterns and frequency of antibodies to the surface, core and e antigens of hepatitis B virus in blood donors and in homosexual patients. J. Med. Virol. (1980), 6, 323-332.

6. Stevens, C.E. and the T.T.V. Study Group, New York Blood Center. Antibody to hepatitis B core antigen in donor blood and the risk of non-A, non-B hepatitis in recipients. Transfusion (1981), 21, 607.

7. Tegtmeier, G.E. and Bayer, W.L. Those 'other agents' in the differential diagnosis of post-transfusion hepatitis. Hepatitis workshop (American Association of Blood Banks, Chicago, November 1981) 67-98.

8. Seeberg, S., Brandberg, Å., Hermodsson, S., Larsson, P. and Lundgren, S. Hospital outbreak of hepatitis A secondary to blood exchange in a baby. Lancet (1981), i, 1155-56.

9. Holland, P.V. Available methods to further reduce post-transfusion hepatitis. Chapter 47, Proceedings of the third international symposium on viral hepatitis. New York. March/April 1981. Eds. Szmuness, W., Alter, H and Maynard, J.E. Franklin Institute Press. pp 563-571.

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Slide 1

14 reports of post-transfusion hepatitis in 1981

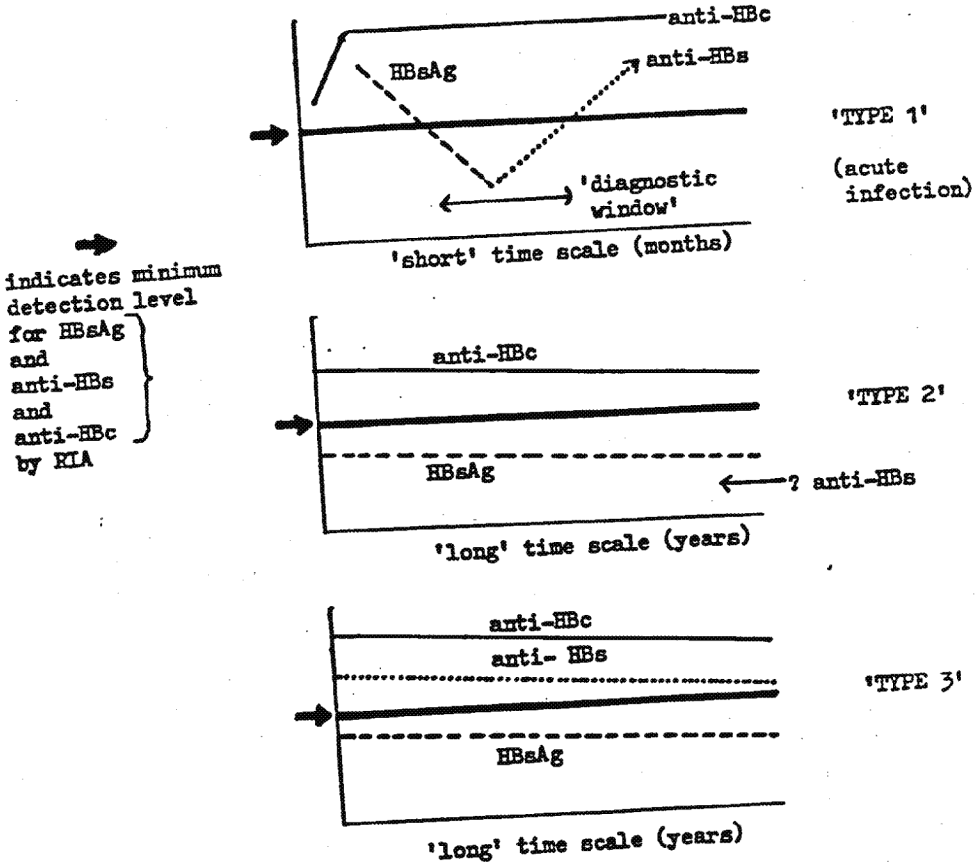
Hepatitis	number occurring	comments
A	1	
B	5	Only 2 due to NLBTC blood, and the suspected donors were not long-term HBsAg carriers
non-A, non-B	8	5 out of 35 donors followed up had elevated LFTs

Slide 2

Summary of the 5 post-transfusion hepatitis B cases in 1981

case	donations involved	number of donors followed	comments
1	8	8	All 8 donors HBV neg.
2	71	57	57 donors HBV neg. Also transfused in Spain
3	2	2	1 donor, anti-HBc pos., anti-HBc IgM neg., anti-HBs, 0.01 i.u./ml.
4	8	7	1 donor, anti-HBc pos., anti-HBc IgM neg., anti-HBs neg.
5	NHS factor VIII (4 lots) Hemofil 54 units of cryoprecipitate	No follow-up	Abortive acute HBV infection in recipient (not jaundiced or ill)

Slide 3



3 situations where anti-HBc screening is advantageous

Slide 4

Non-A, non-B post-transfusion hepatitis in 1981

case	jaundice or symptoms	incubation period (months)	no. of donors involved	no. of donors followed	comments on follow-up (Upper limit normal, GOT & GPT = 30 i.u./l.)
6	Jaundice	1 to 2	>200	0	no follow-up
7	'hepatitis'	1	2	2	both donors had normal LFTs
8	Jaundice	1	5	5	all 5 donors had normal LFTs
9	Jaundice	2	6	5	all 5 donors had normal LFTs
10	Malaise; nausea	to↑ LFTs, 1 month	10	7	1 donor, GOT 64
11	Jaundice	1½	6	6	1 donor, GPT 46
12	Jaundice (high alcohol intake)	1 to 3	8	8	1 donor who admitted high alcohol intake had GOT 45, GPT 47 and further sample showed raised LFTs 7 months after transfusion. 1 donor, GOT 24, GPT 45, but further sample showed normal LFTs 7 months after transfusion
13	Jaundice	1½	2	2	1 donor found with GOT 35, GPT 41 thought to be cause of PTH; also involved in a further case;

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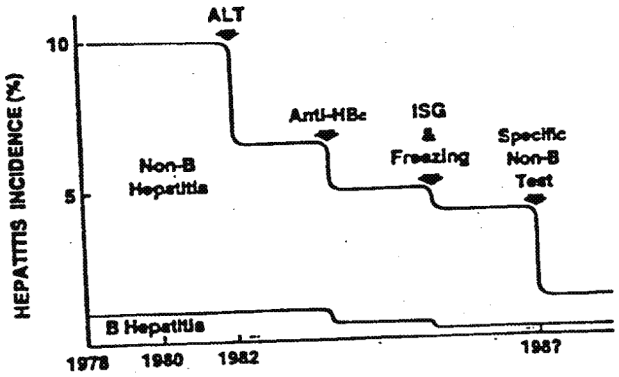
PRELIMINARY NLBTC POLICY FOR NANB PTH ENQUIRIES

1. Confirm that recipient has no markers of current HAV or HBV infections.
2. Only recall donors if <10 are involved (unless samples of all donor sera are stored).
3. Do not recall any donors if commercial blood components have been used.
4. Ask the donors involved if they have ever had hepatitis/jaundice.
5. Perform liver function tests on fresh serum from the donors (especially GPT (ALT) and GOT (AST)).
6. Decide on suitable 'upper limits of normal' for a particular donor population.
7. Re-sample any donors with raised liver enzyme levels; ask about alcohol consumption, obesity or exposure to hepatotoxic agents.
8. Any donors associated with NANB PTH who have raised liver enzyme levels would be removed from the panel.
9. Donors whose liver enzyme levels become normal during follow-up should not act as blood donors until their liver enzymes have been normal for a year.
10. Any donor involved in more than one PTH episode should be removed from the panel.

Slide 6



Estimation of the cumulative effects of ALT testing, anti-HBc testing, use of ISG, and use of frozen-deglycerolized red blood cells (freezing) on the incidence of post-transfusion hepatitis. A specific non-A,non-B hepatitis virus(es) test would likely be the most effective preventive measure.

(From Holland, P.V.[9])

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2. Summary of the 5 post-transfusion hepatitis B cases in 1981.
3. 3 situations where anti-HBc screening is advantageous.
4. Non-A, non-B post-transfusion hepatitis in 1981.
5. Preliminary N.L.B.T.C. policy for non-A, non-B PTH enquiries.
6. Ways to further reduce PTH (from Holland, P.V.[9]).

VIII
IX packaging

600 to 300 m
IX manufacture → BPL
Distribution

NOTES FOR HAEMOPHILIA CENTRE DIRECTORS MEETING

Interim basis for function of IX in vial inhibitor

A number of changes are being made in respect of production of factor IX concentrate of which haemophilia centre directors should be appraised.

1. During the next three months the finishing stages of factor IX production will move almost completely to BPL from PFL. The only way in which Directors will observe this particular change will be in the change of address on the vial label. The label on the product finished at BPL also has a statement about nominal vial contents for factors II, IX and X. An assayed vial contents is provided for factor IX only. This reflects limitations in labelling equipment; the product is subject to exactly the same quality control.

2. The movement of factor IX finishing to BPL means that, in future, factor IX supplies will also be issued from BPL. The precise arrangements for distribution have yet to be agreed, but it is unlikely that BPL will dispatch direct to individual haemophilia centres as did PFL.

3. The presentation of the concentrate will also change during the same period. Water for Injection will, in future, be supplied with the factor IX. This is partly an expression of BPL's intention to present a professional face to the world, but was precipitated by an incident in which a patient suffered a cardiac arrest after infusion of factor IX concentrate mistakenly reconstituted in 2M potassium chloride.

4. A new package will be introduced for factor VIII and for factor IX (the two will be quite similar). The package will comprise an outer cardboard box approximately 10" x 8" x 3", with inner divisions providing storage for 10 vials of concentrate (VIII or IX), 10 vials of Water for Injections and (for factor VIII only) 10 filter needles. Although it will be physically possible to separate the factor VIII (or IX) from the water, we would strongly discourage this.

   Both concentrates show good stability at ambient temperatures (slides provided) so that for periods of storage up to 6 months refrigeration is not really necessary. The factor VIII for instance could be expected to lose less than 10% of its activity on storage for six months at any temperature under 30°C. Type DE(1) factor IX shows even greater stability, losing less than 10% per annum under the same conditions. If the choice is between storing the complete package at reasonable room temperature (say 25°C or less) and splitting the package to allow storage of the concentrate in a fridge, the former is preferable.

   (The product labels still state 'Store in dark below +6°C'. This is in accordance with requirements of the pharmacopoeial monograph.)

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5. In the past, 300iu (10ml vials) of factor IX have been provided for paediatric use. This product will no longer be produced. This is to avoid the possible confusion arising from two different dosage forms in identical vials with very similar labels. To allay any fears that this change will involve waste of a valuable resource, with half of the contents of some vials being discarded, it is worth mentioning that the total amount of factor IX that BPL can produce is limited not by the amount of concentrate available but by the total number of containers that can be handled. It is inmaterial whether the vials contain an adult or a paediatric dose.

6. The amount of factor IX used for the treatment of conditions other than Christmas Disease, and, in particular for treatment of inhibitors to factor VIII, has shown a marked increase during the last year. The product is only licensed for treatment of congenital deficiences of IX, II and X, and these other applications must still be handled on a named patient basis. At the request of one user, a limited amount of unheparinized concentrate, filled at 1000iu/vial is being prepared, specifically for treatment of factor VIII inhibitors.

Figure V.1

PREDICTION OF THE PERCENTAGE OF THE ORIGINAL ACTIVITY REMAINING AFTER STORAGE OF FACTOR VIII CONCENTRATE, TYPE BCRV.
(Based on calculated absolute degradation rates)

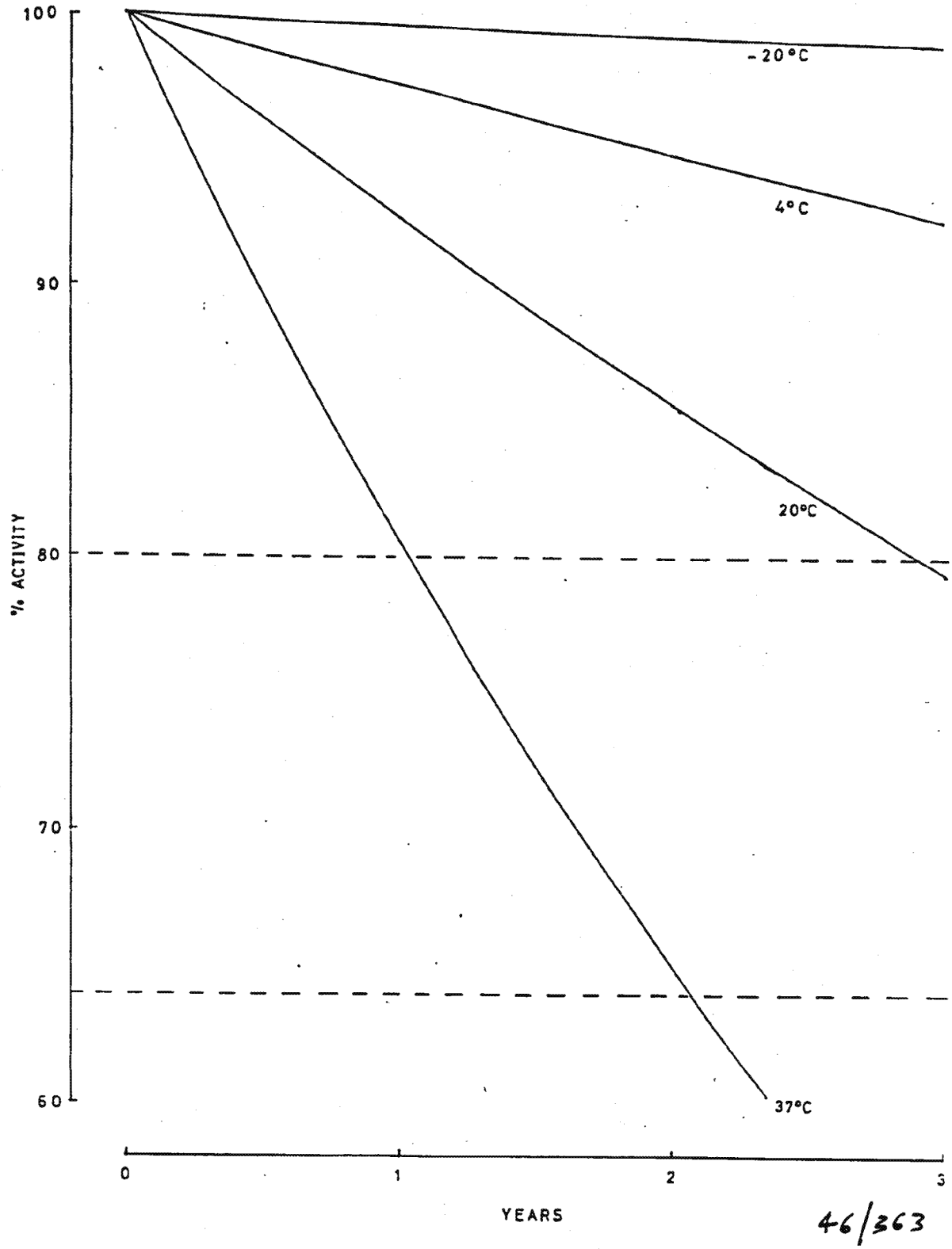

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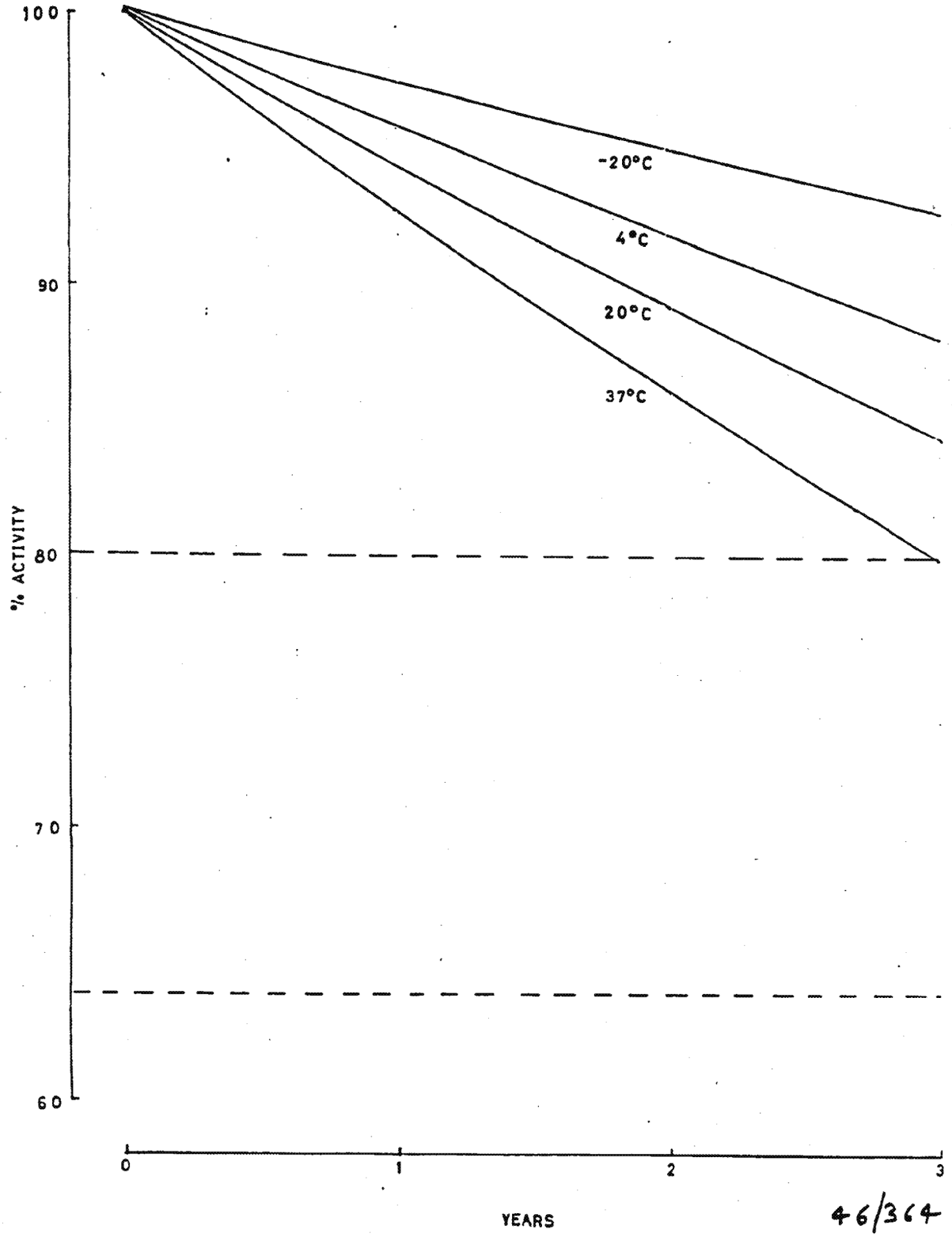
Figure V.2

PREDICTION OF THE PERCENTAGE OF THE ORIGINAL ACTIVITY REMAINING AFTER STORAGE OF FACTOR IX CONCENTRATE, TYPE 9D.
(Based on calculated absolute degradation rates)



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