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Mr. R.A. Kingham,
Small Grants Secretariat,
Department of Health and Social Security,
Alexander Fleming House,
Elephant and Castle,
London SE1

Acted by:

GRO-C

Dear Mr. Kingham,

STUDIES OF THE EPIDEMIOLOGY AND CHRONIC SEQUELAE OF FACTOR VIII
AND IX ASSOCIATED TRANSFUSION HEPATITIS IN THE UNITED KINGDOM

Thank you for your letter of July 27th, indicating the conditional approval to our application for financial support for our project to investigate the epidemiology of factor VIII and IX post transfusion hepatitis.

I have discussed the comments and questions raised with my collaborators and I give below our answers as they relate to the paragraphs in your letter.

1) paragraph 3. INVESTIGATION OF HEPATITIS CASES AT HAEMOPHILIA CENTRES

The early reporting of cases of hepatitis has improved markedly in the past year. This has enabled us to investigate cases properly and deal with any discrepancies. We also request the specimens of acute and convalescent serum for the local diagnostic laboratories for further tests where appropriate.

The question of visits to patients in their own homes has been looked into. This has been done in some Centres, as in the Bournemouth outbreak in 1974, but with over 100 collaborating Haemophilia Centres now involved, this will have to be done locally, unless there are special problems or large outbreaks which justify a visit by myself or one of my collaborators. The consent of the consultant in charge of the Haemophilia Centre would be necessary. Many Haemophilia Centre Directors prefer to do their own follow up. Efforts will be made to apply a standard procedure in the investigation of cases of hepatitis. Variations or deficiencies of information usually arise in the small Centres. Account will be taken of this in the analysis of results by excluding cases or data from Centres where investigation of cases is considered inadequate.

If, however, it is considered essential to have each case investigated by one person, it would be necessary to employ at least one further full time research fellow of registrar grade, and further funds would be necessary to allow visits to Haemophilia Centres or individual patients. The consent of the U.K. Haemophilia Centre Directors would also be necessary, and it is likely that a significant number of them would not be willing to allow their patients to be seen by medical staff other than from their local Haemophilia Centre.

We believe it is better to rely on the investigation by the Haemophilia Centre Director, using as uniform methods as possible, and to accept the fact that occasional cases will be missed.

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2) paragraph 4. STANDARDISATION OF FACTOR VIII THERAPY

The problem of ensuring that patients receive the minimum number of brands and batches of factor VIII was first considered in 1975 when a prospective survey - mentioned under section (ii), page 6, under "chronic sequelae" - of our research application, was being planned. In this study, patients were treated with one product only with the aim of maintaining this regime for at least one year. There were considerable problems with maintaining adequate supplies of factor VIII. Part of this study was undertaken at the Lord Mayor Treloar School, Alton, Hants., where it was found difficult to ensure that patients were treated with the same product in the school holidays, even when they took adequate supplies of freeze dried factor VIII home with them.

With the surveillance scheme now involving over 100 Haemophilia Centres, it will be difficult to ensure uniformity of use of factor VIII, as the opinion of Haemophilia Centre Directors with regard to the optimum use of this product varies considerably. It is our impression, however, that patients on home treatment, and mild haemophiliacs maintained on cryoprecipitate usually receive only one brand of factor VIII over considerable periods. One of the factors associated with cases of transfusion hepatitis, especially non-B hepatitis is a change to a new brand of factor VIII. This problem will be brought to the attention of Haemophilia Centre Directors. It has been found impossible, however, to treat home patients with a single batch for more than 3 months in view of the supply situation. The average consumption of factor VIII per patient per annum is now about 17,000 factor VIII units. At a price of 12 pence per unit, one patient's treatment costs £2,040. 00. This means a very large capital outlay if one patient were treated with one batch of factor VIII even if supplies were available.

With regard to the withdrawal of icterogenic batches, this will only be possible with cases of non-B hepatitis where the incubation period is relatively short. Recent experience involving 2 batches of commercial concentrate contaminated with hepatitis B virus has shown that all bottles of the implicated batches had been used prior to the first patient becoming ill owing to the long incubation periods involved.

3) paragraph 5. STORAGE OF SPECIMENS, DOCUMENTATION AND FILING.

It is intended to store specimens of serum obtained in the follow up survey of patients at Oxford at -40°C . There are, however, storage facilities at -80°C at Manchester with sufficient capacity to store faeces, urine and paired sera from acute cases. It is of course theoretically desirable in view of the fact that unknown viruses may be present in this material that storage should be at as low a temperature as possible. Most hepatitis laboratories store their serum at -20°C or -40°C and there is no evidence from the experience with hepatitis A and B that lower temperatures than -40°C are essential for specimens of serum. Sera from cases of special interest will be stored at -80°C . The deep freeze mentioned in our original grant application has already been purchased from PHLS funds, and will be used solely for the storage of specimens from the Haemophilia Hepatitis Research Project.

A labelling and filing system for specimens, forms and other documentation has been devised at Manchester Public Health Laboratory, and will be introduced at Oxford when the project starts.

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4) paragraph 6. INFORMED CONSENT

The physician responsible for the clinical care of haemophiliac patients usually has a very close relationship with his patients and their families. The purpose of this project will be carefully explained to any patient or member of his family and their consent obtained prior to their inclusion in this project.

5) paragraph 7. FOLLOW UP OF CHRONIC SEQUELAE

The research fellow - Dr. Ghosh - is responsible for collecting clinical information and blood samples under the supervision of Dr. Trowell. Any patient in whom there are abnormal findings will be reviewed in conjunction with Dr. Joan Trowell. Dr. Trowell has run a specialised service in the investigation, diagnosis and management of liver diseases in Oxford for the past ten years, and regularly reviews haemophiliac patients treated at Oxford, thought to have acute or chronic liver disease.

6) paragraph 8. FREQUENCY OF LIVER FUNCTION TESTS AND QUALITY CONTROL.

On reviewing this protocol this section was not intended to read as limiting liver function tests to two occasions separated by six months. This (page 8a) should be changed to read - "As a preliminary, patients in categories b) and c) will have repeat liver function tests performed after one month. They will be followed as Out Patients for six months and at the end of this time, liver function tests will again be carried out. Patients who have abnormal liver function tests for a period of six months will be considered to have chronically elevated serum enzyme levels. If tests become normal during this time, such patients will be excluded from these categories".

It is anticipated that the biochemical and other liver function tests required in the follow up of patients with chronic sequelae will be performed at Oxford.

The preliminary screening of sera for hepatitis B antigen and antibody will be carried out at the Public Health Laboratory under the supervision of Dr. J. O'H. Tobin, Consultant Virologist and Director. Tests for e-antigen and antibody and tests for core antibody and other radioimmunoassay tests will be carried out at Manchester PHL. The PHLs hepatitis laboratories already have a quality control system which ensures the uniformity of techniques and sensitivity of tests. This is supervised from the Central Public Health Laboratory, Colindale.

We are grateful to the Small Grants Committee for their helpful comments on the grant application and I hope our replies have adequately answered the points raised, so that the project can start as soon as possible.

Yours sincerely,

GRO-C

J. Craske.

Consultant Virologist