REVLON HEALTH CARE (UK) LIMITED

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May 19, 1983

Dr. F. E. Preston,
Consultant Haematologist,
Royal Hallamshire Hospital,
Glossop Road,
SHEFFIELD,
S10 2JF.

Dear Dr. Preston,

Dr. Townsend has asked me to send you a draft of the protocol to form the basis of your discussion when she visits you next Tuesday. I enclose the same herewith.

Yours sincerely,

GRO-C

Elizabeth Bryant,
Secretary to Dr. H.A. Townsend

Encs.

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DRAFT PROTOCOL FOR INVESTIGATION OF IMMUNOLOGICAL STATUS OF HAEMOPHILIAC PATIENTS WITH ASSOCIATED LIVER DISEASE

HAT/EB

May, 1983

I. INTRODUCTION

Over the past 18 months there has been increasing awareness that certain groups in society are displaying disorders of cell mediated immunity, susceptibility to opportunistic infection and a high mortality. This acquired immune deficiency syndrom (AIDS) has been observed in homosexuals, Haitians, drug abusers and most recently in haemophiliacs.

It has been recognised for many years that liver disease is common in haemophiliacs. In many cases this is completely asymptomatic but in a few cases persistent symptoms relate to the liver disease. It is appreciated that many of the changes reported in patients with AIDS are seen in chronic aggressive hepatitis. In Sheffield a prospective survey of liver disease in haemophiliacs has been in progress for several years. This affords a unique background on which to base further in-depth investigations in haemophiliacs aimed at relating disorder of immune function to the histology of liver disease.

II. INVESTIGATION TEAM

Dr. F. E. Preston, Consultant Haematologist) Royal Hallamshire Hospital,
Dr. D. R. Trigor, Consultant Physician) Sheffield.

Dr. J.C.E. Underwood, Snr. Lecturer in Histopathology)
)
) University of Sheffield
Dr. R. Rees) Dept. Virology)
Professor C.W. Potter))

III. AIM OF INVESTIGATIONS

1. To assess immunological status of patients with haemophilia with particular attention to those who have had liver biopsies.

2. To correlate findings with the type and amount of Factor VIII treatment.

3. To determine the effect of Factor VIII on the immunological status.

4. To relate abnormalities of immunological status to histological type of chronic liver disease.

IV. DESIGN OF INVESTIGATION

An open comparison over 2 years of haemophiliacs with proven liver disease with age matched haemophiliacs with no evidence of liver disease, and non-haemophiliac patients with chronic liver disease.

V. MATERIALS

Factor VIII will be administered whenever necessary and the nature and quantity will be recorded. Treatment will be followed by serial tests of liver function and immunological state.

VI. PATIENT POPULATION

25 haemophiliacs who have evidence of liver disease and received liver biopsies.

25 age matched healthy haemophiliac controls with no evidence of liver disease.

25 patients with chronic liver disease (proved by biopsy) but no haemophilia.

VII. PLAN OF INVESTIGATION

(i) Patients

3 blocks as described in section VI.

(ii) Periods of Examination

On admission to the study the patients will have

(a) A full histology which will include:

haemophiliac condition (coagulation defect severity) and details of therapy (nature, volume, time received)

any other relevant condition such as malignancy (e.g., lymphoma) or infection (parasitic, fungal, viral or bacterial)

recent fatigue, loss of weight, enlarged glands or malaise

joint involvement

(b) A complete physical examination

(c) Special tests (see ii a)

Clinical status and investigations will be repeated at 6 monthly intervals over the 2 years and at any other time deemed advisable by the investigator. Serial tests of liver function and immunological state will be conducted following administration of Factor VIII.

(iii) Choice and Measurement of Variables

(a) Complete blood picture.
(b) Liver function tests.
(c) T-Cell subset/N K Cell/ monocyte analysis using monoclonal antibodies.
(d) Natural Killer (NK) cell cytotoxicity profile - functional assay.
(e) Neutrophil function.
(f) Monocyte function.
(g) Delayed hypersensitivity skin testing.
(h) Serum complement.
(i) Immunoglobulins.
(j) Lymphocyte count.

(iv) Assessment of Results

The data generated will be assessed at 6 monthly intervals (or at any other time considered necessary) so that meaningful modifications to the investigation can be considered.

VIII. ADVERSE AND TOXIC REACTIONS

Appropriate measures will be taken and the incident reported.

XI. DATA RECORDING

Data will be entered on an appropriately designed format and summaries drawn up for review at 6 monthly intervals.

X. EVALUATION AND STATISTICAL ANALYSIS

To follow.

XI. ETHICAL APPROVAL

Ethical approval will be obtained from the Ethical Committee of the Royal Hallamshire Hospital, Sheffield.

XII. WRITTEN INFORMED CONSENT

Written informed consent will be obtained from adult patients or from the parents or guardians of any children who agree to participate in this investigation.