In confidence

APPLICATION FOR RESEARCH GRANT, 1 April 1978

Dr. John Craske:
"Studies of the epidemiology and chronic sequelae of factors VIII and IX associated hepatitis in the United Kingdom."

Comments

Apart from certain detailed comments (below), I support this proposal because it will give an idea of the incidence of hepatitis associated with various preparations of factor VIII and factor IX concentrates and because it may also show whether it is possible to determine batch sizes of these concentrates which are associated with minimum incidences of hepatitis. Following from this last point, it might then be necessary to investigate the economic aspects of the preparation of such materials. I am less enthusiastic about the survey of recipients of Hemofil in 1974/75 for reasons given in a letter to Dr. Holgate* (copy attached) but I do not wish to press the points in this letter, the chief of which was the possibility of medico-legal action.

Epidemiological surveys of post-transfusion hepatitis are always difficult because of the many complicating factors that crop up and some of these might be avoided if it proved possible to adopt one or more of the comments below.

Detailed Comments

p.6: Incidence of hepatitis B. Have the statistical aspects of information needed about the optimum size of donor pool needed to give the maximum yield of factor VIII and factor IX with minimum risk of hepatitis been considered? Is enough information likely to be gathered in three years to answer these questions?

p.7, line 13: reference 9 not included in bibliography.

p.7: Plan of Investigation

1) Hepatitis surveillance.

This survey has the great advantage that the patients will be seen by a limited number of Haemophilia Centres and therefore supposedly by a relatively small number of doctors and other staff. Nevertheless queries will arise regarding the reports received at Oxford of cases of hepatitis which should be investigated without delay.

For this reason I recommend that Haemophilia Centre Directors should participate only if they agree to notify cases as they occur and to adhere strictly to any procedures specified by those conducting the survey. Immediate investigation of queries can sometimes retrieve missing information or explain misunderstandings which is impossible a year after the event. In my experience of this type of survey, personal visits to the patient and general practitioner have proved important and frequently necessary, rewarding as well as time consuming. I assume that it is expected that much of this part of the work will be done at Haemophilia Centres; uniformity of procedure will therefore be essential. Nevertheless I think the possible need for more visits than indicated should be remembered.

I also wonder whether intermittent help as required, possibly involving different individuals can be regarded as adequate clerical

* (Letter of 20 Feb. to Dr. Craske, copy to Dr. Holgate)

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assistance for Miss Spooner for what will be a gradually increasing work load, but perhaps it is intended to judge this as the survey gathers momentum. Is the information going to be dealt with manually? No mention is made of this very important point.

Batches of concentrate With few exceptions, many report forms usually show that the patient has received more than one make of concentrate and very often that each bottle he's been given has come from a different batch. I would strongly recommend that participating centres undertake to use a given make of concentrate, or at the most two makes, that each patient will be given material from one make and that of this make only bottles from one batch will be used. This would simplify analysis and presentation of results (see last para, p.7) but, more important, would increase the chances of detecting icterogenic material with a greater degree of certainty and permit the withdrawal of icterogenic bottles. There are obvious limits to the application of these proposals but it would be well worth while applying them as far as possible. Their adoption would necessitate the co-ordinated purchase and distribution of commercial material and also the use of rules of procedure in Haemophilia Centres which should in any case strictly follow uniform procedures.

I assume quality control will be exercised over the hepatitis testing at Hepatitis Reference Laboratories and also over the measurement of transaminases and any other laboratory tests at local laboratories.

p.8, first para: Are the organizers confident that the subzero storage for specimens is adequate? Has a uniform and permanent method of labelling and convenient form of storage been devised so that specimens can be retrieved and identified unequivocally? In the last survey I was associated with the cold storage space turned out to have been underestimated.

second para: Has the Working Party ascertained that this information will be obtainable when wanted?

p.8, 2) Follow up of chronic sequelae of factor VIII associated hepatitis.

Will informed consent be obtained from this group of patients and from the two groups of controls? This seems necessary as they are going to be asked to undergo examinations, give specimens, and members of their families may also become involved. It would also seem necessary to inform the general practitioners and also keep them informed as the survey progresses.

p.8a, Selection of patients for further investigation. It is stated that patients in groups b) and c) found to have elevated transaminases will undergo repeat tests six months later. Is this interval too long? This point may be taken up by the expert referee on hepatitis. In the last survey I was associated with, the corresponding adviser advocated an interval of 7 days between the first positive test and the repeat test because an abnormal transaminase level persisting for this length of time was probably indicative of hepatic disturbance whereas a transaminase spike lasting only 2 or 3 days was of doubtful significance. In this survey an attempt was then made to obtain evidence by BSP excretion and other tests. Opinions may, of course, have changed. In the circumstances of the present trial, the recipients with chronic hepatic damage may perhaps reasonably be expected to have persistently abnormal transaminase levels. The application does not make clear

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whether the cryoprecipitate controls are to be retrospective in the sense that it is hoped to be able to find patients or that patients are available who began treatment at about the same time as the Hemofil patients or whether the cryoprecipitate controls will have begun treatment at some later date. In the latter instance, I think a six months' interval between enzyme tests will be too long.

It is assumed that the laboratory investigations described on p.8 will be done in one or more of the Oxford laboratories. If so, quality control possibly becomes less important because all tests will be done under the supervision of the same individuals. However, if for any reasons some tests have to be carried out elsewhere, assurance of uniformity of technique and quality control assume greater importance.

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2.5.78.

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