Cutter

29-500

TO: See below

DATE: August 13, 1980

FROM: M.M. Sternberg

COPIES TO: K.Meyer, M. Mozen
xc: Glen Cureton

SUBJECT: Planned research activity in anti-hemophilic factor.

CC: W. Schaeffler, K. Hamlin, K. Fischer/J. Mink, J. Mjorth/J. Wood, J. Barnette, N. Ashworth, C. Patrick.

Lately, we conducted a review of research status in the field of anti-hemophilic factors [AHF], in particular KoāteR. The importance of the AHF products in the business of Cutter Laboratories prompted our search for definition of problems, priorities setting, technical research approaches and estimates of time-tables.

For the purpose of organizing the thinking process, problems can be divided into three categories, though in reality they may be closely interrelated. These groups of problems are:

1. Increased recovery of AHF from cryoprecipitate.
2. Quality problems of AHF preparations.
3. Development of hepatitis-free AHF.

1. Recovery of AHF from cryoprecipitate

1.1 Presently the overall recovery of AHF from cryoprecipitate to finished product is 41%.

1.2 The feasibility of modifying the current process by an "acid-chill" procedure was shown. The change of process holds the potential of 10-15% improvement in AHF recovery. We estimate to reach the stage of PR lots by November 1980.

1.3 Harwell electrophoresis. Yield and quality improvements are anticipated but work can start only after securing a unit for our use. Agreement with Harwell is in progress (See NPPC reports).

1.4 Ultrafiltration. Research activity is limited to support of manufacturing for implementing the process. Experience of Miles Enzyme Manufacturing in ultrafiltration should be utilized.

2. Problems related to quality

2.1 Reconstitution of dried AHF. The problem seems to be related with desiccation conditions. Research is in progress and scheduled for completion by December 1980.

2.2 Isoagglutinins. The feasibility of using chromatography on synthetic supports [synsorb] has been shown. Scale-up brought up problems which required return to the bench level. There is no indication of when and if the problems will be solved, though other means, such as Harwell electrophoresis, may be a back up in case of failure. Meanwhile, low isoagglutinin titers are secured through typing.

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2.3 AHF in vivo recovery. Low recoveries of AHF after administration are reported. This problem is of a basic nature and we do not have yet a program of research except for clinical surveillance and possibly a clinical study. Awareness is maintained as well as cognisance of the potential of oral AHF.

3. Hepatitis-free AHF

From the groups of problems related to AHF products, this is the most difficult and should be high on the list of priorities. It transcends the immediate impact on sales of yield improvements and quality upgrading, for it is related to the existence of the product in the future. Information from International points to progress made by competitors in achieving hepatitis-free AHF. Biotest, in Germany, is already selling a Factor IX, claimed to be hepatitis-free [information from Reiner Froitzheim, Cutter Tropon] and Behring is deeply involved in research. Success by competitors will put us at a disadvantage and may even induce a ruling by regulatory agencies against selling of hepatitis risk products.

Low key work has gone on at Cutter on and off, yet we have not capitalized enough on the high degree of know-how we achieved in the hepatitis area through the development work of the hepatitis vaccine. Success in achieving a hepatitis-free AHF depends on the concurrence of research by chemists and biochemists with support from virologists capable to test the infectivity of the hepatitis viruses. All these material elements exist at Cutter and make the likelihood of solving the problem very high. The strategy which we are following here is to develop an animal system, the so-called squirrel hepatitis, which was shown to be very similar to the human virus. This system will serve as a testing ground for all the work, reserving the costly chimpanzee tests for the end as a confirmation of results. Until the squirrel hepatitis system is developed we shall rely on a biochemical test, so-called DNA-polymerase activity which may be an indication of virus inactivation.

3.1 Heat sterilization for 10 hours at 60°C seems feasible. However, process variables have to be defined, and ultimate proof of virus destruction supplied. One full-time scientist is expected to determine optimal process conditions within 3-6 months.

3.2 Chemical treatment. Selective inactivation of the hepatitis virus without affecting AHF may be feasible, as indicated by experiments of treatment with iodoacetic acid. This preliminary work has shown that DNA-polymerase is inactivated by iodoacetic acid, whereas losses of AHF activity are reasonable. The same seems to apply in the case of Konyne® and Feiba.

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However, the enzymatic test of DNA-polymerase is at best an indication useful to monitor the work for preliminary screening but no substitute for in vivo results. Work along the line of chemical inactivation of the virus will be now reactivated at a pace concurrent with the development of the squirrel hepatitis test system. This is estimated to take 6 months, at which time results will be evaluated and if warrented, more manpower will be assigned.

4.0 The AHF Task Force. The role of the AHF Task Force in assuring communication across departments was assessed as positive. The Task Force will continue to function, though the convening will be done on a "need be" basis or a maximum of 2 months intervals. Chairing of the AHF Task Force will continue by John Lundblad and a memo on the subject will soon be issued.

GRO-C

MMS/jt

bc: D.D. Schroeder
J.L. Lundblad/G. Mitra

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