Cutter

MILES

TO: W.F. Schaeffler

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FROM: M.M. Sternberg

COPIES TO:

SUBJECT: Virus-free plasma products programs

Several research activities are currently in progress aimed at achieving virus-free plasma products. The reason for several approaches is due to differences in the functional stabilities of the products where virus kill is desired and differences in virus response to the agents.

1. Heating in solution [wet heating] at 60°C for 10 hours. This is the common practice with albumin and Plasmanate which has had over many years a good record of safety from infectivity with hepatitis. Its virus killing effect is dependent on the nature of the adjuvants which are added to the solution in order to protect the plasma protein. The less adjuvant is added the higher the effect of heating. We are using this pasteurizing procedure for Alpha-1-PI and AT-III already in fairly large size batches without any processing difficulty (final filtration). For Alpha-1-PI we prefer to use this procedure rather than a dry heat because of results with marker viruses showing its clearcut superiority. For AT-III we are using the wet heat because it was studied by the Red Cross and tested with good results in Chimpanzees.

2. Dry Heating. We are using this process for Koāte and are completing work with Konyne. It consists in heating in dry state in the final container at 68°C for 72 hours. From the standpoint of processing it is the easiest, less expensive way of all methods. Though results with marker viruses are inferior to the heating in solution, nevertheless, it is effective as shown in Fenwal's experiments against an unknown strain of non-A non-B hepatitis.

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3. Copper orthophenanthroline. We have reached a point where we would like to test the efficacy either alone or preferably with a dry heat combination in Chimpanzees. The remaining potential problem with this method is the fact that it employs orthophenanthroline which may require extensive toxicology work. Nevertheless, we have reduced considerably the level of residual orthophenanthroline and we have not given up hope to find a substitute more acceptable than orthophenanthroline.

4. Chloroform with and without surfactants. We have determined what are the losses of AHF [reasonable under certain conditions] and have work in progress with marker viruses. The method,which was first proposed Purcell and Feinstone, from NIH, has the draw back of leaving a chloroform residue in AHF after the extraction. In my opinion it will be a very difficult problem to solve, probably it will not be acceptable to inject into patients a product containing residual chloroform.

5. Chloroform or ether with dry heat. We propose here to add chloroform or ether to AHF solution effecting thus a destabilization of viruses through interference with the lipid coat. No extraction is performed, and after the product is lyophilized we apply dry heat expecting a synergistic effect. Work is in progress, we do not have yet data to evaluate.

6. Tri-n-butyl phosphate with/without surfactants. This is based on the use of the reagent for the chemical detoxification of certain vaccines. Positive results with marker viruses were claimed by the New York Blood Center. Results at Cutter are not yet available.

7. Extraction with supercritical gases. We are ready to start experiments with a company affiliated with Arthur D. Little in Boston, Massachusetts. If successful it would be superior to the use of common solvents for disrupting lipid coated viruses, because of the fact that no residues will be left.

The above research activities are part of a multidisciplinary team effort involving at this point biochemists and virologists. The product most critical and difficult to render virus-free is AHF, but every other plasma product, in particular those which are in the pipeline will have to be made safe from transmission of known and unknown, or suspected viruses carried by donors of blood and plasma.

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