OFFICE OF THE DIRECTOR OF DEFENSE RESEARCH AND ENGINEERING
WASHINGTON, D. C. 20301

4 February 1965

MEMORANDUM FOR (See Distribution)

SUBJECT: Minutes of the Forty-Second Joint Medical Research Conference

The following were present at the forty-second conference in Room 3-D-1021, The Pentagon, 0900 - 1130, 7 January 1965:

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B/Gen Robert E. Blount, MC, USA, AMR&DC, D/A
Col Jack Bollerud, USAF, MC, AFRST, D/AF
Cdr C. E. Brodine, USN, MC, D/N
Dr. F. J. Frese, Jr., OAD/R, ODDR&E
Col Donald H. Glew, MC, USA, AMR&DC, D/A
Col Herschel E. Griffin, MC, USA, ODASD/H&M (OASD/M)
Dr. Frank W. Hartman, AFMSPA, D/AF
Col Donald L. Howie, MC, USA, AMR&DC, D/A
Capt James R. Kingston, MC, USN, BuM&S, D/N
L/Col John J. Kovaric, MC, USA, AMR&DC, D/A
Dr. Carl Lamanna, ARO, D/A
L/Col William T. Leslie, MSC, USA, Mil. Blood Prog. Agency
Dr. Gerald M. McDonnel, The Center for Health Sciences, L.A., Chairman
L/Col Richard K. Miller, USAF, MC, AFMSPA, D/AF
R/Adm Langdon K. Newman, USN, MC, BuM&S, D/N
Capt John A. O'Donoghue, USN, MC, BuM&S, D/N
Capt Joseph P. Pollard, USN, MC, BuM&S, D/N
Capt Carl E. Pruett, USN, MC, ODCNO(Dev), D/N
L/Col Robert E. Robards, USAF, MC, AFRST, D/AF
B/Gen John M. Talbot, USAF, MC, AFMSPA
Col Colin F. Vorder Bruegge, MC, USA, AMR&DC, D/A

The Chairman, Dr. McDonnel, called the meeting to order. He then extended a welcome to Admiral Newman, who is the new senior representative of BuM&S. The minutes of the forty-first conference, which had been distributed prior to this conference were approved without change. Dr. McDonnel asked whether there was as yet any indication that the pharmaceutical industry was responding satisfactorily to the DOD-HEW (FDA) memorandum of understanding regarding the clinical investigation of new drugs. (See minutes of thirty-first conference). Colonel Howie said that there were no signs that the drug industry considered the agreement adequate protection to re-start the supplying of new drugs to the Department of Defense for testing. He felt that little progress could be expected until an actual test case had been adjudicated formally. The Army legal people are endeavoring to

arrange such a test. Colonel Vorder Bruegge pointed out that the Army feels that we must seek a quick resolution of the difficulty, particularly since the laboratories at Fort Detrick need clearance for the use of their own products. Captain Kingston mentioned that even within HEW there are some difficulties and NIH is currently attempting to get clearance for a trial of new live adeno-virus vaccine at selected Naval stations. Dr. Hartman noted that the current FDA regulations also apply to the clinical testing of such substances as blood-preservation additives and hence are delaying progress in the blood research program. Dr. McDonnel noted that the principal item on the agenda for this conference was the DOD blood research program and asked Colonel Griffin to open the discussion. Colonel Griffin read pertinent abstracts from correspondence between Dr. Cannan of NAS-NRC, Dr. Fisk, DASD(H&M), and the three Surgeons General (copies attached). The chairman then opened the conference for discussion. General Blount said that he invited Colonels Glew, Kovaric and Leslie to attend for the purpose of this discussion. Colonel Kovaric said that the Army is ready to do in-vivo studies on adenine-blood, but is holding off, pending an FDA ruling. The firm which is the sponsor for such ACD-fortified units expects a decision in 6 - 8 weeks, and several investigators are ready to proceed. Part of the problem is procuring human volunteers, especially for cell-survival studies. However, Walter Reed Army Institute of Research is set to go with 24 volunteers. Colonel Griffin asked if we could now report this to NRC and ask them to establish an overall protocol which, if met, would establish adenine-fortified blood as acceptable for clinical use. Speaking for the Navy, Cdr. Brodine pointed out that this technique is not competitive with, nor in conflict with the forzen-blood program sponsored by the Navy, but is complementary to it. At present, glycerolized frozen blood, stored at $20^{\circ}F$, has a shelf life of 1 - 2 years. Cell survivability is good. There has been no attempt yet to frotify this frozen blood with adenine compounds but this technique will definitely have to be investigated. Speaking for the Air Force, Dr. Hartman noted that there are no reports in the literature to indicate that actual in-vivo experiments with ACD blood have been attempted. The Air Force agrees with both Dr. Fisk's office and the NAS-NRC that this research should be done. However, the Biological Standards Division of FDA insists that new drug procedures must be followed. He pointed out that logistically the prolonging of the shelf-life of blood even to 4 - 5 weeks would be a tremendous help to the military. He stated that General Talbot had already solicited from qualified Air Force hospitals proposals to undertake investigations of adenine-fortified blood. Dr. McDonnel asked Dr. Hartman if this problem had been discussed by the Interdepartmental Committee on National Blood Program Research (of which Dr. Hartman is executive secretary). He was told that the matter had not been discussed specifically. Dr. Brodine gave his opinion that considerable work is still required on the pharmacology and biochemistry

of adenine-fortified blood before extensive clinical trials can be undertaken. Dr. Griffin agreed, but pointed out that this would be covered in the NRC protocol. Colonel Leslie asked whether a formal military requirement had been established for prolonging the shelf life of blood and whether it had been determined how much logistics saving would result from such extension. Dr. McDonnel said he was convinced that such studies should be made by the Military Blood Program Agency, which Colonel Leslie represents. Colonel Griffin agreed that the charter of the Military Blood Program Agency certainly made them the logical agency to make such studies. Dr. McDonnel then asked the Services if they were satisfied with the performance of the Military Blood Program Agency. The consensus was that performance was satisfactory, except that it might furnish more support to the research efforts in blood preservation.

Dr. Lamanna asked if the conference felt there was a need for the NRC to prepare a formal protocol and establish criteria for this research effort. Colonel Griffin pointed out that the NRC is offering the guidance of the nation's top experts in establishing the guidance for an over-all program, and the use of such protocol and criteria would increase the acceptability of the research results. The Army, Navy, and Air Force representatives expressed concurrence with this and assured the chairman of this willingness to participate actively in these investigations.

The chairman then designated Colonel Griffin to prepare, on behalf of the conference, the necessary replies to Drs. Fisk and Cannan.

There being no further business before the conference, the chairman adjourned it at 1130.

The next meeting will be at 0900, 11 February 1965, in Room 3-D-1021, The Pentagon.

Frederick J. Frese, Jr.

FREDERICK J. FRESE, JR.
Col, USAF MC
Executive Secretary

Enclosures

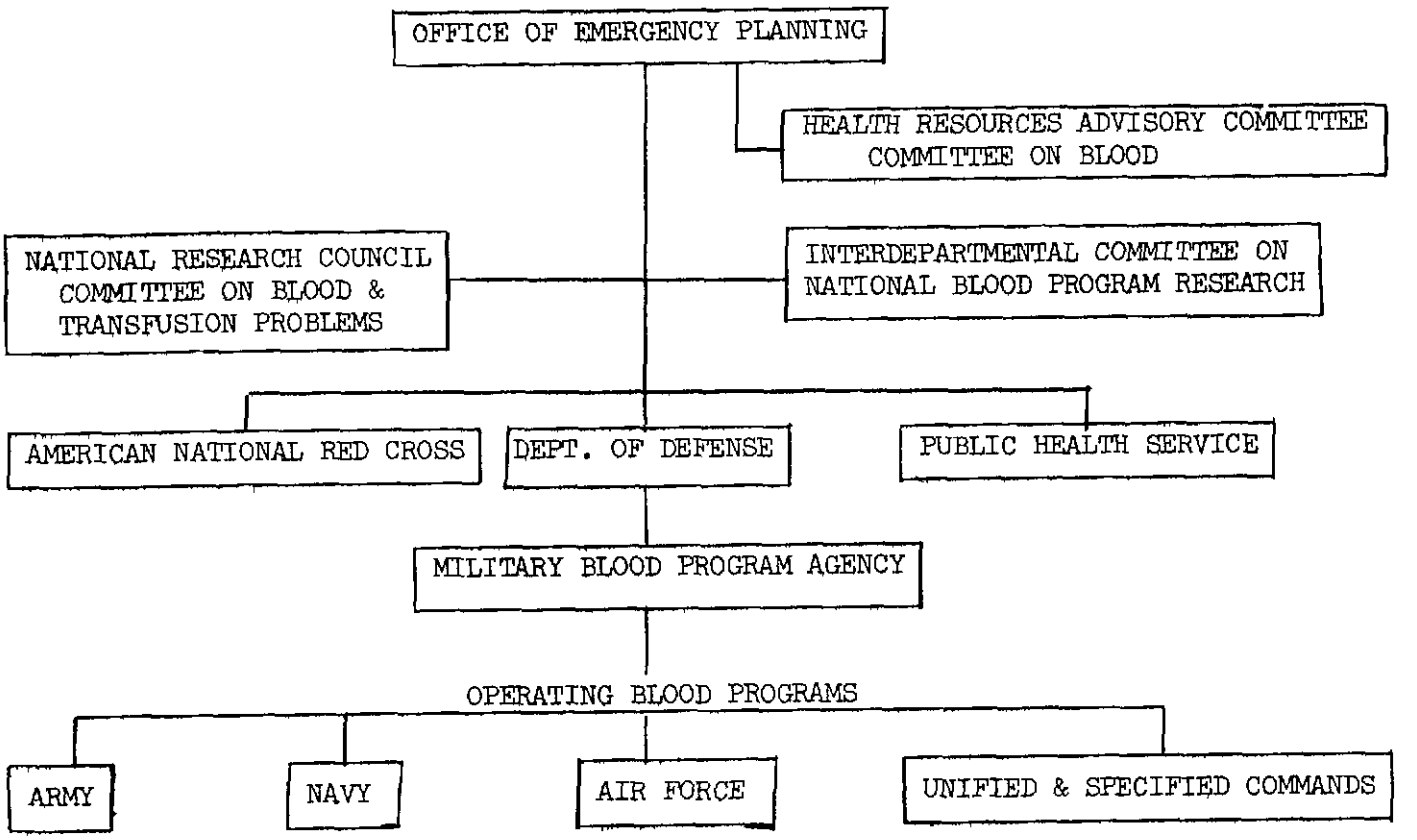
1. Distribution List
2. Chart - Orgn. Natl Blood Prog.
3. Cy M/The Surgeon General of the Army, Navy, AF, dd 12/22/64 sgd Shirley C. Fisk, DASD/H&M
4. Cy Ltr to Dr. Shirley C. Fisk, 12/14/64, sgd R. Keith Cannan
5. Statement Concerning the Evaluation of the Practical Utility of Adenine-Fortified Anticoagulants, 12/14/64

Distribution List

Dr. Charles G. Anderson, Office of Civil Defense, D/A
B/Gen R. E. Blount, MC, USA, AMR&DC, D/A
Col Jack Bollerud, USAF, MC, AFRST, D/AF
Cdr C. E. Brodine, USN, MC, D/N
Dr. E. G. Fubini, ASD/DDDR&E
Col Donald H. Glew, Mc, USA, AMR&DC, D/A
Col H. E. Griffin, MC, USA, ODASD/H&M (OASD/M)
Dr. Wm W. Hammerschmidt, DSB, ODDR&E
Dr. Frank W. Hartman, AFMSPA, D/AF
Col Donald L. Howie, MC, USA, AMR&DC, D/A
Col T. E. Huber, MC, USA, ARO, D/A
Capt J. R. Kingston, MC, USN, BuM&S, D/N
L/Col John J. Kovaric, MC, USA, AMR&DC, D/A
Dr. Carl Lamanna, ARO, D/A
L/Col W. T. Leslie, MSC, USA, Mil. Blood Prog. Agency
Dr. G. M. McDonnel, The Center for Health Sciences, L.A.
L/Col Edwin Myers, AFRST, D/AF
L/Col Richard K. Miller, USAF, MC, AFMSPA, D/AF
R/Adm W. N. New, MC, USN, ODASD/H&M (OASD/M)
Capt John A. O'Donoghue, MC, USN, BuM&S, D/N
Capt Joseph P. Pollard, MC, USN, BuM&S, D/N
Capt Carl E. Pruett, MC, USN, ODCNO(Dev), D/N
Dr. E. M. Reilley, AD-R, ODDR&E
L/Col Robert E. Robards, USAF, MC, AFRST, D/AF
Dr. C. W. Sherwin, DD/R&T, ODDR&E
B/Gen John M. Talbot, USAF, MC, AFMSPA, D/AF
Col Colin F. Vorder Bruegge, MC, USA, AMR&DC, D/A
R/Adm Langdon K. Newman, USN, MC, BuM&S, D/N

FUNCTIONAL ORGANIZATION

NATIONAL BLOOD PROGRAM



ASSISTANT SECRETARY OF DEFENSE
Washington, D. C. 20301

Manpower

22 Dec 1964

MEMORANDUM FOR THE SURGEON GENERAL OF THE ARMY
THE SURGEON GENERAL OF THE NAVY
THE SURGEON GENERAL OF THE AIR FORCE

SUBJECT: Adenine-Fortified Anticoagulants.

Ref: Ltr fm R.Keith Cannan, Chmn, Div/MedSciences, NAS-NRC, 14 Dec 64, to DASD(H&M) w/encl: "Statement Concerning the Evaluation of the Practical Utility of Adenine-Fortified Anticoagulants".

The referenced letter from Dr. Cannan notes the disappointingly slow progress in the development of new anticoagulant solutions which would allow substantial extension of the shelf-life of whole blood. However, he reflects the views of the Committee on Blood and Transfusion Problems, NAS-NRC, that this area of research holds great promise and is now ready for vigorous exploitation. He invites the Department of Defense to assume leadership of a program to develop new anticoagulant solutions for adoption in the near future and offers the assistance of the Division of Medical Sciences and its consultants.

It is requested that you consider this invitation as it relates to your operational needs and research programs. It is further requested that your representatives be prepared to discuss this matter at the next Joint Medical Research Conference, to be held on 7 January 1965.

s/

Shirley C. Fisk, M.D.
Deputy Assistant Secretary
(Health and Medical)

Enclosure - 1
Copy of Ref Ltr w/encl.

cc: DDR&E (Col Frese)

NATIONAL ACADEMY OF SCIENCES
NATIONAL RESEARCH COUNCIL
2101 Constitution Avenue, N. W., Washington, D. C. 20418

Division of Medical Sciences

14 December 1964

Dr. Shirley C. Fisk
Deputy Assistant Secretary
of Defense (Health and Medical)
Office of the Assistant Secretary of Defense
(Manpower)
Room 3B-269, The Pentagon
Washington, D. C. 20301

Dear Dr. Fisk:

Since the introduction of ACD solution almost 25 years ago, there have been no improvements in anticoagulant solutions and hence no extension of the permissible storage period of blood for transfusion.

In the interest of military medicine, the military medical departments have supported research in the hopes of developing some suitable means to extend the storage period of blood. Rather extensive support has been lent to investigation of the preservation of red cells at low temperatures. However, although progress has been made in this field, no acceptable technique for preservation of red cells by this method is now available for general application by the armed forces, and the prospects of developing such a technique do not appear to be in the immediate offing.

The armed forces, notably the Department of the Army, have also provided support on a somewhat lesser scale for studies on the development of new anticoagulant solutions. Again, this research has not yet produced a new method for immediate and general application. On the other hand, as specified in the enclosed statement, the Committee on Blood and Transfusion Problems, NAS-NRC, has expressed a conviction that this area of research does hold great promise and is now ready for vigorous exploitation. However, because the rate of acquisition of data from this area of study has been so disappointingly slow, and because the accumulation of needed information may be further impeded by some recent development, the Committee is agreed that the exercise of agressive leadership by a federal agency in the National Blood Program is needed if full benefit is to be derived within a reasonable period from the work already accomplished.

In consideration of the position that the armed forces already occupy in the field, I am pleased to forward the enclosed statement to you

for your consideration. Should you decide that the Department of Defense is to assume a position of more positive leadership in the development of new anticoagulant solutions, the Division of Medical Sciences and its consultants will be pleased to offer their full cooperation and assistance.

Sincerely,

s/

R. Keith Cannan
Chairman of Division

Enclosure

NATIONAL ACADEMY OF SCIENCES-NATIONAL RESEARCH COUNCIL
Division of Medical Sciences

STATEMENT CONCERNING THE EVALUATION OF THE PRACTICAL UTILITY OF ADENINE-FORTIFIED ANTICOAGULANTS

Committee on Blood and Transfusion Problems
14 December 1964

In the spring of 1962, the Committee on Blood and Transfusion Problems reviewed the information about the effects of adenine on the preservation of red blood cells collected in ACD-adenine solution and stored in the liquid state at 4°C. These data suggested the possibility that the permissible storage period for such cells might approximate six weeks. If this possibility could be proven to be valid, it would be of great practical value in blood transfusion services. However, most of the experimental observations presented to the Committee at that time were from in vitro studies, and because these data could not be correlated with those from studies involving the administration of ACD-adenine-treated blood in full transfusion amounts in man, it was not possible to assess the possible clinical application of the research findings. Accordingly, the Committee recommended that this field of endeavor be supported, that the initial studies be repeated, and then, if appropriate, that the studies be extended.

In October, 1964, the Committee again reviewed the subject and noted that the new information accumulated is still primarily from in vitro studies, but does lend additional support to the proposition that the incorporation of small amounts of adenine into ACD solution into which blood is collected improves the stability of the red cells in storage at 4°C. No experimental findings have become available that would constitute a significant challenge to this proposition. Again, however, few data were presented to the Committee that would permit correlation of the results of in vitro studies with the capability of such cells to survive in recipients after transfusion and to perform their normal physiological functions. In this respect, therefore, the situation remains much the same as it was almost three years ago.

Since 1962, however, there have been two occurrences that complicate the acquisition of the needed data.

First, the Food and Drug administration has approved the Citrate-Phosphate-Dextrose (CPD) anticoagulant for general use. It would seem reasonable, therefore, to explore the claims for the superiority of this anticoagulant over ACD as soon as possible. It would also seem logical to study the relative merits of CPD and adenine-fortified CPD solutions, and then to conduct studies to compare the relative merits of the more effective of these two CPD solutions and the ACD-adenine solution. In addition, the possible effects that residual adenine might have on the production and fractionation of plasma should be investigated simultaneously.

Second, the FDA has issued regulations in implementation of the Kefauver-Harris Drug Amendments of 1962 to the Food and Drug Act of 1906. These regulations introduce new problems involving working relationships among the geographically dispersed laboratories engaged in basic research on the effects of adenine-fortified media on red cells in storage, the laboratories that might undertake applied studies of such media, and commercial producers of safe solutions for in vivo studies on such media in man.

In view of the foregoing considerations, the Committee on Blood and Transfusion Problems therefore strongly recommends:

(1) The expeditious and vigorous pursuit of the required studies to establish the status of the CPD solution and to determine the practical value of adenine-fortified anticoagulants, both ACD-adenine and CPD-adenine, in a general blood transfusion service.

(2) That an operating agency in the National Blood Program assume sponsorship of a program to accomplish this end as a project of high priority in the national interest.

(3) That this agency explore with the Food and Drug Administration the development of suitable answers to problems associated with the provision from commercial sources of the required equipment and intravenous preparations.

The Committee stands ready to assist with the research aspects of the recommended program, particularly with respect to the definition of additional studies that should be undertaken. For example, prior to the clinical evaluation of adenine-fortified anticoagulant, additional pharmacological studies are needed to establish the safety of adenine for more extensive administration to man. The existing information does not indicate that the amounts of adenine required to improve the storage qualities of erythrocytes will prove to be undesirable when multiple transfusions of blood treated with adenine-fortified anticoagulants are given. However, this must be substantiated by critical experimental observations.