June 20, 1952

Lt. Col. Harold V. Ellingson, USAF (MC)
Head, Department of Preventive Medicine
USAF School of Aviation Medicine
Randolph Air Force Base
Randolph Field, Texas

Dear Colonel Ellingson:

Per Dr. Sabin's wire, you will find enclosed an original and seven copies of corrected Page 1 of the research contract proposal for the work on dengue. Will you please substitute this for the original page from which there was a line missing?

I regret very much that this error was made.

Sincerely yours,

Mary A. Jackson, Sec'y to:
Dr. Albert B. Sabin
RESEARCH CONTRACT PROPOSAL

TO: USAF School of Aviation Medicine
Randolph Air Force Base
Randolph Field, Texas

BY: Albert B. Sabin, M. D.
The Children's Hospital Research Foundation
University of Cincinnati College of Medicine
Eiland Avenue and Bethesda
Cincinnati 29, Ohio

SUBJECT OF RESEARCH: PREVENTION AND DIAGNOSIS OF DENQUE

1. Technical Information:

A. SIGNIFICANCE OF PATHOGENIC EFFECTS OF MOUSE-ADAPTED DENQUE VIRUSES ON THE CENTRAL NERVOUS SYSTEM OF MONKEYS, WITH SPECIAL REFERENCE TO THE USE OF THESE VIRUSES FOR HUMAN VACCINATION

The question here is whether progressive adaptation of dengue virus in mice has resulted in the selection of a variant with greater pathogenicity for the central nervous system of primates. Natural and experimental infection of human beings with various strains of dengue virus is not associated with evidence of damage to the nervous system. Intracerebral injection of human dengue virus in monkeys gives rise to inapparent infection, but histological examination reveals evidence of focal neuronal lesions. The same was found in limited tests in monkeys inoculated with early mouse-passage material of low intracerebral titer in mice. The practicability of using this early mouse-adapted virus as a vaccine was demonstrated in tests on over 40 human volunteers. As the adapted virus continued to be passaged in mice, it increased in mouse intracerebral potency, and the intracerebral inoculation of such material in rhesus monkeys now produced in a varying proportion of these animals a paralytic disease, which, in clinical manifestations and pathological changes, closely simulated poliomyelitis. The immunological identity of the virus remained the same. These observations, which were made in this laboratory, were confirmed by Dr. J. L. O'Connor of Australia who privately reported that when the mouse-adapted virus was cultivated in chick embryos it also produced the paralytic disease after intracerebral injection in monkeys.

From a practical point of view, the issue is whether the pathogenic effects in the monkey are due to a qualitative change in the virus, which might entail an unpredictable danger if it were used in human beings, or to the inoculation of larger amounts of virus, which would involve no greater danger for the nervous system than the natural infection. An attempt will be made to resolve this issue by comparing the number of mouse-adapted and chick-embryo-passage viruses with the amounts of these materials required to produce paralysis in intracerebrally inoculated