drug trial has its own bundle of problems, and it is not very useful to set up a step-by-step procedure which is to be used by all drugs in all cases. However, the analysis in this paper brings out so many important points which the usual clinical investigator is either not aware of or simply does not take into consideration that it should be required reading for all the people engaged in clinical trials. I particularly like your method of showing how observed differences could be misleading in the absence of controls. This is especially interesting in your dose response relationship near the end of the manuscript."

I ask that this be included in the record at the proper place.

Senator NELSON. Very well.

Mr. CUTLER. Could we have a copy, Mr. Gordon?

Mr. GORDON. Certainly; I shall have it Xeroxed and give it to you.

(The documents referred to follow:)

[From Bulletin on Rheumatic Diseases, vol. 13, No. 2, October 1962, pp. 287–290]

HYDROXYCHLOROQUINE SULFATE IN RHEUMATOID ARTHRITIS, A SIX MONTH, DOUBLE-BLIND TRIAL[1]

This trial was conducted by the Cooperating Clinics Committee of the American Rheumatism Association, under the chairmanship of Dr. Charles Ragan. In attempting to create an instrument that can promptly and reliably evaluate a new and apparently promising drug, the Committee is acutely aware of the danger of a controlled trial that is inadequately planned and loosely conducted. The pseudoscientific verdict of such a trial is more misleading than the impression of a single experienced and critical clinician. A report[2] of the Committee's activities from 1958 through September 1961 describes the difficulties it met and the methods adopted to reduce them. Having gained experience in a pilot study ("dry run") and in a three month trial of hydroxychloroquine, the Committee decided to conduct a six month trial of the same drug, partly to obtain more experience and partly to learn more about the behavior of the drug. It recognized that there is considerable evidence that antimalarial compounds benefit certain types of rheumatoid patients to some degree under certain conditions; but it wished to know (1) whether a drug-placebo difference could be demonstrated on the available patients by the methods employed and (2) the magnitude of such a difference.

CRITERIA OF ADMISSION TO THE TRIAL

The subjects were to be outpatients, of either sex and any ethnic group, with classical or definite peripheral rheumatoid arthritis (A.R.A. Criteria, 1958 Revision[3]) which had become manifest after the sixteenth birthday and had been present for at least one year before the trial. There were to be present at the beginning of the trial at least three clinically active joints, as determined by tenderness on pressure and/or pain on passive movement. Joint swelling was not used as a criterion of eligibility but was recorded and used in assessment of progress.

Patients with certain specified diseases, such as polyarteritis nodosa, psoriasis, systemic scleroderma, ulcerative colitis and disseminated lupus erythematosus, were excluded, as were patients who, within the previous six months, had experienced pregnancy, childbirth, severe infection or a major surgical operation. Patients who were known or suspected to have ankylosing spondylitis were excluded, but it was not obligatory to screen all patients by sacroiliac radiology. Previous therapies that excluded patients were antimalarials, systemic steroid or phenylbutazone therapy within the preceding two months, and gold therapy within the preceding year, unless a full course within the year had produced no obvious effect.[4]

[1] From the Medical Statistics Unit and the Study Group on Rheumatic Diseases, New York University Medical Center. Mailing address: 112 East 19th Street, Room 1106, New York 3, N.Y.

[2] Mainland, D., *J. New Drugs*, 1:197, 1961.

[3] Ropes, M. W., et al., *Bull. Rheumat. Dis.*, 9:175, 1958.

[4] Probably in all clinical trials there are some implicit restrictions on the type of patient population to which the results can be generalized. Such restrictions are not easy to define and may be overlooked. In this trial, in which the primary objective was a study of the method of opeartion itself, it was desirable to obtain maximum, and willing, cooperation. Therefore it would have been unwise to insist that patients who appeared to be benefiting from another therapy be entered in the trial, or to risk the placebo treatment of patients who, in the opinion of the clinic chief or clinical observer, ought to be available for steroid therapy whenever it might appear desirable.