Here you say that most of your patients—these are your words—most—are being carried on dosage of 300 mg. On the other hand, the upper limit of approved dosage is 200 mg. Now, it seems to me that no doctor could repeat your experiences.

In other words, what I am questioning is can your studies be used as proof of efficacy for this drug?

Dr. ROTHERMICH. What is the date of that letter, sir?

Mr. GORDON. Your letter is dated June 12, 1963.

Dr. ROTHERMICH. This is the point I have made in my report to the JAMA. On long-term trials, we came to realize that patients experienced cerebral side effects worst when they suddenly had the drug thrust on them in high dosage, and we realized that there were certain times of day when they were more likely to have cerebral side effects than others. We also came to realize that if we began at a very low dose and built it up, they were far less likely to have any significant cerebral side effects.

Mr. GORDON. But you still cannot go over 200 mg. now. That is the approved dosage. You cannot go above that, but you went beyond it in your trial. You went up to 300 mg. and 400 mg., too.

My point is this: The studies that you made cannot be used as proof of efficacy of that drug, because nobody can duplicate that dosage today.

Dr. ROTHERMICH. No, I said that in my report to the Journal of the American Medical Association, too.

Mr. GORDON. Yes, I know that.

Dr. ROTHERMICH. That the dosage I used should not be used clinically and therefore physicians could not expect as high a degree of improvement as I had reported—this is stated in that article.

Mr. GORDON. I have it right here.

Dr. ROTHERMICH. You will see it right in the first part, if the synopsis, right at the bottom, that they should not use this high a dosage, that if they used it in smaller dosage and gradually increased it to tolerance, they would then begin to get effects which were not discernible at the early stages. This was proven repeatedly to us by patients, both on single-blind and on what we call double-blind study, although the statistician for the JAMA refused to allow us to use that term. We felt it was inadequate. But we did feel, as we developed greater experience with the drug, we came to realize that there was a significant number of patients who were getting benefit from indomethacin.

Now, what we were trying to show in our studies, and this was for the benefit of the profession, we felt obligated to report to them as fully as possible. We were trying to show what the maximum dosages were and what would happen if those maximum dosages were exceeded. We put six patients in the hospital, at the university, and subjected them to enormous single-dose trials, as much as 350 milligrams in one dose in the morning, and we made intensive studies on them throughout the day, using all kinds of parameters of study, because we felt we had to know what happened to a human with increasing dosage and where therapy was jeopardized by toxic effects.

Now, we were impressed early in our studies by the cerebral side effects, and I emphasized this: that since then we have learned that we can mitigate or minimize by certain techniques of therapy, by