always giving the drug on a full stomach or with milk at bedtime, as we had recommended in the JAMA report; that we avoid a morning dose; and that we avoid having the patient take it in association with caffeine ingestion, because we feel this aggravates the tendency for the cerebral side effects.

We also did learn that there is a certain idiosyncratic reaction, that some patients are exquisitely sensitive to this. I had one patient develop this in very bad form on 25 mg., whereas many patients can take much more and get no side effects.

Did I answer your question?

Mr. GORDON. Not exactly.

Dr. ROTHERMICH. Well, what do you want me to say?

Mr. GORDON. You are aware that 200 mg. is the maximum dosage approved by the FDA? That we can agree on.

Dr. ROTHERMICH. Yes.

Mr. GORDON. You also stated that most of your patients were on 300 mg., which was above the Food and Drug Administration limit, and that it cannot be duplicated today.

Then I asked you whether this could be used as proof of efficacy, given the present limitation by the Food and Drug Administration on dosage. I do not think I got a clear answer from you.

Dr. ROTHERMICH. I thought I answered quite clearly. I said that we got a remarkably high percentage of good and excellent results, but that in many of these cases the dose was at levels in excess of what should be used in general practice, and that physicians could not expect a comparable high percentage of good effects because they would necessarily have to use smaller doses.

Mr. GORDON. Let me read another excerpt from one of your letters. This is a letter from you to Merck & Co., dated October 12, 1963, in which you state:

> Indocin has an excellent beneficial effect in some cases of peripheral rheumatoid arthritis but only a good effect in a large percentage and there is a complete failure or ineffectiveness in a distressingly high percentage of such cases.

Does that add to what you said before?

Dr. ROTHERMICH. No, I think it simply amplifies it. I think, yes, I would say today that indomethacin will prove of significant clinical—because of the statistician, I have to avoid the word "significant"—that it will prove to be of appreciable clinical benefit, worthwhile for the physician to give his patient, in something over 50 percent of the patients—about 50 or 55 to 60 percent, in that area, on the limited dosages we have.

Mr. GORDON. This is Indocin as against nothing. How about Indocin as against aspirin?

Dr. ROTHERMICH. Now, I think this brings out a point that I appreciate. Many physicians around the land have a sort of all-or-none attitude toward treatment of rheumatoid arthritis. They give the patient this drug and if it is not beneficial, they stop it, and then they give him that drug. We do not believe in this, and I have said in other papers that combinations of therapy are vastly important in rheumatoid arthritis—that aspirin will contribute, let us say, 10- to 15-percent benefit; Indocin may add another 20-percent benefit; small doses of a corticosteroid may add another 30-percent benefit. Even giving paren-