There is just no connection between those two phrases. If the disease is cyclical, it would be difficult if not impossible to have a patient established and well controlled on indomethacin or any other therapy.

On the contrary, if any disease is under good control by an effective therapy, the introduction of a placebo would probably result in a relapse. Parallel examples of this could be demonstrated by the introduction of placebo in patients with congestive heart failure who are well controlled on digitalis therapy, patients with diabetes who are well controlled on insulin therapy, and patients with thyroid deficiency who are well controlled on thyroid therapy. Clinicians know that in such instances severe relapse would consistently follow each placebo trial. Applying the term "cyclical" to rheumatoid arthritis would suggest a lack of actual clinical experience with the disease. It is true that the disease is characterized in some degree by exacerbations and remissions, but these are highly capricious, both in onset and duration, and do not have any rhythmic circular aspects as suggested by the word "cyclical." A patient with rheumatoid arthritis may have an exacerbation with continuing activity of the disease for a year or two or more, and then he may suddenly develop a remission, that is, disease inactivity, for a variable period lasting a month, several months, or in a rare case, permanently. Exacerbations are much more protracted and tenacious, and remissions are usually brief and seldom total. Furthermore, even if the disease were cyclical, the introduction of a placebo would certainly not "probably be followed by a relapse." The introduction of a placebo relapse when the disease was apparently well controlled by a certain drug is evidence itself that the drug was actually controlling the disease, and this is reinforced when relapse is precipitated on more than one occasion by the repeated introduction of placebo.

Mr. GORDON. Doctor, I have here an article from Clinical Pharmacology and Therapeutics, by Drs. Albert M. Katz, Carl M. Pearson, and Joseph N. Kennedy.[1] I should like to read something from it:

> All eight subjects who received the drug (with benefit) followed by placebo experienced severe exacerbations within 24 hours of the change. One patient had a severe exacerbation lasting four days, after he was symptomatically the same as when taking indomethacin. Once again, he was given the drug, but derived no further benefit. The experience in this case cast some doubt upon the validity of accepting an exacerbation which occurs after a drug has been discontinued or replaced by a placebo as proof of the drug's efficacy.

Would you comment on that?

Dr. ROTHERMICH. I would agree that one case does not prove anything.

Mr. GORDON. He talks about eight subjects.

Dr. ROTHERMICH. He only mentions the one case, though, as an exception to that.

Mr. GORDON. Yes, and his conclusion is that the experience in this case casts some doubt upon the validity of accepting an exacerbation which occurs after a drug has been discontinued or replaced by a placebo as proof of the drug's efficacy.

Dr. ROTHERMICH. Do you not yourself think that one case out of eight is rather a weak statement?

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[1] See p. 3277, infra.