The duration of several studies is unusually long and the study populations relatively small. It does not appear reasonable that initial study standards, blinds, etc. could be maintained throughout these long periods. The inconsistency in which patients were observed bears this out.

Mrs. Tillman's report indicates the difficulties in reviewing these studies and in attempting to verify their summaries. These studies do reflect different standards of performance and interest among investigators. All indicate a spotty and poor picture of getting clinical evidence that has some meaning and reliability.

If one *must* use the information from these studies in considering the effectiveness of this drug and the acceptability of this NDA, he will need to assume that these studies provides valid and substantial evidence and are acceptable pieces of clinical work. This is a considerable assumption; or best, these studies are suggestive of a drug advantage over placebo. How much of an advantage and for how long a duration it persists cannot be determined from these data.

Results stated were Placebo weight loss per week—0.43 lbs., Fenfluramine 20 mg. weight loss per week—1.00 lbs., Fenfluramine 40 mg.—weight loss per week—0.54 lbs., and Dextroamphetamine weight loss per week—0.86 lbs. According to my calculations the average weight loss per week was—1.06 for Placebo—1.41 for Fenfluramine 20 mg.—1.06 for Fenfluramine 40 mg. and —0.89 for Dextromphetamine. My calculations and their calculations agree on the number of dropouts.

Without protocols I was not able to do very much in assessing the correctness of these statements. Entries on the case records for some studies lead me to believe that the blind were jeopardize or broken. For example, in Study #2050, there were dosage entries written at the top of the individual case records such as: 40 mg., 20 mg., etc. In another study (2002) the drugs were identified as p+p, p+f, p+m, etc.

As shown on the first page of my report these are very old studies, nearly all were completed in early 1967. Some are still stated to be incomplete. In one study (2009) there was a considerable dropout rate of about 50% in all drug groups. Only 30 subject finished 5 weeks of the study. The placebo had the smallest dropout rate, 33 percent.

I attempted to verify the summary data in #2025. In this study patients were given Fenfluramine for 8 weeks, and Placebo for 8 weeks. The firm reports an average weekly weight loss of: Fenfluramine—1.70 lbs., Placebo—1.46 lbs.

There were no placebo body weights listed on the data sheets; therefore, I could not verify this average. I computed an average for Fenfluramine patients that completed 60 days in this study. It is 0.42 lbs/week loss based on 28 patients.

On four of the case records medication is entered as "Caps" 40 mgm.

For Study #2016 none of the patients followed protocol which required crossover on 3 drugs. Some had crossover in two drugs with the identity of the second Rx in doubt. Of the 34 only 21 had some treatment with two drugs.

The protocol further states that observations were made every two weeks following the start of medication.

Very few subjects satisfied this requirement on both drugs. The treatment and visit regimen is very inconsistent and variable.

Only two subject were observed every two weeks for as long as 4 weeks.

Only two subjects were observed every two weeks for a long as 6 weeks.

Some patients were observed often irregularly for as long as 12 weeks on one drug. Their comparable duration on the control ranged from 2 to 7 weeks.

Some subjects had only 6 weeks on one Rx and only two or less on the crossover.

The durations of treatment both on a single drug and on its counterpart are so variable and spotty that the data cannot be summarized meaningfully. Further compounding difficulties in working with these data is duplication of case numbers for different subjects and different case numbers for the same subject.

Study #2020 was a double-blind, cross-over, randomized. Total length of study was 9 weeks, included 2–3-week peroids. Drug administered were 30 mg. Fenfluramine capsules and Placebo capsules. On the reference to raw data sheet the total average weight loss for those subject receiving Fenfluoramine was 1.4 pounds per week as compared ot 0.34 pounds per week on Placebo. My calculation averaged—1.33 pounds per week weight loss on Fenfluramine which included all subjects. Of those that completed the study (n=17), the average weight loss on the drug was 0.96 and for the Placebo average weight loss per week was 0.56.