headline implies that the results were obtained with "only one or two tablets a day."

(3) The mailing piece does not show fair balance. It attempts to exaggerate safety with a quotation from one paper (Finnerty), but, in an attempt to exaggerate efficacy claims, presents the report by Smith without revealing that twelve of the author's 45 patients had side effects such as nausea, vertigo, weakness and dizziness while on Salutensin, and that dosage in these cases had to be reduced in order to reduce the side effects. Further, the original Smith report in the NDA points out that several patients had side effects which were not "minimized" by reduction in dose and that two additional patients had side effects while on Salutensin; one with nausea, and another with abdominal pain. The Smith report shows that some patients on Salutensin experienced side effects on dosages (2 tablets daily) within the range recommended by the company.

Examination of the Salutensin Mailing Piece designated as "SH 3919 RV-2" disclosed the following:

1. The information in this mailing piece is lacking in its treatment of the drug's side effects, etc., as described above in the analysis of mailing piece No. SH 3852 RV.

2. The promotional section of this mailing piece contains the same faults as described above in relation to mailing piece No. SH 3852 RV, plus additional errors concerned with the use of two additional research papers.

a. The mailing piece misrepresents the work of Spiotta (reference #6, a report to Bristol Laboratories) and a graph "adapted from Spiotta."

(1) The company seriously misleads by failing to tell the reader that the study represented by the graph was on only one patient. As evidence, see use of same graph in the enclosed October 1961 mailing piece which specified that this is the result of a study of a single case. What is more, there were only two patients in the Spiotta study who received serial additions of the ingredients of Salutensin in the order shown in the graph, namely Saluron, protoveratrine A, and then reserpine.

(2) The company fails to inform the reader that when all the ingredients were added each of the 7 patients in this phase of this study was finally receiving 200 mg. of hydroflumethlazide, 0.5 mg. of reserpine and 0.8 mg. of protoveratrine A per day (equivalent to 4 Salutensin tablets) and that not all of the patients were receiving the three components in the same order shown in the graph. The failure to disclose this is misleading because the headline in the promotional section of the mailing piece implies that the graphed results were obtained with "only one or two tablets a day."

(3) The company also fails to tell the reader that Spiotta studied additional patients who received only 2 of the 3 ingredients of Salutensin; that he found, for instance, results with hydroflumethiazide plus reserpine which were similar to those with Salutensin in some cases. Such information does not support the idea in the promotion that Salutensin is better than a combination of only two of its three components, and that protoveratrine A is needed for more successful antihypertensive therapy. It is apparent that the Spiotta study (and it is the only study in the NDA on the serial addition of each Salutensin component) involved an insufficient number of patients to warrant making *any* sound judgment regarding the comparative efficacy claim which the headline states; "instead of just thiazide-reserpine, use Salutensin."

b. The mailing piece presents the work of Thomas (reference #8, a report to Bristol Laboratories) and a graph purporting to show the effectiveness of Salutensin in longstanding hypertension of moderate severity. The reader is led to believe that all 40 patients received only Salutensin, and that the dose, as claimed in the headline of the promotion, was "one or two tablets per day" for all patients. On the contrary the approved package insert itself merely states the following about results with Salutensin in the Thomas study:

(1) "Thomas noted that in *many* patients it was possible to eliminate hydralazine which patients had been taking previously." (Emphasis added)

(2) "Statistical analysis of the data indicated that the supplementary dose of reserpine could be considerably reduced while they were on Salutensin in order to maintain satisfactory control of their hypertension." At least ten of the patients were taking supplementary doses of reserpine.

(3) "A few of the patients required the addition of other antihypertensive (reserpine, hydralazine, inversine, Singoserp, chlorothiazide) agents with Salutensin in order to maintain satisfactory control of their hypertension." The "few" patients referred to above numbered at least ten.