Propoxyphene vs. codeine: Since propoxyphene is a "weak" narcotic, oral codeine is the most appropriate standard of comparison. My review of the literature in 1966 [Beaver, 1966] led me to the conclusion that propoxyphene hydrochloride was definitely less potent on a milligram basis than codeine, my best estimate of the relative potency of the two drugs being that propoxyphene is ½ to ⅔ as potent as codeine. In the interval, no definitive relative potency assay comparing graded doses of the two drugs has appeared, but the results of a few more recent clinical studies are generally consistent with the above estimate [Moertel et al., 1972; Sunshine and Kantor, 1960; Forrest, 1970]. Two other studies [Gruber, 1977; Young, 1978], designed to evaluate the analgesic effect of two consecutive doses of each of the study medications, suggest that propoxyphene napsylate 100 mg is approximately equianalgesic to codeine 60 mg, but deficiencies in data presentation make it impossible for me to judge the validity of this interpretation.

Propoxyphene vs. aspirin, acetaminophen or APC: The results of studies I reviewed in 1966 and a few more recent studies comparing propoxyphene hydrochloride 65 mg or propoxyphene napsylate 100 mg with aspirin 650 mg [Moertel et al., 1972], acetaminophen 650 mg or 1000 mg [Moertel et al., 1972; Hopkins et al., 1973; Berry et al., 1975] or APC 2 tablets are consistent with the evaluation which I presented to this Subcommittee in 1970; namely, that propoxyphene at recommended doses is certainly no more, and probably less, effective than usually used doses of aspirin, acetaminophen or APC.

Efficacy of propoxyphene as a constituent of drug combinations: Relatively little propoxyphene is used as a single-entity analgesic. Well over 80 percent of the prescriptions for propoxyphene products are for combinations of propoxyphene with acetaminophen, APC or aspirin. The rationale for these combinations is the same as that which underlies combinations of codeine and other yet more potent narcotics with these same antipyretic-analgesics; namely, production of more intense analgesia than can be provided by using a single agent and reduction of side effects by reducing the dose of any one analgesic. Although experimental evidence to substantiate these theoretical rationales is far from ideal or complete, there is a substantial body of evidence from well-controlled clinical analgesic trials to indicate that combinations of appropriately chosen doses of antipyretic-analgesics with narcotics do, in fact, achieve these objectives [Beaver, 1966; Beaver, 1975].

The slopes of the log dose-response curves of analgesic drugs are relatively flat, with the result that even successive doubling of the dose produces only modest increments of analgesic effect. Narcotics and antipyretic-analgesics such as aspirin are known to produce analgesia by different mechanisms, and the simple additive effect of a narcotic and an antipyretic-analgesic given together is often significantly greater than the analgesia achieved by doubling the dose of either drug administered alone. Furthermore, antipyretic-analgesics probably exhibit a ceiling of analgesic effect at about the usually used doses (650–1000 mg) and the usefulness of higher doses may also be limited by increased incidence of adverse effects and serious cumulative toxicity. Increasing doses of codeine, propoxyphene and other narcotics are associated with progressively increasing incidence and severity of gastrointestinal and central nervous system side effects and increased risk of drug dependence. The problem of providing adequate pain relief in the face of the above noted limitations of currently available analgesics may sometimes be circumvented by combining an optimal dose of an antipyretic-analgesic with an orally effective narcotic in a modest dose which is reasonably safe and well-tolerated.

Older relevant studies for both codeine and propoxyphene combinations are cited in my 1966 review. There are a few more recent studies which appear to demonstrate a significant increase in analgesic effect produced by the addition of propoxyphene to acetaminophen [Hopkinson et al., 1973], APC [Bauer et al., 1974] and aspirin [Wang and Sandoval, 1971]. Moertel and his associates showed a small increase in the effect of aspirin 650 mg produced by the addition of propoxyphene napsylate 100 mg, but the difference was not statistically significant.

ADVERSE EFFECTS OF PROPOXYPHENE

Adverse effects of propoxyphene at therapeutic dose level: At recommended dose levels (propoxyphene hydrochloride 65 mg or propoxyphene napsylate 100 mg Q4H, PRN for pain), propoxyphene produces an extremely low level of adverse effects. In fact, most studies are unable to demonstrate a significantly higher