emetics, antidepressants, tranquilizers, or alcoholic beverages during the study.

The following single agents and drug combinations were evaluated in each patient: placebo, 650 mg of aspirin, 65 mg of caffeine plus 650 mg of aspirin, 32 mg of pentobarbital sodium plus 650 mg of aspirin, 25 mg of promazine hydrochloride plus 650 mg of aspirin, 75 mg of ethoheptazine citrate plus 650 mg of aspirin, 100 mg of propoxyphene napsylate plus 650 mg of aspirin, 75 mg of ethoheptazine citrate plus 650 mg of aspirin, 100 mg of propoxyphene napsylate plus 650 mg of aspirin, 25 mg of pentazocine hydrochloride plus 650 mg of aspirin, 9.76 mg of oxydone plus 650 mg of aspirin, and 65 mg of codeine sulfate plus 650 mg of aspirin. Oxycodone is not marketed and was not available to us in pure form. We therefore employed the marketed Nucodan which contains oxycodone salts plus a minute amount of homatropine terephthalate and a small dose of an analeptic drug, pentylenetetrazol.

put in separate envelopes. To prevent any degradation resulting from interaction between drugs during storage, aspirin and the other component of the combination were always delivered in separate capsules, not mixed in the same capsules. Regular commercial forms of each study drug were used. Lactose (USP) was employed as a placebo and also as a filler for all study drugs. Each patient was given a single dose of each of the study preparations and placebo in randomized sequences according to the latin-square method (10 such latin squares, each 10×10 in size). One drug preparation was directly followed by another, and there was no planned placebo or no-treatment interval between active drugs. Each patient received only one test sequence of each of the study preparations.

Patients were instructed to take the planned single dose whenever they felt definite pain, but no more often than every six hours. The intervals between doses were variable, therefore, depending on the requirement of the patient for analgesia, but none were shorter than six hours. A corresponding variability occurred in the total period required for each patient study (median time for completion, five days; mean, nine days). In essence, this study was designed to reproduce the conditions under which a physician prescribes an analgesic with the direction that it be used every six hours as needed for pain.

With each dose, patients were asked to record the time of administration, the time when the onset of definite pain relief was noted, and the time when pain returned. They were also asked to record what percentage of their initial pain was gone at the time when they obtained maximum relief from the medication. Specific inquiry was made regarding the following side effects: upset stomach, nausea, vomiting, sleepiness, dizziness, impaired thinking, and excitement. Patients were also asked to mention any additional side effects they may have experienced. This information was recorded on a separate form for each drug dose.

It should be emphasized that these observations were recorded by the patient himself immediately after each drug-dose experience. They were not recorded or interpreted by a medical observer. It should also be emphasized that this was a study only of single-dose administration, not of prolonged administration.

Statistical analysis was done in stages. First, the possible effects of sequence of drug administration were evaluated. These proved to be negligible and, consequently, the data were reanalyzed ignoring sequence effect. Significance testing of differences of pairs of drugs, after overall

Table 1.—Comparative Therapeutic Effect of Analgesic Preparations As Reported by 100 Patients

Analgesic Preparation	Mean Percent Pain Relief*†	Rank Sum*‡
Codeine sulfate, 65 mg+aspirin, 650 mg	63(S)	429(S)
Oxycodone, 9.76 mg+aspirin, 650 mg	63(S)	430(S)
Pentazocine hydrochloride, 25 mg+aspirin, 650 mg	59(S)	490(B)
Propoxyphene napsylate, 100 mg+aspirin, 650 mg	55(NS)	511(NS)
Promazine hydrochloride, 25 mg+aspirin, 650 mg	51(NS)	556(NS)
Pentobarbital sodium, 32 mg+aspirin, 650 mg	50(NS)	581(NS)
Caffeine, 65 mg+aspirin, 650 mg	48(NS)	603(NS)
Ethoheptazine citrate, 75 mg+aspirin, 650 mg	48(NS)	619(NS)
Aspirin, 650 mg	51(NS)	554(NS)
Placebo	33(I)	726(I)

*Letters in parentheses indicate significance: S, significant superiority to aspirin alone ($P<.05$); B, borderline superiority to aspirin alone ($P \approx .05$); NS, no significant difference from aspirin alone; I, significant inferiority to all other preparations ($P<.05$).

†Least significant difference for superiority ($P=.05$) is 6.2, on the basis of a one-sided test for superiority of a preparation when compared to aspirin.

‡Least significant difference for superiority ($P=.05$) is 61.8, on the basis of a one-sided test for superiority of a preparation when compared to aspirin.

Table 2.—Sedative Effect of Analgesic Preparations Among 100 Patients

Analgesic Preparation	% of Patients
Promazine hydrochloride, 25 mg+aspirin, 650 mg	40*
Pentobarbital sodium, 32 mg+aspirin, 650 mg	27*
Oxycodone, 9.76 mg+aspirin, 650 mg	24
Pentazocine hydrochloride, 25 mg+aspirin, 650 mg	21
Codeine sulfate, 65 mg+aspirin, 650 mg	20
Propoxyphene napsylate, 100 mg+aspirin, 650 mg	18
Ethoheptazine citrate, 75 mg+aspirin, 650 mg	16
Caffeine, 65 mg+aspirin, 650 mg	14
Aspirin, 650 mg	11
Placebo	13

*Significant increase in sedation over placebo ($P<.05$).