preted in this manner. Repeated examination of the animals failed to reveal cogwheel rigidity or a tremor at rest.

Discussion. The fact that convulsions did not occur at the 25-mg/kg dose level indicates roughly that the greater the dose of chlorpromazine, the greater is the likelihood of seizures. Although the doses used in our experiments are quite high and exceed the usual dosages ordinarily employed in clinical practice they are comparable to the human dosage regimen (3400 mg of chlorpromazine in one day) reported by one clinic(6). Species difference prohibits quantitative extrapolation of these data to the clinic. However, the current widespread use of chlorpromazine warrants speculation as regards at least 2 clinical situations, (1) in epilepsy, and (2) in management of barbiturate and alcohol withdrawal(1,7,8,9). The use of chlorpromazine or any compound with convulsant properties may be hazardous in these situations.

Summary. Chronic administration of chlorpromazine in doses ranging between 44 and 77 mg/kg caused major convulsions in 4 non-epileptic monkeys and induced behavior suggestive of hallucinations in 3 of the same animals. The possible clinical significance of these findings was discussed.

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A Method for Evaluating both Non-Narcotic and Narcotic Analgesics. (23345)

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A simple and reliable method for evaluating non-narcotic analgesics in laboratory animals has long been desired. We, therefore, have developed the following method for its testing. The method is based upon the antagonism by both non-narcotic and narcotic analgesics of a "syndrome" induced by intraperitoneal injection of a phenyl quinone. The use of a similar syndrome produced by organic iodinated compounds has been reported by Vander Wende and Margolin(1) for testing narcotic analgesics in rats. However, the method was claimed not to be suitable for evaluating non-narcotic analgesics.

Method. In CF #1 male mice, a typical "syndrome" is produced by intraperitoneal injection of 0.25 ml of 0.02% aqueous solution of 2-phenyl-1,4-benzoquinone, henceforth referred to as phenyl quinone. This compound is dissolved in 5% ethyl alcohol and distilled water, and the solution maintained at 37°C. The "syndrome" is characterized by intermittent contractions of the abdomen, twisting and turning of trunk and extension of hind legs, beginning 3 to 10 minutes after injection and persisting for more than one hour. Only those mice that exhibit the "syndrome" repeatedly within 10 minutes following injection of phenyl quinone are used. All untreated mice will exhibit the "syndrome" at least once in a 5 minute period. Therefore, after administration of the test drug, a 5 minute observation period is repeated at 15-minute intervals. As the "syn-

TABLE I. Antagonism to the "Syndrome" of Non-narcotic Analgesics in Mice.

Drug*	Form administered	ED_{50} (C.L., p = .05) † mg/kg	Time of peak effect (min.)
Sodium acetylsalicylate	Aqueous solution	182 (137-242)	30
		160 (130-197)	45
Acetylsalicylic acid	Gum tragacanth suspension	165 (133-204)	30
Acetophenetidin	*Idem*	260 (186-364)	30
Aminopyrine	Aqueous solution	98 (80-120)	15

* Drugs are admin. orally. † C.L. = Confidence limits.

drome" occurs, the mice are removed from the cage. Those remaining are considered to show an analgesic effect. Several non-toxic graded doses of the substance being tested are spaced logarithmically and administered to different groups of mice. The dose-response curve is obtained by basing observations on the all-or-none response. The ED_{50}'s are determined according to the Litchfield and Wilcoxon Method(2).

Results. By this method, the approximate time of peak effect of the drug being tested can also be estimated. The ED_{50}'s and the time of peak effects for the 3 non-narcotic analgesics are summarized in Table I.

The method is also suitable for testing narcotic analgesics and the data obtained are compiled in Table II.

It was found that the "syndrome" can also be prevented if the analgesics are administered before injecting the phenyl quinone. No attempt was made to explore possible reuse of the mice.

In preliminary studies, attempts were made to elucidate the mechanism of this "syndrome" and its possible relation to pain sensation. It was found that barbiturates (phenobarbital sodium, pentobarbital sodium or butabarbital sodium), at doses producing loss of body righting reflex, did not prevent the "syndrome." Tranquilizers (meprobamate or chlorpromazine hydrochloride) prevented the "syndrome" only at doses producing marked depression, as did ethyl alcohol. Mephenesin prevented the "syndrome" only at paralyzing doses. However, since both non-narcotic and narcotic analgesics at less than depressant doses prevented the reaction to phenyl quinone, this suggests a high degree of specificity. The "syndrome" seems not to be associated with intestinal spasm which may be produced by the phenyl quinone injection, since atropine sulfate, adiphenine hydrochloride or dicyclomine hydrochloride, at doses exhibiting marked anticholinergic and antispasmodic activities, failed to prevent reaction. The "syndrome" ceased following administration of antihistaminics (tripelennamine hydrochloride or diphenhydramine hydrochloride) at doses producing stimulation. At one-half the dose producing stimulation, frequency and intensity of the "syndrome" was less than for the controls. It will be recalled that histamine was once proposed as the chemical mediator in cutaneous pain perception. Procaine hydrochloride given orally failed to prevent the "syndrome" at subconvulsive doses. However, intraperitoneal injection of 0.5% solution suppressed the "syndrome" immediately for 4-9 minutes. This clearly demonstrates that the "syndrome" is associated with centripetal impulses which arise following injec-

TABLE II. Antagonism to the "Syndrome" of Narcotic Analgesics in Mice.

Drug*	Form administered	ED_{50} (C.L., p = .05) † mg/kg	Time of peak effect (min.)
Morphine sulfate	Aqueous solution	1.15 (.88-1.50)	30
Meperidine hydrochloride	*Idem*	4.00 (3.10-5.20)	15
		6.30 (4.40-9.00)	30
Codeine phosphate	"	6.40 (4.78-8.55)	15
Methadone hydrochloride	"	.78 (.57-1.09)	30

* Drugs are admin. subcut. † C.L. = Confidence limits.

tion of phenyl quinone into the abdominal cavity. Much work (including spinal animals) remains to be done in order to elucidate the mechanism of this syndrome.

Discussion. It is not known whether the "syndrome" is closely associated with pain and the method may also lack some of the critical requirements for an ideal analgesic-testing method as outlined by Goetzl *et al.* (3). However, it has been shown that the "syndrome" caused by a noxious stimulus exerted in the abdominal cavity can be specifically blocked by local anesthetics (administered locally) and by analgesics (administered systemically). Furthermore, there is a good correlation between clinical efficacy of a number of analgesics and their potency as established by this method. In addition, the activity ratios of several narcotic analgesics are in general agreement with the experimental results reported in the literature. Therefore, it seems that the present method would serve best in evaluating, with the greatest clinical predictability, analgesic potency in laboratory animals.

Summary. A simple method has been designed for evaluating both non-narcotic and narcotic analgesics. The method is based upon the specific antagonism of analgesics to the typical "syndrome" produced by intraperitoneal injection of 2-phenyl-1,4-benzoquinone in mice. The antagonism occurs at doses far below those producing depression or other toxic effects. There is also a good correlation between clinical efficacy of a number of analgesics and their relative potency as established by this method. The endpoint is sharp, and the method is simple and quantitative.

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Purified Diets for Ruminants.* (23346)

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It is established that the greater proportion of the carbohydrates in the diet of ruminants is absorbed as lower fatty acids of which acetic, propionic and butyric predominate(1). It appears, moreover, that on a roughage diet little or no enzymatically digestible carbohydrate escapes ruminal fermentation to the volatile acids(2,3), and that acetic acid is a major tissue metabolite of ruminants(4,5). Thus, it can be reasoned that the peculiarity of ruminant nutrition in contrast to that of the simple-stomach animal may be in the kind of substrate in the diet serving as the primary source of energy rather than in terms of new nutritional entities.

Procedure.† The formulas of the experimental diets are presented in Table I. Diet 1 was formulated along the lines of purified diets used for small laboratory animals; diet 2 contained acetic, propionic and butyric acids to simulate the predominant volatile acid end products of ruminal fermentation on a forage diet(6); diet 3 contained cellulose to simulate a roughage diet. Thirteen lambs, 1 to 3 weeks old, were separated from their dams and placed on a regimen of fortified fresh cow's milk(7) administered *via* nippled bottles. At approximately 3 months of age, 12 of these lambs were allotted at random to the experimental diets in a randomized block design; the extra lamb was assigned arbitrarily

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