recurrent ulcer. Patients having the smaller segmental gastrectomy (40 to 60%) have not been followed for a sufficiently long time to permit full clinical evaluation of the operation(7). No recurrent ulcer has yet been observed; however, significant acid peptic digestion in the gastric juice was observed in 2 of 20 patients (grades 3 and 5; 10%).

It is too early, therefore, to conclude that the smaller segmental gastric resection (40 to 60%) will protect against recurrent ulcer in the same measure as the larger segmental resection.

Summary and conclusions. Measurements of acid and pepsin values and determination of degree of digestion attending perfusions of the cat esophagus with gastric juice, obtained from patients after gastric resection for duodenal ulcer, have been made. These results indicate that esophageal perfusion employing the gastric juice of patients previously operated upon is a sensitive method for evaluating the likely protective effect of such operations against recurrent ulcer. Following procedures known to be associated with recurrent ulcers, gastric juice from some patients can be shown to have proteolytic digestive power not unlike that seen with untreated duodenal ulcer. After operations known from clinical experience to protect fully against recurrent ulceration, the gastric juice of patients uniformly shows acid peptic digestion in the range of normals. This technic of assessment indicates that the protection afforded by some gastric resections is inadequate and that recurrence is likely to follow. The operation affording the greatest protection is definitely the larger (85-90%) segmental resection. Lesser grades of protection appear to be provided by the smaller (40-60%) segmental resection and the Billroth II procedure. Next in line would appear to be the protection afforded by tubular resection with antral denervation. Least protection against recurrent ulcer would appear to be afforded by tubular gastric resection and the Billroth I operation.

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Convulsions and Bizarre Behavior in Monkeys Receiving Chlorpromazine. (23344)

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That chlorpromazine may have convulsant actions in addition to its "tranquilizing" properties is suggested by a number of reports in the literature. Thus, in patients with epilepsy, Bonafede(1) reported that although addition of chlorpromazine to the therapeutic regimen without change in anticonvulsant medication did not augment seizure rates, reduction of the dosage of anticonvulsant drugs while chlorpromazine was being given was followed by an increased number of seizures in 26 out of 78 patients, one of whom died in status epilepticus. Bente and Itil(2) observed that intravenous injection of 50 mg of chlorpromazine augmented paroxysmal activity in the electroencephalograms of epileptic patients, and in one of their subjects a major seizure occurred later. Likewise, Kopeloff *et al.*(3) found that, in monkeys with focal cortical cicatrices produced by topically applied discs of alumina cream, intravenous injection of 2 or 10 mg/kg of chlorpromazine accentuated focal spike and sharp wave electroencephalographic activity, and on some occasions also

induced "spontaneous" seizures. Also, Das *et al.*(4) noted that in cats with midbrain transections ("cerveau isolé" preparations), intravenous injection of 0.2-0.5 mg/kg of chlorpromazine produced transient high voltage spike-wave discharges, and in 2 of these with basis pedunculi intact, convulsions developed. In addition, attention may be directed to the occasional occurrence of psychoses in man during therapy with chlorpromazine, as reported by Mality *et al.*(5).

These data suggest that chlorpromazine does exert convulsive actions, and that this property constitutes a hazard in therapy only in patients with preexisting epilepsy. However, in the course of a study designed for a different purpose (an attempt to produce a Parkinsonian syndrome) we found unexpectedly that, at certain dose levels, chlorpromazine can produce both seizures and hallucinatory-like behavior in "normal" monkeys. Since these findings may be of clinical significance they are reported briefly herewith.

Method. Four monkeys (*Macaca mulatta*) weighing 7.3 to 13.4 kg were used. The first dose of chlorpromazine (25.0 mg/kg) was given intramuscularly. Thereafter, the drug was given orally once-a-day. A uniform dose schedule was not practicable; in general, the dose was increased from 25 to 77 mg/kg for 13 to 22 days (Fig. 1). The temporal incidence of major convulsions was recorded in a special activity cage in which a spring-mounted floor was attached to a phonograph crystal pickup. The amplified crystal output drove an EEG oscillograph and pen-writing unit which recorded on very slowly moving paper (0.5 mm/sec). All animals except monkey No. 1 were monitored in this cage for 6 to 11 days before the drug was administered. Activity recording was continuous during the period of drug administration and withdrawal. Repeated attempts to induce seizures by vigorously prodding the animals were made throughout the experiment. Monkey No. 1 was not placed in the activity cage until the dose had been increased to 77 mg/kg and the first unexpected seizure was actually witnessed. Electroencephalograms were obtained occasionally while the animals were receiving the larger doses of chlorpromazine.

Results. Gross behavioral changes observed after administering the drug warrant brief summary. Grimacing and unprovoked aggressiveness, characteristic of the Rhesus monkey, were decreased. However, if animals were handled they resisted and tried to

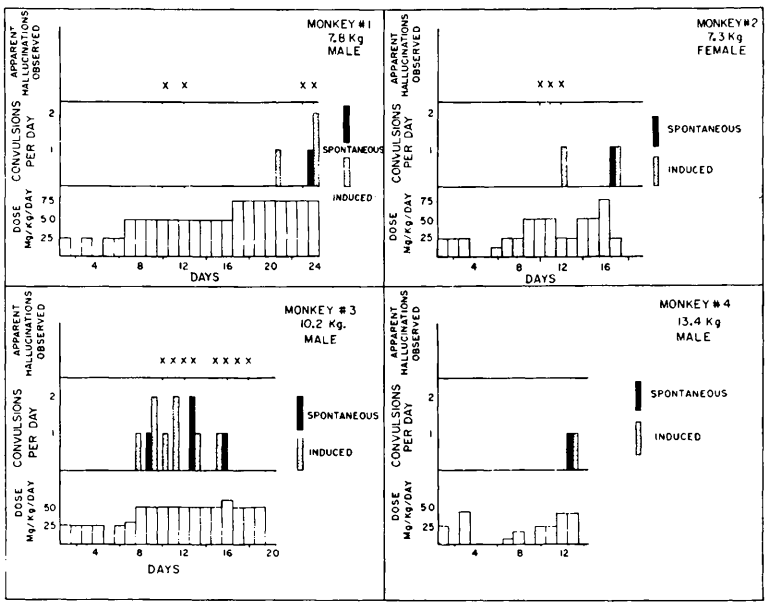

FIG. 1. Dose regimen and seizure incidence.

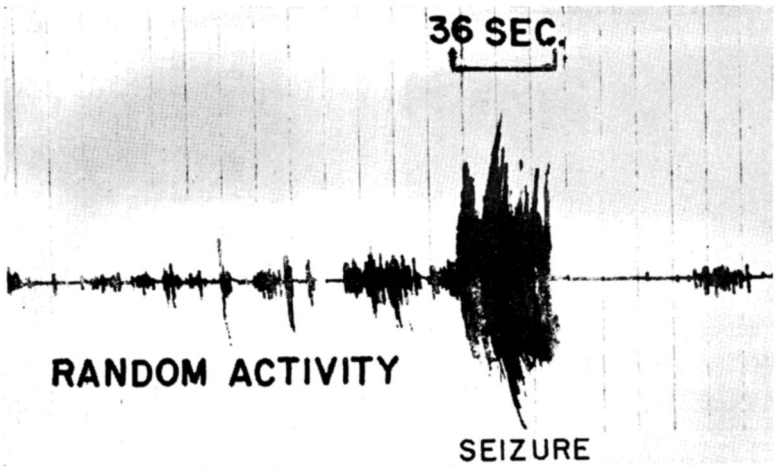

FIG. 2. Spontaneous convulsion, monkey No. 4.

bite. Tremulousness during movement or effort was a striking and consistent motor effect observed after the drug. This "action" tremor was rapid in frequency, small in amplitude, and involved all extremities.

Neither spontaneous nor induced seizures (observed after prodding or chasing) occurred before the drug was administered. In contrast, both of these kinds of major convulsions were observed in every animal while taking chlorpromazine. The total number of convulsions per animal ranged from 2 to 12. Details of seizure occurrence and dose regimen are depicted in Fig. 1. None of the animals had convulsions at the 25 mg/kg dose level. On the other hand, convulsions occurred in every animal on higher dosages which varied from 44 to 77 mg/kg a day. Animal No. 1 may have had convulsions when given 52 mg/kg of chlorpromazine, but activity data is lacking as indicated under method. The seizures involved all 4 extremities in rapid myoclonic jerking which lasted 30 to 80 seconds and probably resembled metrazole more than strychnine induced convulsions. The pattern as recorded in the activity cage is shown in Fig. 2. The longest interval between last dose of drug and final induced convulsion was 12 hours (monkey No. 1). In addition, animal No. 3 stopped having convulsions 3 days before the final dose of chlorpromazine. Seizures, therefore, were interpreted as not being due to withdrawal of chlorpromazine. Furthermore, the animals were not rendered permanently epileptic.

During these experiments the animals lost weight. However, daily administration of a multivitamin preparation (2 Unicaps) plus pyridoxine (20 mg) did not prevent seizures in the only animal treated in this way.

Monopolar scalp lead electroencephalograms did not reveal substantial differences from control tracings when the animals were quiet. Unfortunately, EEGs recorded during the occurrence of myoclonic jerks or focal seizures were obscured by muscle artefacts.

Bizarre behavior suggestive of hallucinations was observed in 3 monkeys. Monkey No. 3 searched the cage floor as though looking for an imaginary object, and occasionally leaped backward as if he were afraid of something. At other times, between seizures, the animal would repeatedly reach out and apparently grasp an imaginary object which would often be carried to his mouth. In animals Nos. 1 and 2, prominent movements of head and eyes resembling oculogyric crises and retrocollic spasms were observed, but these episodes were difficult to differentiate from the hallucinatory-like behavior already described.

The chief behavioral changes compatible with a Parkinson-like syndrome were hypokinesia as well as increased flexion posture of trunk and limbs. Facial masking was equivocal unless a reduction of grimacing is inter-

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-