all dosages in the following text refer to the salt form of the drugs. Clotting in the needle was prevented by the prior administration of heparin (400 units/kg. intraarterially).

Cryogenine was administered intraarterially during continuous preganglionic stimulation at frequencies ranging from 0.1–1.0 Hz. Following injection of the drug, ganglionic transmission was monitored continuously for 2 hr. Cryogenine (50–750 mcg.) failed to produce any detectable changes in either spike amplitude or afterpotential contour evoked by supramaximal or submaximal preganglionic stimulation. The submaximal stimulation was determined by selecting the voltage that would produce a ganglionic spike one-half the amplitude of that obtained with supramaximal preganglionic stimulation. It was determined that cryogenine (50–750 mcg.) did not evoke ganglionic firing. Moreover, no changes in the resting demarcation potential were observed as the result of cryogenine administration. Similarly, there was no evidence of asynchronous postganglionic discharge evoked by cryogenine (750 mcg.) in ganglia conditioned by repetitive supramaximal preganglionic stimulation (30 Hz. for 30 sec.) or in ganglia pretreated with *d,l*-isoproterenol HCl (2 mcg.).

Ganglionic discharges evoked by acetylcholine Cl (10 mcg.), 1,1-dimethyl-4-phenylpiperazinium iodide (5 mcg.), serotonin creatinine sulfate (10 mcg.), or KCl (500 mcg.) were unaffected by cryogenine (750 mcg.) administered 5 or 60 sec. earlier.

The postganglionic firing evoked by the intraarterial administration of tetramethylammonium Cl (5–10 mcg.) was not modified in ganglia pretreated with cryogenine 15 sec. earlier. Furthermore, the biphasic ganglionic demarcation potential produced by tetramethylammonium Cl (10 mcg.) and 1,1-dimethyl-4-phenylpiperazinium iodide (5 mcg.) was unaltered by the previous administration of cryogenine (750 mcg.). The postganglionic firing produced in response to physostigmine salicylate (200 mcg.), oxotremorine picrolonate (75 mcg.), and 4-(*m*-chlorophenylcarbamoyloxy)-2-butynyltrimethylammonium Cl (25 mcg.) was unaffected by the administration of cryogenine (750 mcg.) prior to or during the evoked asynchronous discharges. Moreover, there were no apparent alterations in the enhanced level of firing evoked by these agents in ganglia pretreated with *d,l*-isoproterenol HCl (2 mcg.) or in ganglia conditioned previously by repetitive supramaximal preganglionic stimulation (30 Hz. for 30 sec.). Cryogenine (750 mcg.) failed to prevent the complete abolition of the "muscarinic" firing that occurred almost immediately following the administration of atropine sulfate (2 mcg.).

In ganglia pretreated with cryogenine immediately prior to or 30 sec. before injection of 1,1-dimethyl-4-phenylpiperazinium iodide (5 mcg.), tetramethylammonium Cl (10 mcg.), levarterenol bitartrate (0.5 mcg.), epinephrine bitartrate (0.5 mcg.), or methacholine Cl (50 mcg.), no observable antagonism or enhancement of the ganglionic blockade produced by these compounds was noted.

The lupine alkaloids (cytisine, sparteine, *etc.*) are reputed to possess a nicotinelike common denominator pharmacologically and some structural similarities with possible metabolic degradation products of cryogenine. Previous studies demonstrated, however, distinct differences between the two groups in regard to cardiovascular, anti-inflammatory, and psychopharmacologic activity (2–4, 9). The present study showed cryogenine to be devoid of any ganglionic activity at the relatively high dose levels employed. Numerous nonsteroidal anti-inflammatory drugs presently in clinical use inhibit vasoconstriction produced by a variety of vasoactive agents (10). While the anti-inflammatory efficacy of cryogenine does not appear to be related to gangliotropic activity, its actions might still be explained by interference with inflammatory mediators or tissue reactions at the neurovascular or cellular level.

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Urinary Excretion of Chlorpromazine and Chlorpromazine Sulfoxide in Four Patients on Different Days

Keyphrases ☐ Chlorpromazine and sulfoxide—urinary excretion, human ☐ Urinary excretion, chlorpromazine—daily variations

Sir:

Urinary concentrations of chlorpromazine in individuals receiving this drug were determined (1–3). The results showed wide variations among the persons tested, in spite of the fact that the same dose was administered. However, the data do not indicate whether a patient excreting low quantities of the drug on the day of

collection will always excrete low amounts or whether he might differ in the excretion of chlorpromazine on different days. To determine if daily variations do exist, we measured the urinary concentrations of chlorpromazine and one of its metabolites, chlorpromazine sulfoxide, in four patients with schizophrenic reactions for 6–8 days.

Four male patients (identified as C, F, K, and M) with schizophrenic reactions, who had been hospitalized for more than 1 year[1] and who had been on chlorpromazine for more than 6 months, were chosen for this study. Drug therapy was discontinued for 2 days before the first urine collection. During the study, all four patients received 200 mg. chlorpromazine orally in tablet form each day at 7:45 a.m. No other medication was given, except that C received 75 mg. of desipramine hydrochloride[2] daily.

The daily routine of the patients, with the exception of the urine collections, remained undisturbed. Because of hospital routine, urine was collected at 7:00 a.m., followed by three collection periods of 7:00 to 11:00 a.m., 11:00 a.m. to 1:00 p.m., and 1:00 to 3:00 p.m. Hollister *et al.* (3) showed that, within an 8-hr. period, patients normally excrete half the daily medication. Upon collection, the urines were refrigerated, frozen, and assayed within 3 weeks.

The assay method was essentially the method described by Salzman and Brodie (4). Urines were thawed and stirred; a 10-ml. aliquot was made alkaline and heated in a boiling water bath for 15 min. After cooling, chlorpromazine and chlorpromazine sulfoxide were extracted with heptane–isoamyl alcohol. The extract from the organic phase with 0.1 *M* acetate buffer, pH 5.6, was read as chlorpromazine sulfoxide, and the 0.1 *N* HCl extraction was read as chlorpromazine in a Beckman DU spectrophotometer at the appropriate wavelengths. Calculations were based on internal standards containing both chlorpromazine and chlorpromazine sulfoxide[3].

Figure 1 shows the partial excretion patterns of chlorpromazine and chlorpromazine sulfoxide in the four patients. The urinary concentrations of chlorpromazine and chlorpromazine sulfoxide are in the same range as those reported for other patients (1–3). A comparison of the pattern of excretion of chlorpromazine and chlorpromazine sulfoxide by the same patient on different days shows that the chlorpromazine pattern was rather consistent in Patients M, F, and C, whereas K showed considerable variations. The excretion pattern of chlorpromazine sulfoxide on various days was most similar in Patients M and F and most dissimilar in Patients C and K. The ratio of the concentrations of chlorpromazine sulfoxide to chlorpromazine varied least in Patients M, F, and K and most in Patient C. Patient M received his chlorpromazine dose in liquid form for the last 4 days of this study; this did not change his typical excretion pattern. A comparison of the urinary excretion of chlorpromazine and chlorpromazine sulfoxide on a given day among the four patients shows the variations others have reported.

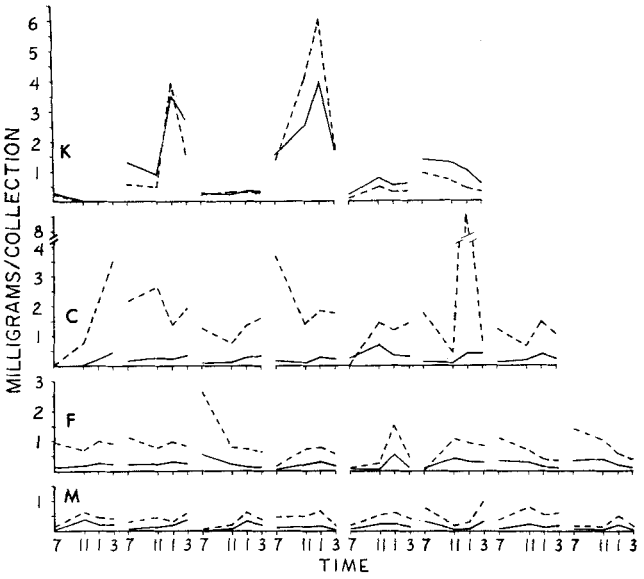

Figure 1—*Partial daily excretion pattern of chlorpromazine and chlorpromazine sulfoxide in four patients receiving 200-mg. tablets of chlorpromazine daily at 7:45 a.m. Daily collection was started at 7:00 a.m. followed by three periods of: 7:00 to 11:00 a.m., 11:00 a.m. to 1:00 p.m., and 1:00 to 3:00 p.m. Collections were on successive days with a 4-day interval indicated by space in baselines. Key: chlorpromazine, —; and chlorpromazine sulfoxide, - - -.*

In summary, the partial excretion pattern of chlorpromazine and chlorpromazine sulfoxide after administration of 200 mg. of the drug was studied in four patients with schizophrenic reactions for 6–8 days. Two patients remained rather consistent, while the other two showed relatively large daily fluctuations in chlorpromazine and chlorpromazine sulfoxide excretion during this period. The results indicate the need for more long-term studies on drug metabolism and excretion in individual patients.

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[2] Norpramine.
[3] Provided by Smith Kline and French Laboratories, Philadelphia, Pa.