showed enlargement of cells with vacuolar degeneration of cytoplasm, enlargement of nuclei and nucleoli. Furthermore, the number of mitoses was decreased. Numerous cells showed nuclear alterations as commonly encountered during necrosis such as pyknosis, karyolysis and karyorrhexis. 3. Histopathological examination of organs of mice treated with SK 3818 and SK 4614 revealed lesions similar to the ones occurring during administration of nitrogen mustards: intestinal damage and depletion of myeloid and lymphoid system with leucopenia (granulocytopenia and relative increase of mononuclear cells) in the peripheral blood.

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The Central Nervous Depressive Effect of Khellin. (19055)

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Khellin, a glucoside isolated from the plant *Ammi visnaga*(1-3) has been tested clinically in recent years as an antispasmodic agent and a coronary dilator, principally in the management of angina pectoris. Clinical results from different laboratories are varied both as to its efficacy as a smooth muscle relaxant and its toxic effects(4-8). Insomnia, somnolence, light-headedness, dizziness, nausea and vomiting have occurred in patients receiving therapeutic doses of the drug. While the pharmacological action of Khellin on the cardiovascular system and the smooth musculature has been extensively investigated (9-11), no study apparently has been made of its central nervous action. In our toxicological studies, it was observed in mice that Khellin both depresses and excites the central nervous system. Depression occurs prior to excitement, which appears only with large doses. The depression is mild but of long duration. Excitement begins with an increase in motor activity, followed by clonic convulsions indicating stimulation of nervous centers above the medullary levels. Such an action may produce some of the toxic effects of Khellin in man.

Since sedation is of value therapeutically in patients suffering from angina pectoris or from chronic bronchial asthma(12,13), the central depressive action of Khellin may be likewise effective in the relief of angina or asthmatic attacks. With such a view in mind, the central nervous depressive action of Khellin was investigated in cats, rats and mice. The results are presented in this report.

Methods and results. A. *Anti-caffeine effect.* This was determined with jiggle cages in rats receiving a stimulating dose of caffeine by the procedure of Schulte and associates(14). Activity was measured and recorded in terms of the total number of revolutions of the work

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TABLE I. Effect of Khellin on Activity of Rats Stimulated by Caffeine.

Caffeine, mg/kg S.C.	Khellin		Work performance		
	mg/kg oral	Toxic signs	Revolutions, 5 hr	Diff. in activity	% reduction of activity*
0	0		25.4		
30	0		97.1	61.7	
30	2.5		69.2	43.8	29
30	10		61.2	35.8	42
30	20		38	12.6	79.6
30	40	Slight depression	23.3	−1.9	100

* $\frac{\text{Activity by caffeine alone} - \text{activity by caffeine plus khellin}}{\text{Activity by caffeine alone}} \times 100.$

TABLE II. The Anticonvulsant Property of Khellin.

Anti-electroshock activity							Antimetrazol activity		
Cats			Rats		Mice		Rats		
Dose, mg/kg oral	Toxic signs	Rating	PD_{50}, mg/kg oral	Toxic signs	PD_{50}, mg/kg oral	Toxic signs	Dose, mg/kg oral	Toxic signs	Rating
200* single	Mod. dep.	1+	42	Sl. dep. at 30	250	Sl. dep. at 25	500§	Sl. dep.	4+
100† 2 daily	Deep dep.	3-4+					250	"	4+
							125	"	3+
50† 2 daily	Sl. dep.	0-1+					63	"	1+
							31	None	0

* 3 cats, one died next day.
† 3 " all " " ".
§ Lethal.

TABLE III. Combined Hypnotic Effect of Khellin and Pentobarbital Sodium in Mice.

No. animals used	Khellin, mg/kg oral	Pentobarbital-Na, mg/kg Ip.	Sleeping time		"P"
			Mean ± S.E. (min)	Diff.*	
40	0 (control)	50	23.44 ± 1.04		
40	1	50	37.15 ± 1.04	13.71	.01
20	2.5	50	50.12 ± 1.09	26.68	.01
20	5	50	91.20 ± 1.15	67.76	.01

* Difference in avg sleeping time between controls receiving pentobarbital only and mice receiving pentobarbital plus khellin.

adder throughout the experiment of 5 hours. Caffeine alkaloid, 30 mg/kg in 5 ml of 0.9% saline, was given subcutaneously; within 2 minutes, Khellin suspended in 7% gum acacia was administered orally. Fifteen male Sprague-Dawley rats weighing around 150 g, without food for 16 hours, were used for each dose level. The results in average values are given in Table I. It is seen that 10 mg/kg of Khellin, a non-hypnotic dose, will suppress about half the activity induced in rats with 30 mg/kg of caffeine.

B. *Anticonvulsant property.* The anticonvulsant activity of Khellin was investigated against electro-shock convulsions in cats by the method of Putnam and Merritt(15) and in rats and mice by the method of Toman, Swinyard, and Goodman(16), and against metrazol-induced convulsions in rats by a procedure described elsewhere(17). As the results in Table II indicate, the anticonvulsant activity of Khellin is attributable to its sedative and hypnotic effect. Khellin is more toxic for the cat than for the rat or the mouse. No excitement occurred in the cat after ingestion of a lethal dose of Khellin.

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C. *Hypnotic effect.* Hypnosis does not occur in animals receiving increasing dosage of Khellin. To study the influence of Khellin on hypnosis, the joint effect of Khellin and pentobarbital was determined in mice by the duration of sleep. The increase in sleeping time due to Khellin was taken as a measure of its central depressive effect. The results in Table III were obtained in groups of 20 and 40 mice which received a suspension of Khellin in 7% gum acacia orally half an hour before 50 mg/kg of pentobarbital was injected intraperitoneally. The duration of pentobarbital-hypnosis was definitely prolonged with 1 mg/kg of Khellin; with 5 mg per kg it was 4 times as long as that by pentobarbital alone.

Summary. Khellin has been shown to be effective in suppressing excitement in rats induced by caffeine. At slightly depressive levels, it is more effective against metrazol than against electrically induced convulsions. The central nervous depression produced by Khellin is mild but of long duration; with increasing dosage this is followed in mice by excitement.

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Factors Contributing to the Difference in Propylthiouracil Goitrogenesis in Rats and Guinea Pigs. (19056)

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In marked distinction to the rat, dietary thiouracil goitrogenesis in the guinea pig requires prolonged administration of the drug (1,2). On the other hand, administration of thyroid stimulating hormone readily produces a goiter(3). It seems probable that the explanation of this species difference would be concerned with one or all of the following classes of factors: (1) the concentration and effectiveness of thiouracil in the thyroid; (2) the rates of synthesis, excretion and utilization of the thyroid hormone; and (3) the threshold for increased thyrotrophin production and the goitrogenic capacity.

This report is concerned with two questions: (1) Is propylthiouracil equally effective in inhibiting thyroid hormone synthesis in both the rat and the guinea pig, and (2) Is thyroid hormone synthesized at comparable rates in these species. We have investigated these problems by measuring the effect of propylthiouracil on the rate of I^{131} incorporation into the protein of rat and guinea pig thyroid slices *in vitro*. That I^{131} incorporation under these conditions represents thyroid hormone synthesis has been shown by the work of Morton and Chaikoff(4).

Methods. Guinea pigs weighing 600-800 g, and Sprague-Dawley rats weighing 150-250 g were used regardless of sex. They had been fed stock diet for at least 2 weeks prior to use. The animals were sacrificed by a blow on the head, and the thyroids were rapidly removed, trimmed, weighed and transferred to iced containers. The glands were sliced as uniformly as possible. This usually meant division of each lobe into 3 to 4 slices for the guinea pig, and into 2 for the rat. When necessary, the lobes from several animals were combined to furnish sufficient tissue for the separation procedures outlined below. All glands were divided at the isthmus, and slices from one lobe were incubated with propylthiouracil, while those from the other lobe were used in the

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