Results and Discussion.—The results of these experiments are presented in the Table. It will be seen that administration of methionine half an hour after irradiation brought back the excretion levels of creatine and N'-methyl-nicotinamide to normality, but it does not appear to have any effect on the excretion of creatinine. This continued to be high as in the case of untreated irradiated animals.

Administration of methionine half an hour before irradiation does not seem to control the increased excretion of creatine and creatinine. The only effect it had was to restore the N'MeNA levels to normality. Similarly, the excretion of nitrogen continued to be high in both the groups, thereby showing that the increased catabolic activity is not reversed by methionine.

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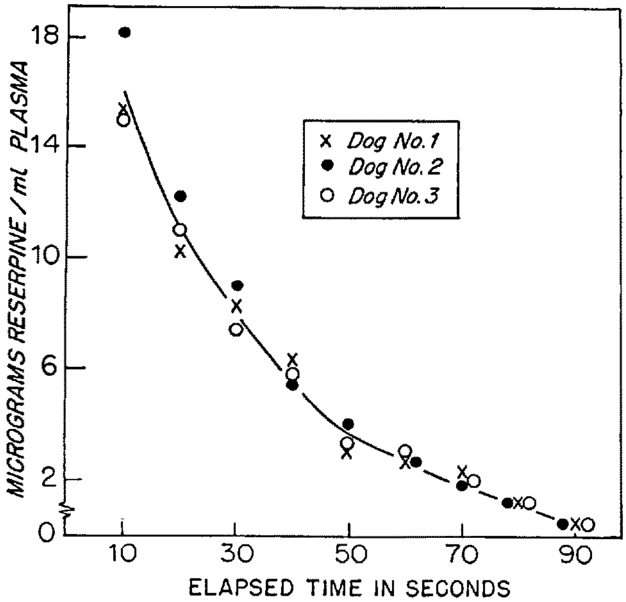
Zusammenfassung

Die Möglichkeit wurde geprüft, durch Zugabe von Methionin die Kreatin-, Kreatinin-, N'-Methylnicotinamid- und Stickstoffmengen nach Bestrahlung wieder herzustellen. Bei Methioninzugabe eine halbe Stunde nach Bestrahlung kehrte die Kreatin- und N-Methylnicotinamidmenge im Urin zur Norm zurück; wurde aber Methionin vor der Bestrahlung verabreicht, so blieben die Ausscheidungsmengen von Kreatin, Kreatinin und Stickstoff hoch.

Plasma Disappearance and Urinary Excretion of Reserpine (Serpasil®) in the Unanesthetized Dog*

Recent studies in the rat[1] and rabbit[2] indicate that the sedative effect of reserpine may not be related in time to the concentration of the drug in arterial plasma, but rather, to changes in brain 5-hydroxytryptamine concentration. Since *in vitro* and *in vivo* observations[3] suggest that there is a distinct species difference in the way reserpine is metabolized, the distribution of reserpine in arterial plasma of the dog, as a function of time, was investigated in an attempt to explain the particular sensitivity of this animal to small doses of the compound. The study was also to serve as a preliminary model for investigation of the renal handling of the drug.

A microcolorimetric method, based upon a general reaction for organic bases[4], was developed and utilized for the analysis of reserpine[5]. 6 experiments were performed on 3 unanesthetized female mongrel dogs weighing between 12·0 and 14·3 kg. They were trained and allowed free access to Purina Dog Chow and tap water. 25 ml of tap water per kg of body weight were given by mouth through a stomach tube one-half hour prior to the beginning of each experiment to insure adequate hydration and urine flow. Each animal was loosely restrained to a dog board in the supine position and an indwelling catheter placed in the bladder. The femoral artery was exposed under local anesthesia (distilled water) and a polyethylene catheter inserted into the proximal end. Control samples of urine and blood were taken. 15 min were allowed for surgical recovery. Reserpine, 1·5 mg/kg body weight, was then injected into the left external jugular vein over a 3 s interval, and arterial blood samples were taken at 10 s intervals for the next 2 min. The midpoint of the injection time was designated as zero time. Catheterized urine samples were collected at 30 and 60 min, and 24 and 48 h samples were cage-collected.



Arterial plasma disappearance of reserpine in the unanesthetized dog. The points plotted for each dog represent the averages of two experiments, and the resultant curve is a visual approximation. The broken line on the ordinate indicates the lower limit of sensitivity of the analytical method.

The disappearance of reserpine from arterial plasma is shown in the Figure. After intravenous administration, there was a prompt appearance of reserpine in arterial plasma with an average peak concentration of 16 μg/ml occurring during the first 10 s sample. Reserpine concentration then rapidly diminished to levels of less than 1·5 μg/ml of arterial plasma within 90 s.

Recovery of reserpine from urine is shown in the Table. Less than 2% of an injected dose of reserpine was recovered from urine within 24 h, and negligible amounts were found in the course of the next 48 h.

Sedation became evident at approximately 2–3 h after drug injection and persisted for 24–28 h. Tarry stools (markedly guaiac positive) were observed in all animals 3–6 h after injection. Stools were negative for occult blood within 24–48 h after injection. All dogs recovered fully in the course of one week.

The findings of a rapid disappearance from arterial plasma and low urinary excretion of reserpine are in general accord with observations of Sheppard *et al.*[1] in the rat using radioactive tracer doses of reserpine. Hess *et al.*[2], using 5 mg/kg of body weight in the rabbit,

* A grant for this study and the reserpine (serpasil ®) used in these experiments, were generously given by CIBA Pharmaceutical Products, Inc., Summit, New Jersey.

[1] H. Sheppard, R. C. Lucas, and W. H. Tsien, Arch. int. Pharmacodyn. *103*, 256 (1955).

[2] S. M. Hess, P. A. Shore, and B. B. Brodie, J. Pharmacol. *118*, 84 (1956).

[3] H. Sheppard, R. C. Lucas, and W. H. Tsien, Arch. int. Pharmacodyn. *103*, 256 (1955). – S. M. Hess, P. A. Shore, and B. B. Brodie, J. Pharmacol. *118*, 84 (1956). – H. Sheppard and W. H. Tsien, Proc. Soc. exp. Biol. Med. *90*, 437 (1955).

[4] B. B. Brodie and S. Undefriend, J. biol. Chem. *158*, 705 (1945).

[5] E. A. De Felice (to be published).

Recovery of reserpine from urine

Dog number	Cumulative percentage of injected dose recovered as reserpine*			
	30 min	60 min	24 h	48 h
1 12·0 kg	0·18	0·25	1·4	1·6
2 13·5 kg	0·12	0·40	1·9	2·0
3 14·3 kg	0·24	0·39	1·6	1·7

* Figures represent averages of two experiments performed on each animal.

found urinary excretion to be of a similar magnitude, but the disappearance from plasma was somewhat more delayed. Observations of Sheppard *et al.*[1], Hess *et al.*[2], Numerof *et al.*[6], and Glazko *et al.*[7] indicate that the rapid disappearance of reserpine from arterial plasma reflects a quick degradation of the compound and not extensive binding in tissues. In addition, Hess *et al.*[2] claim that the same duration of sedation, or of change in brain 5-hydroxytryptamine, is induced whether a small or a large dose of reserpine is administered. Therefore, it is unlikely that reserpine is acting through a degradation product.

Since the sedative effect of reserpine was most marked at a time when most of the drug had disappeared from plasma, the results of this paper are in accord with the hypothesis[2] that the central effect of sedation is not mediated through reserpine *per se*, but conceivably through 5-hydroxytryptamine changes in brain.

The disappearance of reserpine from arterial plasma does not appear to explain the marked sensitivity of the dog to small doses of the drug, but there is other evidence that this animal metabolizes reserpine differently than other species[8].

The negligible urinary excretion of reserpine precludes further studies on the renal handling of the drug.

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Résumé

La réserpine administrée par voie intraveineuse chez le chien à dose de 1,5 mg/kg de poids du corps disparaît rapidement du sang artériel. Les quantités de réserpine retrouvées sont de 1,5 μg/ml au bout de 90 s. Il n'y a pas de corrélation entre les quantités de réserpine contenues dans le sang et le début ou la durée de la sédation produite. Au bout de 48 h, moins de 2% de la dose injectée est retrouvée dans l'urine. Etant donné la rapidité avec laquelle la drogue disparaît dans du sang, on ne s'explique pas l'hypersensibilité du chien à son égard. L'excrétion rénale négligeable de la drogue chez le chien ne permet pas d'espérer que des études de clairance rénale éclaircissent le mécanisme d'action de la réserpine chez cet animal.

[6] P. Numerof, M. Gordon, and J. M. Kelly, J. Pharmacol. *115*, 427 (1955).

[7] A. J. Glazko, W. A. Dill, L. M. Wolf, and A. Kazenko, J. Pharmacol. *118*, 377 (1956).

[8] H. Sheppard and W. H. Tsien, Proc. Soc. exp. Biol. Med. *90*, 437 (1955).

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Short-term Oscillations in Sign of Phototaxis in the Eyed Hawk Caterpillar (*Smerinthus ocellata* L.)

In a previous communication[1], we have discussed the cyclic changes in phototaxis occurring in the later instars of the Eyed Hawk's larval life. The data then presented always referred to the average behaviour of a group of larvae of the same age, but in our experiments we have recorded the movements of each larva individually. Further analysis of these records has revealed an interesting fact. At all ages during the 3rd to 5th instars, periods in which the larva crawls towards the light alternate with periods in which it moves in the opposite direction (Fig. 1). This suggests that the sign of the caterpillars' phototaxis is subject to somewhat irregular short-term oscillations between positive and negative.

However, before we can accept this conclusion, another possible explanation must be considered. The occurrence of bouts of crawling in the 'wrong' direction in larvae showing an over-all preference for a given orientation, might be regarded merely as a sign that the phototaxis of these larvae is rather weak, the wrong movements being chance deviations from the 'intended' course. The following argument can be advanced against this hypothesis as the sole explanation of our findings. Figure 2 illustrates our scoring method (for further details, see the earlier paper). It will be seen that the sum of the two angles comprising our 0 directions is $^2/_3$ of the angle comprising either the + or the – directions. Hence, if the bouts of wrong scores were due to errors made by the larvae, we should expect the number of 0 scores to be greater than (or at least equal to) $^2/_3$ of the number of wrong scores in each test, as large chance deviations, leading the larva into the wrong sector, will be less frequent than smaller ones which take it only into the 0 sectors.

The facts do not confirm this expectation. In only 43 out of 133 larvae tested at varying ages in the 3rd to 5th instars, the difference expected on the hypothesis under consideration was actually found. In all others, the number of 0 scores was smaller than $^2/_3$ of the number of wrong scores. Moreover, the expected difference occurred more frequently among larvae giving a relatively small proportion of wrong scores than among

[1] L. de Ruiter and IJ. van der Horn, Nature *179*, 1027 (1957).

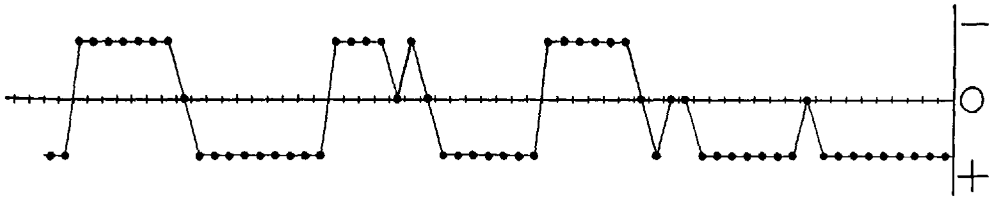

Fig. 1.—Third instar larva, observed at one-minute intervals. Alternation of movements towards and away from the light source (indicated by dots above and below the abscissa, respectively). Time scale: minutes.