crepancy between the findings in patients with obstructive jaundice and in our experimental animals. 2. The rapid increase in thoracic duct lymph following common duct obstruction confirms the work of Mayo and Greene (5) indicating that the preferential route through which bile acid reaches the blood stream is through the lymphatics.

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Alkyl Nitrites XVI. Comparative Depressor Responses of Octyl Nitrite and Glyceryl Trinitrate. (18623)

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Studies from this laboratory on the pharmacology of high molecular weight alkyl nitrites (1) led to the use of octyl nitrite (2-ethyl-n-hexyl-1-nitrite)(2) in the treatment of angiospastic disease. Octyl nitrite exerts a vapor pressure of 3.3 mm at 25°. This permits the compound to be used clinically in an inhaler and administered by inhalation for the purpose of producing prompt coronary dilatation. Comparisons of the relative efficacy of octyl nitrite and glyceryl trinitrate as therapeutic agents have been made by Freedberg *et al.*(3) and Russek and Anderson(4). The latter investigators found that the inhalation from the octyl nitrite inhaler elicited a therapeutic response comparable to the sublingual administration of 1/200 to 1/300 grain glyceryl trinitrate tablet.

We have been concerned for more than a decade in the mechanism of action of the organic nitrates and nitrites(5,6). Our studies have shown that their actions on a cellular level involve different enzymic components in arterial tissue. The purpose of this study is to assess the relative potency as depressor agents of octyl nitrite and glyceryl trinitrate, and to explore their absorption.

Methods employed. Mongrel dogs weighing from 6 to 13 kg were used in these experiments. The animals were anesthetized with ether. Blood pressure was recorded from the carotid artery with a mercury manometer. Electrocardiograms were made with a "Cardiette." Intravenous injections were made into the saphenous vein; all injections were diluted to 5 cc with normal salt solution. Inhalations of octyl nitrite were achieved by removal of the tracheal ether bottle and replacing it with a 100 cc container into which 0.2 cc of octyl nitrite had been placed.

Results. In 10 dogs, octyl nitrite was administered sublingually in doses of 0.2 cc. There were 12 doses given. Not any of these elicited a depressor response, indicating that octyl nitrite is not absorbed from the buccal mucosa of the dog. Dissolving octyl nitrite in alcohol did not promote its absorption through the buccal membranes. Similarly, amyl nitrite was not absorbed sublingually. In the same dogs, glyceryl trinitrate was administered in the form of the official 1% spirit in doses of 0.2 cc. There were 11 doses given. In all of the 9 animals a depressor response was produced. There were wide variations in depressor response evoked by

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3. Freedberg, A. S., Spiegl, E. D., and Riseman, J. E. F., *Am. Heart J.*, 1941, v22, 519.

4. Russek, H. I., and Anderson, W. H., personal communication.

5. Krantz, J. C., Jr., Carr, C. J., Forman, S. E. and Cone N., *J. Pharm. and Exp. Therap.*, 1940, v70, 323.

6. Krantz, J. C., Jr., Carr, C. J., Bryant, H., *J. Pharm. and Exp. Therap.*, 1951 in press.

TABLE I. Depressor Responses of Octyl Nitrite and Glyceryl Trinitrate in the Dog. (Percentage fall in blood pressure).

	Octyl nitrite		Glyceryl trinitrate	
	Inhalation (.2 cc/dog)	Intravenous (1 mg/kg)*	Sublingual (.2 cc/dog)	Intravenous (.36 mg/kg)*
High	53.4	32.3	25.0	40.0
Low	16.7	9.8	8.5	25.0
Mean	33.4 $\sigma = \pm 9.4$	22.4 $\sigma = \pm 5.9$	17.0 $\sigma = \pm 5.8$	30.0 $\sigma = \pm 4.7$

* Dose of glyceryl trinitrate equivalent to that of octyl nitrite on a molar basis depending upon the nitrate and nitrite groups present in the respective molecule.
$C_3H_5(NO_3)_3 \simeq 81.9\%\ 3(NO_3)$ $C_8H_{17}NO_2 \simeq 28.9\%\ NO_2$

the sublingual administration of glyceryl trinitrate. The intravenous injection of the drug prior to the sublingual administration produced a refractoriness to the depressor response by buccal membrane absorption.

When octyl nitrite was placed in the inhaler bottle in quantities of 0.2 cc it evoked a marked depressor response in 10 dogs. The effect was prompt, occurring in about 10 seconds; the average fall of blood pressure was 33.4%. The duration continued until the respirator container was withdrawn. It appears therefore that depressor responses of great magnitude can be achieved with octyl nitrite over long periods of time as long as the vapors reach the alveoli. We(2) have shown previously that the coronary arteries share this response. There were no significant changes in the electrocardiograms of these dogs following the administration of these drugs with the exception of the characteristic tachycardia.

The two compounds were injected intravenously into 10 dogs at varying intervals to determine their relative depressor potencies. The assays were made on a molar basis dependent upon the nitrate or nitrite groups in each molecule (glyceryl trinitrate 81.9% nitrate; octyl nitrite 28.9% nitrite).

The data are shown in Table I.

Assays were also made on an equal weight basis to determine the minimal concentration which would elicit a depressor response (4 mm). When administered intravenously in 1 cc doses the threshold depressor concentration for octyl nitrite ranged from 1:250 to 1:1000. The threshold depressor concentration for glyceryl trinitrate when administered intravenously in 1 cc doses was found to range between 1:1000 to 1:10,000.

The data reveal that in this series of 10 dogs, glyceryl trinitrate is the more potent depressor. This obtains when the drugs are administered on an equal molar nitrite-nitrate basis. It is again manifested in the threshold concentration studies.

The studies revealed again the varying degrees of sensitivity to the depressor response which obtains in different dogs. Of special interest is the fact that sensitivity or refractoriness to a vasodilator of the nitrate type does not necessarily indicate that the same condition will obtain with the vasodilator of the nitrite type.

Summary. (1) Octyl nitrite unlike glyceryl trinitrate is not effectively absorbed through the buccal membranes of the dog. (2) Octyl nitrite is a powerful depressor agent in the dog when administered by inhalation. (3) Intravenously in the dog the depressor potencies of octyl nitrite and glyceryl trinitrate are in the ratio of 1 to 1.34 on a molar basis, depending upon the nitrite and nitrate groups respectively present in each molecule. On an equal weight basis the depressor threshold for glyceryl trinitrate was found to be between one-fourth and one-tenth that of octyl nitrite.

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