

mone in the injected extracts. Administration of the same hormonal treatment to 3 hypophysectomized non-exposed rats resulted in complete repair of the germinal tissue along with marked development of the interstitial cells of the testis.

It is concluded that the degenerative changes described in the male gonad are due to a direct

inhibitory action of the low atmospheric pressures on the germinal tissue of the testis. The histological and gonadotropic hormone content changes in the anterior lobe of the pituitary, for the period of low pressure exposure employed, probably represent a reflection of this inhibition.

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Local Anesthetic Activity of a Number of New Monohydrochlorides of Dialkylaminomethyl Phenyl *p*-Aminobenzoates.*

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The present studies are concerned with an appraisal of the local anesthetic activity of a number of new phenyl *p*-aminobenzoates (Table I) synthesized by Dr. R. L. Shriner[†] and associates in the Department of Organic Chemistry, University of Illinois. The technic described by Rose¹ was used to detect dermal anesthesia. Aqueous solutions of the compounds were injected in 0.1 cc volumes in guinea pigs shaved free of hair and the presence or absence of anesthesia determined by faradic stimulation of each area injected. Solutions prepared just prior to testing were used because precipitation of all derivatives is apparent shortly after preparation. As shown in Table I the new aminobenzoates produced insensitiveness to electrical stimulation for 79-99 minutes in 1.0% and 31-79 minutes in 0.5% concentration. In both 1.0% and 0.5% solution all compounds produced hyperemia followed in most cases by necrosis at the site of injection.

In order to assess topical activity, freshly prepared aqueous solutions of derivatives (I-IX) were instilled into, and allowed to re-

main in the conjunctival sac of rabbits for 2 minutes. Anesthetic activity was determined by touching the cornea with the rounded end of a fine glass rod. Absence of the winking reflex was taken as evidence of anesthesia. As shown in Table I, compounds I, II, and III in 1.0% solution were inactive. While definite anesthesia was not observed, a sluggish reflex occasionally was noted for 5-10 minutes after application of these substances. In 1.0% concentrations IV, V, VI, VII, VIII and IX exhibited anesthetic activity for average periods of 21-73 minutes (Table I). The depth of anesthesia after V, VIII and IX was greater than that produced by IV, VI and VII. In the present studies, local application of 1.0% cocaine hydrochloride caused anesthesia for an average duration of 18 minutes. The corneal reflex was abolished for an average of 50 minutes after compound IX in 0.5% solution but in this concentration all of the other derivatives were ineffective.

Since IX appeared to be the most interesting of the new compounds, its acute toxicity after subcutaneous injection in mice was compared with that of cocaine hydrochloride. The MLD of IX was found to be approximately 300 mg/kg and that of cocaine between 100-150 mg/kg (Table II).

Summary. Intradermally in guinea pigs the hydrochlorides of 9 new dialkylaminomethyl phenyl *p*-aminobenzoates were found

* This investigation was supported in part by the D. J. McCarthy Foundation.

† Samples of these compounds were made available for the present experiments by Dr. R. L. Shriner, Department of Organic Chemistry, University of Indiana.

¹ Rose, C. L., *J. Lab. Clin. Med.*, 1929, **15**, 128.

TABLE I.
Duration of Local Anesthesia.

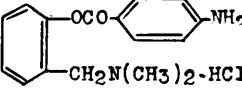
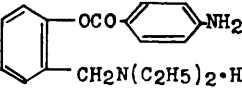
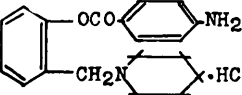
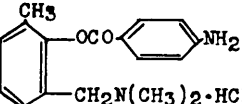
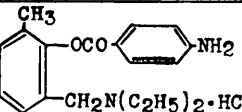
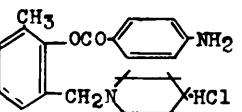
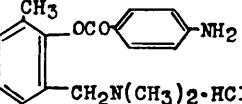
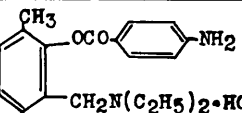
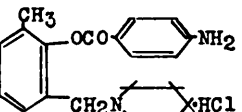
Formula	Code No.	Decomposition. °C.	Duration of Anesthesia in Guinea-pigs (Intracutaneous injection)		Duration of Corneal Anesthesia in Rabbits	
			Minutes		Minutes	
			1.0%	0.5%	1.0%	0.5%
	I	125-135°	88	69	0	-
	II	120-128°	94	62	0	-
	III	118-130°	79	31	0	-
	IV	185-190°	93	62	28	0
	V	180-185°	87	59	30	0
	VI	168-176°	92	75	21	0
	VII	199-203°	88	32	34	0
	VIII	143-149°	99	79	39	0
	IX	193-195°	93	66	73	50

TABLE II.
Subcutaneous Toxicity in Mice.

Compound	Dose, mg/kg	Mice died/Mice used
IX	250	2/13
	300	8/10
	350	9/10
	400	10/10
	500	10/10
Cocaine	75	2/10
	100	4/10
	150	9/10

to produce local anesthesia in 1.0% and 0.5% solution but all caused tissue damage at the site of injection. In 1.0% solution certain of

these derivatives abolished the corneal reflex after instillation in rabbit eyes. The hydrochloride of (2-piperidinomethyl-) 4,6-dimethylphenyl *p*-aminobenzoate (IX) was less toxic subcutaneously in mice and exhibited greater topical activity in rabbits than cocaine hydrochloride but practical application of the anesthetic action of IX or any of the new compounds is complicated by their instability in aqueous solution.

I wish to express my thanks and appreciation to Dr. A. E. Livingston for helpful suggestions and encouragement.

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Antihemorrhagic Vitamin Effect of Honey.*

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While working on the role of honey in the prevention and cure of nutritional anemia in rats, one of the authors was impressed by the fact that the coagulability of blood in the rats receiving a honey supplement was so high that it was sometimes extremely difficult to draw samples for the hemoglobin determinations. The natural antihemorrhagic vitamins K are fat soluble substances. However, Warner and Flynn¹ have shown that there are water soluble substances which show antihemorrhagic activity. Therefore, it was considered advisable to test honey for the presence of factors influencing the coagulability of blood.

The method followed was a slight modification of the vitamin K assay devised by Almquist² using chicks. Herring meal was used in the basal diet instead of sardine meal and the temperature of the thermostat in which

coagulability was determined was 37°C instead of 38°-39°C. In this procedure the only variable is the prothrombin level of the blood. Under these conditions the coagulability is referred to as "prothrombin time." Almquist² has found that a direct proportionality exists between $10 \times$ (reciprocal of the prothrombin time, in seconds) and the log ($10 \times$ vitamin K intake).

Three series of experiments were performed, shown in Tables I, II and III. These were carried out at different times using 3 different but fresh preparations of thromboplastin for determination of prothrombin time. Each series required a different set of normal and negative controls.

In the first series, shown in Table I, mixed sweet clover and white clover honey, alfalfa and buckwheat honey were tested. The first 2 were mixed with the vitamin deficient ration in the ratio of 1:4 by weight; the buckwheat honey was added to the ration in the ratio of 1:3. The supplements were offered for 4 days to the vitamin K deficient chicks after the depletion period. The control chicks were given a solution of 2-methyl-1,4 naphtho-

* Paper No. 1995, Scientific Journal Series, Minnesota Agricultural Experiment Station, St. Paul.

¹ Warner, E. D., and Flynn, J. E., *Proc. Soc. Exp. Biol. and Med.*, 1940, **44**, 607.

² Almquist, H. J., *J. Assn. Off. Agr. Chem.*, 1941, **24**, 405.