parts of a fiber's distribution were not equally responsive. From point to point the discharge varied, but always with a general gradient of increasing activity from the periphery toward the center of the field. Again, the fatigue of repetitive stimulation of one point certainly acted most intensely at that point, as did the denial of access of aqueous humor to any portion of the cornea. Finally, adaptation was appreciable only at the point stimulated, for a second stimulus applied as closely as possible to a first to which adaptation was complete, resulted in a second vigorous discharge in the same nerve fiber.

Putting these facts together, the sensory ending in the cornea emerges as all the terminal tissue of one nerve fiber. This is a unit, activity in any part of which probably involves the whole. Moreover, there is no evidence that activity in this unit influences in any way the activity of closely associated units. Functionally, the total corneal sensory mechanism appears as an aggregate of units, and not as a continuum. No evidence has been forthcoming of the presence of more than one sensory mechanism in the cornea. By analogy with the human, this should be pain. More convincingly, the wide extent of the ending, and the spread of activity throughout it, reflect one of the characteristics of the pain sense as subjectively studied, its lack of any but the most general localization. Likewise, the initially rapid, but then often incomplete adaptation of the mechanism repeats another aspect of the same subjective experience. Therefore, perhaps, one may see in the properties of the sensory mechanism studied in the cornea, peripheral determinants of the central processes resulting in the sensation of pain.

7776 C

Oral Toxicity of Ortho-n-alkylphenols to White Rats.*

HAROLD W. BROWN AND PAUL D. LAMSON.

From the Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tenn.

In a search for an active non-toxic ascaricide which has been going on in this department for several years, several series of alkylphenols have been studied for their ascaricidal action as well as

* The funds for carrying out this work were given by the International Health Division of the Rockefeller Foundation.

their toxicity. It was found that in the 6-alkyl-meta-cresols[1] and the 4-n-alkyl-resorcinols[2] that the oral toxicity to rats decreased with increase in length of the alkyl radical. We wish to report the findings on the oral toxicity of ortho-n-alkylphenols. These substances were synthesized in this laboratory by Dr. R. W. Stoughton, Dr. R. Baltzly, and Mr. A. Bass.

The method of giving these substances to the rats has been described previously.[1] Five per cent ethylene glycol was added to phenol in order to liquefy it so that it might pass down the stomach tube. The alkyl-phenols are, however, liquids. The results of these toxicity studies are given in Fig. 1.

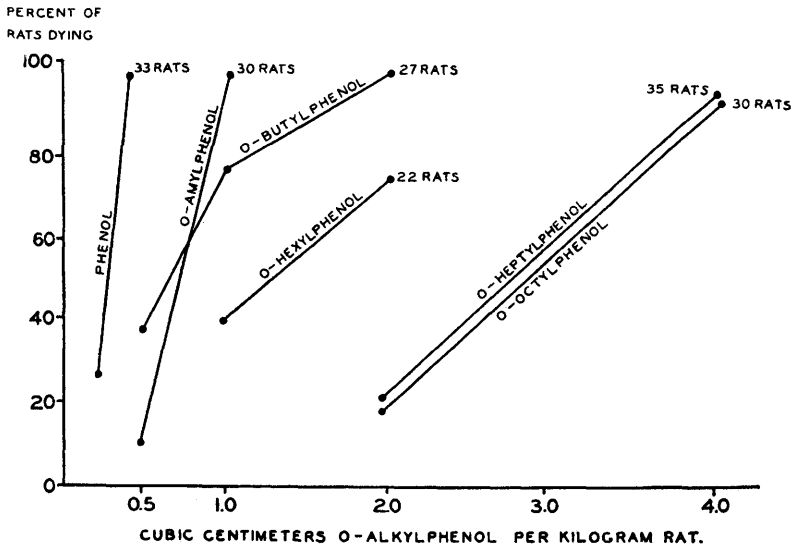

FIG. 1.
Toxicity of Ortho-alkylphenols to White Rats.

It will be seen that the toxicity of these substances decreases with increase in length of the alkyl radical. This is more strikingly shown in Table I, where the amounts of the different members of the series which resulted in the death of 50% of the rats are compared.

The members of these series of ortho-alkylphenols up to and including ortho-hexylphenol caused death rather quickly. Most of the rats died in from 2 to 6 hours while practically all of them were dead in from 8 to 12 hours. The ortho-heptylphenol and the ortho-

[1] Lamson and Brown, *J. Pharm. and Exp. Ther.*, in press.
[2] Lamson, Brown and Ward, *J. Pharm. and Exp. Therap.*, in press.

TABLE I.
Toxicity of 4-n-alkylresorcinols, ortho-alkylphenols and 6-alkyl-meta-cresols. Toxicity expressed as cubic centimeter of drug lethal to 50% of the rats.

resorcinol	0.25	phenol	0.30	m-cresol	0.35
				methyl-m-cresol	0.73
				ethyl-m-cresol	0.53
propylresorcinol	0.45			propyl-m-cresol	0.73
butylresorcinol	0.50	o-butylphenol	0.65	butyl-m-cresol	1.10
		o-amylphenol	0.70	amyl-m-cresol	1.50
hexylresorcinol	0.70	o-hexylphenol	1.30	hexyl-m-cresol	2.30
heptylresorcinol	1.30	o-heptylphenol	2.75	heptyl-m-cresol	3.32
		o-octylphenol	2.80	octyl-m-cresol	4.0
				nonyl-m-cresol	4.0

octylphenol acted more slowly and it was from 12 to 36 hours before those dosed with these substances died. At autopsy the rats usually showed considerable gastric enteritis and bloody fluid in the intestines. Convulsions were noted only in those rats given phenol. These began several minutes after dosing the rats and continued for several hours. That the decrease in toxicity of the higher alkylphenols is not entirely due to lack of absorption is shown by the fact that approximately 90% of a 2.0 cc. dose of n-ortho-heptylphenol is absorbed by both man and dog.

It will be seen in Table I that the alkylphenols of this series were appreciably less toxic than the alkylresorcinols with the corresponding number of carbons in the alkyl radical.

Conclusions. 1. The oral toxicity of ortho-n-alkylphenols to white rats decreases with the increase in length of the alkyl radical. 2. This decrease in toxicity with increase in length of the alkyl radical corresponds to our toxicity findings in series of 6-alkyl-meta-cresols and 4-n-alkylresorcinols. 3. Ortho-n-alkylphenols are less toxic than n-alkylresorcinols with the corresponding length of alkyl chains but show little difference in toxicity from the 6-alkyl-meta-cresols with the same number of substituted carbon atoms.