

lowers the pH of the feces of hens from a range of 7.1 to 6.4 to a range of 6.1 to 5.3, depending on the dosage and the period of time over which it is given. In 9 infested hens to which the emulsion was given for a period of time sufficient to cause a similar lowering of the pH of the feces, a complete cessation of the discharge of oocysts was noted in 5 cases and a reduction in the intensity of the oocysts discharge was observed in the other 4.

Summary. Lowering of fecal pH, in hens naturally infested with *Eimeria*, by means of an emulsion of lactic acid in agar, mineral oil, and water has been found to be more satisfactory in reducing or stopping oocyst discharge than the administration of various drugs, including carbon tetrachloride, tetrachlorethylene, methyl violet, acetarsone, and diphenylamine.

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Oral Toxicity of Certain Alkyl Resorcinols in Guinea Pigs and Rabbits.*

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Two alkyl resorcinols have recently been discussed in relation to the treatment of certain parasitic infestations: Lamson *et al*¹ suggesting hexylresorcinol in ascariasis and uncinariasis, and Faust² and Ratcliffe³ proposing heptylresorcinol ("di-hydranol") particularly in amebiasis. We believe that clinical trial of new drugs in man may proceed with greater satisfaction than otherwise, if it is made after a critical study of the toxicity of such agents in various genera of mammals for the purpose of reaching an approximate quantitative estimate of the *toxic range* of the materials, and of determining what pathological effects for which it may be expedient

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¹ Lamson, P. D., Wood, C. B., and Brown, H. W., *PROC. SOC. EXP. BIOL. AND MED.*, 1930, **27**, 1017; Lamson, P. D., Brown, H. W., Ward, C. B., Robbins, B. H., *Ibid.*, 1930, **28**, 191.

² Faust, E. C., *PROC. SOC. EXP. BIOL. AND MED.*, 1930 **27**, 905.

³ Ratcliffe, H. L., *J. Parasit.*, 1930, **17**, 113.

to watch when used clinically and against which to guard. The data presented by Leonard and his associates,⁴ while indicating that the toxicity of these drugs is "clinically negligible," do not seem to have been derived from a critical quantitative study. There is, however, a more significant reason from theoretical grounds for investigating quantitatively the toxicity of the alkyl resorcinols; in many series of related compounds containing alkyl radicals, it has been observed that toxicity in the series increases with increase in the number of carbon atoms in the straight carbon chain, and it is desirable to ascertain to what extent these observations may be expanded into a "law" relating chemical constitution to pharmacological action.

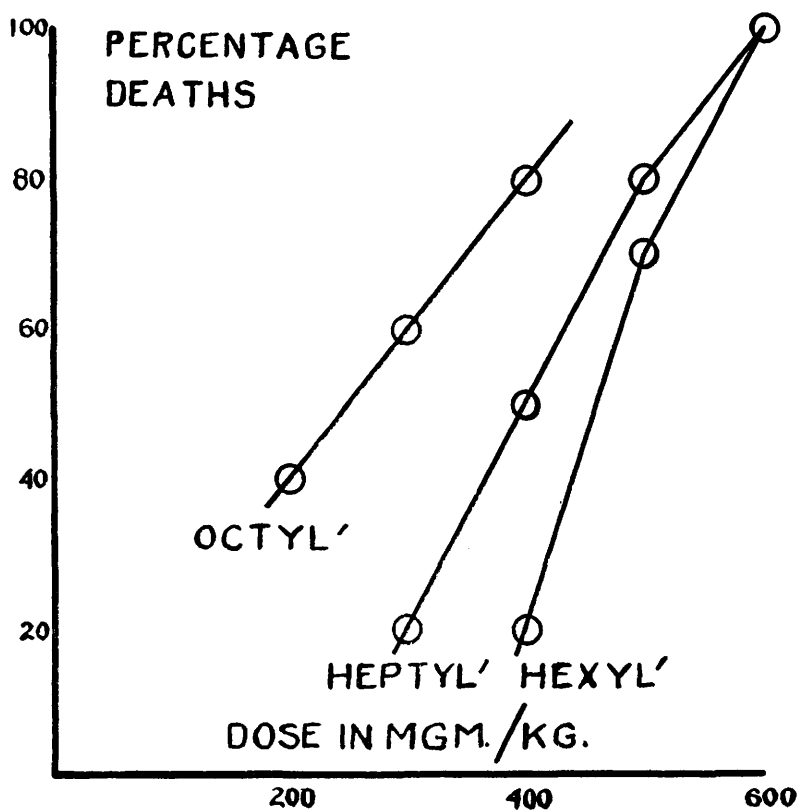


FIG. 1.

Graphical representation of the toxic range of hexyl-, heptyl-, and octyl-resorcinol in single oral doses to guinea pigs. Ten or more animals were used at each point indicated by a circle on the graphs.

⁴ Leonard, V., *J. Am. Med. Assn.*, 1924, **83**, 2005; *J. Urol.*, 1924, **12**, 585; Leonard, V., and Feirer, W. A., in press.

The toxic ranges of crystalline hexyl-, heptyl-, and octyl-resorcinol (kindly furnished by Dr. Veader Leonard) in single oral doses in 115 guinea pigs were estimated by a general technique discussed elsewhere.⁵ The animals were observed for 15 days after administration, and were compared with controls kept under similar conditions. The lethal range for guinea pigs of the 3 compounds is indicated graphically in Fig. 1. A definite increase in toxicity and a widening of the toxic range occurs with increase in the number of carbon atoms in the alkyl radical. The average lethal dose or M.L.D. of each respective drug may be estimated by dropping a perpendicular to the base line from the 50% death point on the graph of its lethal range.

Our toxicity studies in rabbits did not include enough animals to permit of a similar comparison to be made of these agents. We found in 6 rabbits that a single oral dose of 750 mgm. per kg. of hexylresorcinol in 10% concentration in ethylene glycol was tolerated with no significant effect except a transitory loss of weight and slight diarrhea. But 6 other rabbits, to which equivalent oral doses were given of the drug in crystalline form in gelatine capsules, all died within 5 days. This confirms Lamson's belief that the drug in solution is less toxic than when crystals are given. Three rabbits survived the oral administration of 750 mgm. per kg. of heptylresorcinol in 5% solution in olive oil with only slight symptoms of anorexia and loss of weight, but 3 others died within 5 days after giving 1 gm. per kg. of the same solution of the drug. In 5 equally divided doses at 2 day intervals, 3 rabbits tolerated 1500 mgm. per kg. of the same material with symptoms of diarrhea and loss of weight. Octylresorcinol in crystalline form killed 2 of 3 rabbits at 500 mgm. per kg. by mouth. While there is some evidence, therefore, in rabbits of increasing toxicity with increase in carbon content of the alkyl side chain in this series of related compounds, it is not as definite as in guinea pigs.

In lethal doses of these resorcinol derivatives, rabbits lost about one-third their original body-weight, and anorexia, lethargy, and diarrhea were noted. Immediately before death the animals became comatose, appeared very weak and emaciated, muscles were stiff, eyes were sunken, ears were drooped, and reflexes were sluggish. Respirations in one animal fell to 54 per minute, temperature was 34.2°C. and pulse rate was 114 per minute. At necropsy the animals usually were found with the liver moderately congested, the

⁵ Burn, J. H., *Physiol. Rev.*, 1930, **10**, 146; Anderson, H. H., and Leake, C. D., *Am. J. Trop. Med.*, 1930, **10**, 249.

gall bladder distended, the stomach full with erosion of the mucous membranes, and with a few small petechial hemorrhages in the intestines. The kidney was the only tissue showing definite microscopic abnormalities. Dr. Stacy Mettier noted numerous areas of focal necrosis, with extensive hyaline degeneration of the epithelial cells lining the tubules, and with some desquamation of these cells. All 3 compounds in crystalline form are irritating to the mucous membranes of the eyes of rabbits, causing a marked pan-ophthalmitis within 24 to 48 hours after application of a single small flake. Octylresorcinol is very irritating to the skin and mucous membranes of the face and hands of one of us, producing a vesicular dermatitis on parts of the skin coming in contact with the agent.

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Comparative Actions of Sympathomimetic Compounds: Responses of Cocainized Rabbit's Intestine.

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The extensive use by Tainter and others of the cocaine sensitization-desensitization phenomena in studies of the circulatory actions of sympathomimetic compounds, made it desirable to determine whether the same phenomena could be elicited with intestinal muscle. Some data were available in papers by Tainter and Chang¹ and Thienes and Hockett.² In no case, however, had the study of excised intestine been sufficiently extensive to indicate the range of spontaneous variation in the responses to successive administrations of the amines. We, therefore, investigated the influence of cocaine upon the responses of excised rabbit duodenum to epinephrine, tyramine, ephedrine and barium, controlling the results by observations of the responses to repeated applications of the same drug in the absence of cocaine. The changes in tonus, amplitude, and rhythmic activity were correlated as much as possible.

The tissues were fresh and active, the majority being taken from recently killed rabbits. Some tissues, however, were kept on ice for 24 hours; this procedure has been found by Burn and Tain-

¹ Tainter, M. L., and Chang, D. K., *J. Pharm. Exp. Therap.*, 1927, **30**, 193.

² Thienes, C. H., and Hockett, A. J., *PROC. SOC. EXP. BIOL. AND MED.*, 1928, **25**, 793.