trypan red, mercurochrome, rose bengal and sodium fluorescein, strikingly prevent the heat-coagulation and mercuric-precipitation of horse serum and egg albumin, and also the alkaloidal precipitation by Mayer's reagent. These powerful protective actions *in vitro* appear to be associated with the physical (colloidal) properties of these dyes, in agreement with a similar mechanism of protection exerted by some of these dyes on the actions of potent toxins and drugs *in vivo*. The possible significance of the mechanism of these common protective phenomena, for chemotherapy in general, is briefly discussed.

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The Toxicity of Nupercaine.*

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Among the requirements of an ideal local anesthetic agent is prolongation of action. Attempts have been made to meet this requirement, especially in connection with quinine derivatives, but tissue injury at the site of injection has generally precluded clinical use of such agents.[1] Uhlmann[2] introduced the diethyl-ethylene-diamide of butyloxycinchoninic acid (nupercaine, N.N.R.). In Europe this drug came into immediate favor, but a number of deaths were reported[3] following its use. Papers on the toxicity of nupercaine have been published,[4] but since these are not in agreement and did not take up the question of protection, further study seemed indicated.

We began with a 1% solution of nupercaine, but due to tissue irritation, we changed to a 0.5% solution. Rabbits were used and the drug was given subcutaneously or intravenously, with or without

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1 Dixon, W. E., and Premankur De, *J. Pharmacol. Exp. Therap.*, 1927, **31**, 407. Millzner, R. J., and Leake, C. D., PROC. SOC. EXP. BIOL. AND MED., 1929, **26**, 526.

2 Uhlmann, F., *Narkose u. Anesth.*, 1929, **2**, 168; *Arch. Internat. Pharmaco. Therap.*, 1929, **36**, 253.

3 Keyes, E. L., and McLellan, A. M., *Am. J. Surg.*, 1930, **9**, 1.

4 Bond, W. R., and Bloom, N., *J. Lab. Clin. Med.*, 1931, **16**, 447. Laubender, W., *Deutsche Med. Wchnschr.*, 1930, **56**, 1658. Lipshitz, W., and Laubender, W., *Klin. Wchnschr.*, 1930, **9**, 968.

protection. For protection we used paraldehyde administered in water emulsion by stomach tube.

Subcutaneous injection of nupercaine gave rise to convulsions on an average of 17 minutes from the time of injection. During this period there was first depression, then followed nervous excitement with loss of coordination, and finally clonic convulsions. Respiration became rapid, while the pulse was slow and irregular. Those animals recovering took 2 to 3 hours before they seemed normal. In those that died, the respiration stopped a few seconds before the pulse. The lethal dose (LD_{50}) of 8.5 mg./kg. is one-twelfth of the minimal lethal dose for cocaine given subcutaneously as reported by Knoefel, Herwick, and Loevenhart.[5]

Rabbits receiving an intravenous lethal dose of nupercaine died in less than a minute, and usually without any muscular effect whatever, although some had one severe convulsion. Kymographic studies indicated that nupercaine is similar in action to cocaine on intravenous administration in lethal doses.[5] Those receiving a tolerated dose showed the same symptoms as those given subcutaneous injections, but the reaction set in immediately and did not last as long. The lethal dose (LD_{50}) of 2.5 mg./kg. is one-sixth of the minimal lethal dose for cocaine given intravenously.

The rabbits receiving paraldehyde by stomach tube before the subcutaneous injection of nupercaine show the amount of protection offered by a typical cerebral depressant. In animals under the influence of paraldehyde, very little reaction to nupercaine is noted. A slight twitching of the legs and a marked slowing of the pulse is

TABLE I.
Data on Toxicity of Nupercaine in Rabbits.

Mode of Administration	Dosage in mg./kg.	Animals Used	No. Died	No. Lived
Injected subcutaneously	5	8	0	8
	7.5	8	3	5
	10	8	5	3
	15	5	5	0
" intravenously	2	8	2	6
	3	8	6	2
	5	5	5	0
" subcutaneously with 15 mm./kg. paraldehyde orally at same time	10	8	1	7
	20	8	2	6
	30	4	4	0
Injected intravenously when 15 mm./kg. paraldehyde had been given orally 15 minutes before	5	8	6	2

[5] Knoefel, P. K., Herwick, R. P., and Loevenhart, A. S., *J. Pharmacol. Exp. Therap.*, 1930, **29**, 397.

usually observed. As in the case of other types of local anesthetics, hypnotics protect against nupercaine injected subcutaneously, increasing the lethal dose about 3 times, but on intravenous injection, little protection is obtained.

Absorption of nupercaine when given subcutaneously is very slow, but it is 12 times more toxic than cocaine when given in that manner, and only 6 times more toxic if given intravenously. This indicates that, compared with cocaine, nupercaine attacks the central nervous system more readily than the heart. All the phenomena observed in this study are in accord with that explanation of intoxication from local anesthetics which has already been discussed.[5]

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Preservatives for Bacteriophage Suspensions.

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That bacteriophage possesses therapeutic value in certain types of bacterial infections is becoming more and more evident.[1] The increasing demand for 'phages intended for therapeutic use raises a question, applicable to all biological products, as to the choice of a suitable preservative. While filtration through a sound candle generally fulfills the requirements as to sterility, it is well known that this is not absolute proof against the development of so-called "secondary cultures". Besides this there is also the possibility of accidentally introducing organisms in ampouling the filtrate for shipment.

In choosing preservatives for 'phage products 2 considerations must be borne in mind: (1) The preservative must be bactericidal without in any way impairing the potency of the 'phage and (2) the concentration of the germicide which is employed should be such that it will not be toxic for the patient in the amounts which would be administered with large doses of 'phage. In studies designed to elicit the value of 'phage as a therapeutic agent, a third consideration enters. Here it is important to reduce the concentration to a level which will insure bacteriostasis in the ampoule and will not, on further dilution by body fluids (urine, etc.) after admin-

[1] Schultz, E. W., *California and Western Medicine*, 1932, in press.