Summary. Cysteine hydrochloride injected directly into spontaneous and inoculated carcinoma caused necrosis and extrusion of necrotic material but produced permanent regression in only one animal. Partial regression of one tumor was without effect on the growth of a second untreated tumor.

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Some Effects of Anesthetic Mixtures Dissolved in Oil on Motor Nerves in the Cat.

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Since the introduction of local anesthetic substances dissolved in oil by Yeomans, Gorsch and Mathesheimer,[1] mixtures patterned after the original have been extensively used by proctologists.[2] Recently the use of these substances has spread to other clinical specialties.[3, 4] Injections of the various mixtures regularly produce anesthesia lasting from several days to as much as one month, and occasionally longer.[5] Variable amounts of muscular relaxation for similar periods are also obtained.

The usual explanation for the prolonged effect is gradual release of the anesthetic materials from the oily vehicle whereby a long continued depressant effect on the functional activity of the nerve endings is obtained.[1, 6] However, on the basis of Donaggio's[7] work with long continued application of aqueous local anesthetic solutions, one might expect irreversible organic changes leading to nerve degeneration. Degeneration as a result of the injection of local anesthetics in oil has been suggested in only one[8] of the many clinical papers examined, and apparently no animal experiments followed by histological examination of the nerves have been performed.

In this laboratory cats were injected in an attempt to determine

1 Yeomans, F. C., Gorsch, R. V., and Mathesheimer, J. L., *M. J. and Rec.*, 1928, **127**, 19.

2 Green, W. W., *Tr. Am. Proct. Soc.*, 1937, **38**, 153.

3 Hollander, E., *Arch. Neurol. and Psychiat.*, 1938, **40**, 743.

4 Hunter, G. W., *Am. J. Obst. and Gynec.*, 1939, **38**, 318.

5 Block, L. H., Greene, B. L., and Wiltrakis, G. A., *Illinois M. J.*, 1938, **73**, 238.

6 Manheim, S. D., and Marks, M. M., *Am. J. Surg.*, 1938, **39**, 86.

7 Donaggio, A., *Gior. ital. di anest. e di analg.*, 1937, **3**, 325.

8 Steinberg, N., *New England J. Med.*, 1936, **215**, 1019.

the effects of anesthetics in oil on the peripheral motor nerves. For this purpose 3 preparations were tried. The first was a locally prepared mixture containing procaine base 1.5, butesin 6.0, benzyl alcohol 5.0 and sterilized oil of sweet almonds, U.S.P., q.s. 100.0. The other 2 were proprietary mixtures supplied by the manufacturers.* One contained nupercaine hydrochloride (alpha-butyloxy-cinchoninic acid-diethyl-ethylene-diamide hydrochloride) 0.5, benzyl alcohol 10.0, phenol 1.0, and sterilized oil of sweet almonds q.s. 100.0. The last mixture tried contained eucupine base (isoamylhydrocuprein) 0.1, ethylaminobenzoate 3.0, benzyl alcohol 5.0, and sterilized oil of sweet almonds q.s. 100.0.

Initial experiments with the procaine and nupercaine mixtures were directed towards the femoral and sciatic nerves. Neither solution produced a complete block of the motor fibers when as much as 5 cc was injected around the trunks of these nerves. Various degrees of weakness lasting for hours or days were obtained, but after 10 trials including exposure of the nerves and direct injection into their sheaths the attempts were abandoned.

The subcutaneous tissues of the face were then infiltrated to test the effect on branches of the facial nerve. This method had the advantage of acting on the nerve supply of a muscle, the *orbicularis oculi,* which is easily tested for paralysis. Injections were made with a 22 gauge needle and the material was introduced slowly and in such a manner as to obtain wide distribution of the oil and also to prevent large local accumulations. The injections were done under light ether narcosis and the amounts varied between 3 and 5 cc depending on the size of the animal.

Four trials each with the procaine and nupercaine mixtures produced an immediate complete paralysis of the *orbicularis oculi* in every case. Complete paralysis as evidenced by absence of movement of the lids on corneal stimulation lasted from 3 hours to 3 days in the case of the procaine mixture and from 2-21 days with the nupercaine mixture. Partial paralysis indicated by incomplete closure of the lids and weakness on forcible opening lasted several additional days. Four trials with the eucupin mixture, 5 cc in each case, did not produce evidence of paraysis for more than one hour. A fifth 5 cc injection caused a paralysis which lasted for 12 days. Six injections of 5 cc of sterilized almond oil were not followed by paralysis nor by any discernible evidence of weakness.

Ten to 30 days following the injections, the cats were killed with

* Nupercaine, Ciba Pharmaceutical Products, Inc., Summit, N. J. Eucupin, Rare Chemicals, Inc., Nepara Park, N. Y.

chloroform and the facial nerve and its branches were carefully dissected out and placed in 1% osmic acid for 24 hours. Portions of each specimen were then teased in glycerine and examined. In the 3 instances of complete paralysis of the *orbicularis oculi* lasting 14 days or longer, degeneration of the fibers to the muscle was complete. The histological picture was one of the typical Wallerian degeneration such as follows the traumatic section of a nerve. In 2 of these animals 30 days had elapsed and the muscle was again active. In these cases regenerating fibers were numerous. In all of the other animals injected with an active solution varying numbers of degenerating fibers were seen in the branches of the facial nerve on the injected side. In those receiving eucupin without effect the abnormal fibers were not numerous but were well above the number that might be expected to occur in a normal animal.[9] With the other 2 preparations the number of degenerating fibers was greater and in general corresponded to the duration of the paralytic effect of the injection.

The state of degeneration indicated that the fibers so affected were killed almost immediately; *i. e.*, in no case was there seen a mixture of early and late degenerative changes suggestive of a prolonged functional depression followed by physical disintegration.

No more than a very occasional fiber exhibiting degeneration was seen following the injection of almond oil alone. Most of the branches from specimens so treated were composed exclusively of intact fibers.

The conclusion reached is that oil solutions of the local anesthetics owe their prolonged action, at least in part, to degeneration of nerve fibers in the injected area. Complete motor block of more than 4 days is accompanied by complete degeneration of the motor nerves to the paralyzed muscle. Subsequent restoration of function is due to regeneration.

Summary. Mixtures of local anesthetic substances dissolved in oil were injected into the subcutaneous tissues of the face in cats. Paralysis of the *orbicularis oculi* muscle was invariably obtained with solutions containing either procaine base or nupercaine hydrochloride. The paralysis lasted from several hours as a minimum to a maximum of 21 days. Histological examination of the tissues 10-31 days after injection revealed degeneration of facial nerve fibers in every case. The amount of degeneration varied from a few scattered fibers to complete in some branches. In general the amount of degeneration corresponded to the duration of the paralysis. Injections of the oil vehicle alone caused no paralysis and no degeneration.

[9] Duncan, D., *J. Comp. Neurol.*, 1930, **51**, 197.