would insure complete paralysis from 2 to 4 hours. As shown in Table I, the total dosage in many cases far exceeded the latter value. Greater reliance was obtained with functional criteria, and all stages were tested, from no observable change to complete striated muscle paralysis.

In general the E. E. G. in the drugged animal conformed to that recorded in the normal condition. There was some evidence that the magnitude of the pick-up in certain cases was reduced after the animal was erythroidinized, but the wave-form remained undisturbed. A series of supplementary doses, introduced subsequently, each one sufficient to produce complete muscular paralysis, likewise failed to disturb the E. E. G. On occasion, the E. E. G. was permanently distorted following the injection of a single massive dose (sufficient to produce complete paralysis for more than 4 to 6 hours). This effect was probably due to disturbed metabolism (reduction in the amount of available oxygen) since the blood pressure falls, temporarily, following the injection of even moderate dosage of the drug.[5,7] When artificial respiration was eliminated, the E. E. G. disappeared, to reappear undistorted, or permanently impaired, depending upon the length of the unrespirated interval. This effect, however, was not due to the direct action of the drug upon the cortex, but rather the indirect consequence of the lack of oxygen required to sustain normal cortical metabolism. Unlike the mammal, the curarized frog survives without tracheal insufflation due to the presence of the accessory skin respiratory mechanism. The disappearance of the E. E. G. in the curarized frog therefore, is more likely produced by the reduction in available oxygen rather than the *direct* effect of curare upon the cortex, as maintained by Feitelberg and Pick.[8]

Libet et al. have also reported the persistence of the cortical activity in curarized dogs subjected to metrazol.[9] No extended tests were made by these investigators with curare alone, and the metrazol disturbed the E. E. G. considerably. Their results, however, are in agreement with the present data in that the E. E. G. did not disappear following curarization, or, for that matter, after the metrazol took effect.

Summary. So long as proper artificial respiration is given, normal cortical activity, as measured by the E. E. G., persists undisturbed in both the dog and the monkey during complete striated muscular paralysis induced with erythroidine. The difference in results reported here with mammals and that previously reported by other workers in the frog (complete elimination of the E. E. G.) is interpreted to be due to a reduction in the available oxygen necessary for normal cortical metabolism in the latter organism.

[9] Libet, B., Fazekas, J. F., and Himwich, H. E., *Am. J. Psychiat.*, 1940, **97**, 366.

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Some New Choline Esters with Cycloplegic and Mydriatic Action.*

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Choline derivatives such as acetylcholine and carbamylcholine (doryl) produce constriction of the pupil and contraction of the ciliary muscle. The halide salts of these compounds have little effect on the surface tension of water, *i.e.*, they are relatively surface-inactive; as surface activity has a profound influence on many biologic phenomena, it was believed choline derivatives which were surface-active might have an enhanced or even

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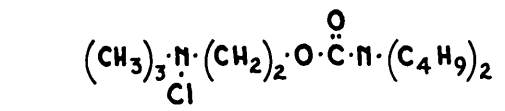
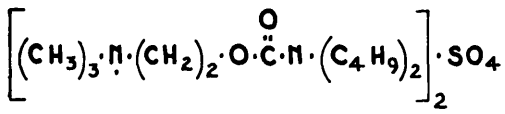
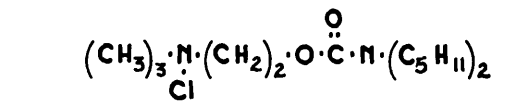
TABLE I
Surface-active Carbamylcholine Derivatives



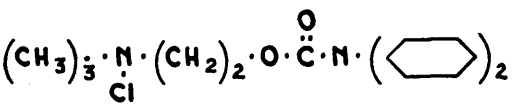
Di-n-butyl-carbamylcholine chloride
and
Di-iso-butyl-carbamylcholine chloride



Di-n-butyl-carbamylcholine sulphate



Di-n-amyl-carbamylcholine chloride



Di-phenyl-carbamylcholine chloride

different pharmacological effect. Investigation of this possibility necessitated synthesis of new compounds in which highly hydrophilic choline salts were combined by an ester linkage with highly hydrophobic groups. The resultant elongated molecules would be predominantly hydrophilic at the choline end and predominantly hydrophobic at the opposite end. Molecules with this structure would be surface-active.

The first series of surface-active choline esters have been synthesized (Table 1). The $-NH_2$ radical of carbamylcholine was replaced by water insoluble amines. Five to 10% solutions of the chloride salts of these drugs have a water-air interfacial tension of less than 50 dynes per cm at 25°C. In the albino rabbit, mydriasis develops promptly after a single instillation of each of these solutions into the conjunctival sac. The mydriasis results from paresis of the iris sphincter for the drugs produce no pupillary changes in eyes in which the iris sphincter has been removed surgically. In the human eye, mydriasis is accompanied by cycloplegia. The action of the new drugs, therefore, resembles that of atropine and is opposite to that of carbamylcholine and acetylcholine.

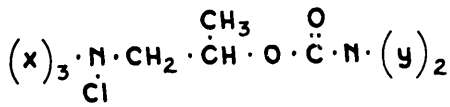
Substitution of ethyl for the methyl radicals of the quaternary ammonium group increases the mydriatic action of these new drugs, but decreases the cycloplegic properties. Replacement of the methyl by propyl and butyl radicals reduces the intensity of both mydriatic and cycloplegic effects.

Branched chain compounds, *e.g.*, di-isobutyl carbamylcholine, are pharmacologically less active than the corresponding straight chain isomers.

The members of the beta-methyl carbamylcholine series (Table II) have the same qualitative effects on the eye as the corresponding carbamylcholine compounds.

The aromatic derivatives, *e.g.*, diphenylcarbamylcholine chloride, have less mydriatic and cycloplegic properties than corresponding

TABLE II
β-methyl-carbamylcholine Derivatives



x = Methyl, Ethyl, Propyl radicals
y = Butyl, Amyl, Phenyl radicals

di-n-butyl compounds, particularly in the human eye.

Instillations of 7.5% aqueous solutions of di-n-butyl carbamylcholine chloride were made into the conjunctival sacs of rabbits several times daily for 4 weeks. No evidence of injury to the intraocular tissues was noted by either histologic methods or by ophthalmoscopy and slit lamp biomicroscopy. A transient, superficial, punctate disturbance of the corneal epithelium frequently followed instillations of more concentrated solutions. A similar disturbance was noted in the human eye.

Systemic pharmacology and toxicology of the new compounds are to be studied by one of us† in partial fulfillment of requirements for a doctorate degree, and will be reported separately; however, no systemic effects have been noted following instillations into the conjunctival sac of adult patients.

The only clinical application of the new drugs has been in routine intraocular examination and cycloplegic refraction. For this purpose, di-n-butyl-carbamylcholine sulfate has been the most satisfactory. Two instillations of a 7.5% solution into the conjunctival sac produce mydriasis and cycloplegia beginning within 20 minutes and becoming maximal in 60 to 90 minutes. The reactions of the intraocular muscles usually return to normal 7 to 12 hours after administration. The duration of action is, therefore, relatively short. In this respect, di-n-butyl-carbamylcholine resembles homatropine rather than atropine.

A comparative study of di-n-butyl-carbamylcholine sulfate and homatropine was made on 400 patients. Each patient received 2 instillations of 5% homatropine hydrobromide in one eye and 2 instillations of a 7.5% solution of the new drug in the other. There was little difference in the degree of mydriasis and cycloplegia produced by the two drugs; however, cycloplegia and particularly mydriasis was less prolonged following di-n-butyl-carbamylcholine.

Only the most promising members of the new class of drugs have been investigated. Synthesis and pharmacologic investigation of surface-active choline esters other than the carbamate series are being continued.

Summary. A new class of choline esters with mydriatic and cycloplegic properties is reported. For routine examinations, di-n-butyl-carbamylcholine sulfate produces cycloplegia and mydriasis comparable in degree to that produced by homatropine; however, the new compound has the advantage of producing a shorter period of visual disability.

† N. G. White.