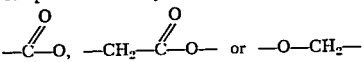
action at the neuromuscular junction. Any promising agents found are to be subjected to *in vivo* studies in animals and perhaps, finally, in man. *Methods:* The sciatic nerve-sartorius muscle preparation of the frog was bathed in Ringer's solution containing appropriate concentrations of each drug to be tested. The intracellular resting potential and the action potentials evoked in response to motor nerve stimulation were recorded at the neuromuscular junction at various times. *Results:* Most of the choline analogues tested produced a depolarizing block. In a concentration of 5×10^{-4} M., benzoylcholine depolarized the endplate below −50 mV., the critical membrane potential. (Similar results can be produced by succinylcholine at 10^{-5} M. and acetylcholine at 3×10^{-6} M.) Some compounds in the phenacetylcholine series (formed by introducing a methylene group between the carbonyl carbon atom and the benzene ring in benzoylcholine) produce a similar degree of postjunctional membrane depolarization when applied at a concentration of 10^{-5} M. One of the diquaternary derivatives of phenacetylcholine was an especially potent depolarizing agent. At 10^{-6} M. it reduced the postjunctional membrane potential to below −50 mV. The ethocholine derivatives produced a nondepolarizing neuromuscular block. Phenacetylethocholine blocked transmission at a concentration of 10^{-4} M. (compare *d*-tubocurarine which blocks at 5×10^{-6} M.). Contrary to our expectations, di- and triquaternary analogs were not more potent than the monoquaternary phenacetylethocholine. Compounds in the phenoxy-acetylcholine and ethocholine series were more easily hydrolyzed than those mentioned above, but they lacked potent neuromuscular blocking properties. Several derivatives of phenacetylcholine were prepared by quaternarizing the nitrogen with different groups. Preliminary data indicate that some of these compounds are especially potent blocking agents. (Supported by NIH Grants GM 09069 and NB-04988.)

The Uptake, Distribution and Elimination of ^{14}C-labelled Lidocaine in the Dog. JORDAN KATZ, M.D., *Department of Anesthesia, Stanford University, Palo Alto, Calif.* In an attempt to determine the distribution of lidocaine after intravenous injection, initial work in rats indicated that the liver contained about 33 per cent of injected drug by 15 minutes (Katz, J.: ANESTHESIOLOGY in press). Muscle also contained significant amounts of drug (24 per cent by 5 minutes, falling to 16 per cent by 15 minutes). In other organs there were rapid decay curves after the initial measurement at one minute postinjection. In order to elucidate further the distribution and subsequent elimination of the drug in a larger species, experiments were undertaken in the dog. *Methods:* Female mongrel dogs anesthetized with I.V. pentobarbital (30 mg./kg.), were intubated and maintained on N_2O/O_2 and intermittent succinylcholine anesthesia. Hydration was accomplished with a 5 per cent dextrose in Ringer's lactate solution. Laparotomy was performed and in two animals the common bile duct was cannulated. The urinary bladder was catheterized. One hour after closure of the laparotomy wound, and when the animals were stable, ^{14}C-labelled lidocaine was injected rapidly intravenously. Arterial blood, urine and bile samples were collected at intervals for as long as five hours. Biopsies from the quadriceps muscle were taken at intervals. After laparotomy in a second group (eight animals) liver and fat biopsies were taken in addition to muscle, arterial blood and urine collections. Biopsies of kidney and gut were taken from specific animals. *Results:* Blood levels fell rapidly from 16.8 per cent of injected dose in plasma at one minute to 9.1 per cent at five minutes. At one, two and four hours plasma levels were 4.7, 3.4, and 1.9 per cent, respectively. This pattern was essentially similar to that noted in rats with, of course, a different time base. Concentrations in the liver rose rapidly to 24.5 per cent of injected dose by three minutes and remained in that range until 30 minutes after injection, when concentration began to decline. Muscle held as much as 40 per cent of the injected dose from 5 to 30 minutes before levels declined. When counts/minute/mg. of tissue were made, muscle was found to have low affinity for the drug. The maximum counts were 4.6 cts./min./mg. of muscle compared to 35 cts./min./mg. liver. Higher counts were

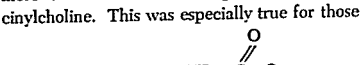
found also in other highly-perfused organs (kidney and gut). This indicates that muscle is important in distribution only because of its mass (about 45 per cent of the animal weight). The liver, however, actively concentrates the drug. Presumably, this is the site of the metabolism of lidocaine. In the other highly-perfused organs, levels declined rapidly, following the general shape of the plasma decay curve.

The urine showed radioactivity within minutes. If a urinary output of between 0.5 ml. and 2.0 ml./min. is maintained, an average of 10.8 per cent of the injected radioactivity can be recovered within one hour. By five hours postinjection the mean recovery was 42.3 per cent of the initial dose. The greatest part of the recovered radioactivity is metabolite (Katz, J.: Unpublished data). The bile contained less than 1 per cent radioactivity after five hours in one animal and less than 3 per cent in another. Assuming normal urinary function, the biliary system probably is not an important excretory pathway for this compound. *Conclusion:* ^{14}C-labelled lidocaine appears to be distributed in highly-perfused tissues. The liver actively concentrated the drug. Presumably this is the site of metabolism of the drug. Muscle has a low affinity for the drug, compared to other tissues.

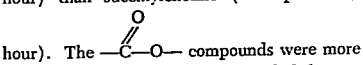
Progress in the Development of Potential Neuromuscular Blocking Agents. RICHARD J. KITZ, M.D., SARA GINSBURG, PH.D., and JOANNES KARIS, M.D., *Departments of Anesthesiology, Neurology and Physiology, College of Physicians and Surgeons, Columbia University, New York, N. Y.* More potent and specific skeletal muscle relaxants are needed in anesthesiology if side effects are to be avoided. Depolarizing drugs such as succinylcholine have the disadvantages of (1) producing cardiac arrhythmias, (2) causing muscle pains, (3) producing a desensitization type of myoneural block, (4) increasing intraocular pressure, (5) requiring plasma cholinesterase for rapid destruction and (6) not having pharmacological antidotes. Nondepolarizing drugs do not have the above disadvantages but have (1) relatively long durations of action which (2) frequently require reversal of neuromuscular blockade by drugs which may have profound effects on cardiac action and other systemic effects. Short-acting, nondepolarizing agents which do not require other compounds as antidotes would be useful. A program was established to design, synthesize and test compounds to meet these specifications. *Method:* The basic gallamine triethiodide molecule was chosen for modification. Using standard organic chemical techniques, three series of compounds were synthesized by introducing



linkage between the ethocholine and benzene ring moieties of the gallamine structure, forming ester instead of ether links. These compounds are potentially susceptible to spontaneous and enzymatically-catalyzed hydrolysis, thus limiting their duration of action. Mono, di-, and triquaternary derivatives of the choline and ethocholine analogues were synthesized, forming the benzoylcholine (ethocholine), phenacetylcholine (ethocholine), and phenoxyacetylcholine (ethocholine) series. Approximately sixty derivatives are theoretically possible, of which half have been synthesized, their structures verified, and are under study. The spontaneous and enzymatically-catalyzed (by acetylcholinesterase and plasma cholinesterase) rates of hydrolysis (destruction) of these compounds were measured *in vitro* with an automatic, precision *p*H stat. Their effects on the single-fiber preparation of the myoneural junction of the frog sartorious were also studied *in vitro* (reported separately by Karis, J. *et al.*). *Results:* In general it was found that some of these new ester compounds were more unstable than either gallamine or succinylcholine. This was especially true for those



containing the group. 1,2-Benzenedioldiacetylethocholine hydrolyzed spontaneously 120 times faster (32 per cent/hour) than succinylcholine (0.27 per cent/



hour). The compounds were more susceptible to hydrolysis by purified human