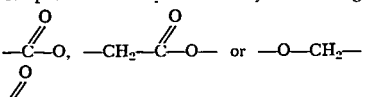
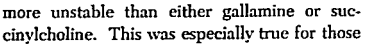
found also in other highly-perfused organs (kidney and gut). This indicates that muscle is important in distribution only because of its mass (about 45 per cent of the animal weight). The liver, however, actively concentrates the drug. Presumably, this is the site of the metabolism of lidocaine. In the 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 The greatest part of the recovered radioactivity is metabolite (Katz, J.: Unpublished data).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.

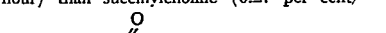
Progress in the Development of Potential Neuromuscular Blocking Agents. RICHARD J. KITZ, M.D., SARA GINSBURG, PH.D., and JOANNES KARIS, M.D., *Departments of Anesthesiology, Neurology and Physiology, College of Physicians and Surgeons, Columbia University, New York, N. Y.* More potent and specific skeletal 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

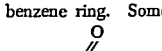


group. 1,2-Benzenedioldiacetylethocholine hydrolyzed spontaneously 120 times faster (32 per cent/hour) than succinylcholine (0.27 per cent/



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

plasmacholinesterase. This enzyme destroys benzoylcholine 25 times faster (14 per cent/hour) than succinylcholine (0.54 per cent/hour). This rate could be increased still further (to 21 per cent/hour) when a NO_2 group was introduced into the para position on the benzene ring. Some of the drugs containing



—CH_2—C—O— linkages undergo spontaneous hydrolysis (0.3 per cent to 4.6 per cent/hour) in addition to hydrolysis by human red cells (2.3 per cent/hour) and plasma cholinesterase (20 per cent/hour), well in excess of the rates measured for succinylcholine. The choline derivatives were potent depolarizing agents whereas the ethocholine compounds possessed curare-like activity (reported separately by Karis, J. *et al.*). *Summary:* Several series of potential neuromuscular blocking agents have been synthesized and are under study. Their high rates of spontaneous and enzymatically-catalyzed hydrolysis should make their *in vivo* activity short-lived. The study of these and other new compounds is continuing; *in vivo* investigations are planned. (Supported by USPHS program Project Grant GM 09069-05.)

Electrocystometry by Percutaneous Sacral Nerve-root Stimulation. THOMAS KOELZ, M.D., and HUGH D. WESTGATE, M.D., *Department of Anesthesiology, University of Minnesota Medical Center, Minneapolis, Minn.* Normal urinary bladder function is a result of well integrated somatic and visceral nervous activity. Micturition requires reciprocal actions between detrusor force and outflow resistance. The most commonly accepted theory of bladder innervation is that detrusor contractions are a result of parasympathetic activity arising from the conus medullaris primarily via S3 with accompanying fibers from S2 and S4, and contraction is accompanied by reciprocal inhibition of sympathetic impulses to the internal sphincter. Neurogenic vesical dysfunction can be due to disruption of any of the numerous centers or pathways involved, specifically, to poor reciprocal response of the detrusor and outlet (dyssynergia), efferent pre- or post-ganglionic disease, defective bladder sensation, or detrusor myopathy. With these three areas for study, the anesthesiologist becomes involved principally in determining efferent pre- and postganglionic responses via electrocystometry and in determining the presence or absence of dyssynergia by the use of various blocks, *e.g.*, pudendal block. It is felt that patients who have retained neural input to the bladder with response to electrostimulation should not have urinary diverting procedures but should be treated on the basis of remaining function, *i.e.*, internal sphincterotomy, pudendal neurotomy, and sympathectomy. The evaluation of a patient with bladder dysfunction should therefore include electrocystometry for information regarding pre- and postgaglionic neural disease and also bladder biopsy to detect early detrusor myopathy. Bladder biopsy is performed by a urologist; electrocystometry by an anesthesiologist. Electrical stimulation of the second, third and fourth sacral nerve roots bilaterally can be used to measure integrity of the efferent neural pathways and detrusor contractility. We have shown that electrical stimulation of these roots in curarized dogs produces detrusor activity, voiding and defecation. *Method:* Twenty-three patients were studied for sacral-root stimulation in the following manner: an indwelling catheter was inserted and the bladder filled with warm benzalkonium chloride (Zephiran®) solution. The catheter was connected to a pressure transducer and a continuous record of pressure changes was made. Spinal anesthesia with either 5 per cent lidocaine or 1 per cent dibucaine was administered. Needle electrodes insulated with teflon except for the tip were inserted through the second, third and fourth sacral foramina bilaterally. A pulsating current identified the nerve root being stimulated. After all needles were placed, bladder pressure changes were recorded following tetanic stimulation of each sacral root. *Results:* In a normal response following sacral-root stimulation there was little or no response to S2 stimulation, a maximal response to S3 and a lesser response to S4. Commonly one side was dominant, with little response from the opposite side. Abnormalities in response varied from no response at all in some patients with meningomyeloceles to only slightly reduced responses in some patients with multiple sclerosis or diabetes mellitus. Patients with difficulty in voiding and dysuria may have definite unilateral innerva-