photo fluorometric method was used for thiopental analysis. *Anencephalic infant:* The malformation having been diagnosed radiologically during labor, the mother was given a total of 2,250g. of thiopental in divided doses over a period of 2½ hours preceding delivery. Blood samples were obtained promptly after birth from both umbilical vessels and again at the age of 20 minutes (cardiac puncture). A maternal venous sample was withdrawn at delivery. The infant, weighing 2,200 g. expired 22 minutes after birth, tissue samples were obtained shortly thereafter. The highest concentration of thiopental was found in the subcutaneous fat, undoubtedly due to prolonged administration of the drug and its very high lipid solubility. Both lobes of the liver contained similar and substantial amounts of the barbiturate. On the other hand thiopental concentration in the spinal cord was surprisingly low. *Guinea pigs:* Distribution of thiopental in fetal tissues was determined following intermittent administration of the drug to the mother, or after its single injection into the umbilical vein of individual fetuses. For the intermittent intravenous technique 2 pregnant guinea pigs received injections of 0.5 ml. of 1.25 per cent thiopental totaling 50 and 62.5 mg., respectively, over a period of 45–60 minutes preceding abdominal delivery. Fetuses were stunned upon delivery, blood samples obtained (cardiac puncture) and organs removed for analysis. For the single injection into the fetal circulation two pregnant guinea pigs anesthetized with an intravenous injection of secobarbital (10 mg./kg.) were used. Prior to delivery of each fetus a loop of umbilical cord was exteriorized through a small incision in the amniotic sac and 2.5 mg. of thiopental 0.5 per cent was injected into the umbilical vein over a period of one minute. The cord was clamped at the end of the injection and the fetus sacrificed 2 minutes later. *Summary:* Thiopental concentrations in the fetal brain and spinal cord were equally low in both groups of experiments. When thiopental was injected directly into the fetal circulation extremely high levels were found in the middle lobe of the liver. This lobe is perfused mainly by the umbilical vein and on a weight basis contained almost one half of the injected dose. The fetal liver thus occupies a strategic position and decreases the amount of thiopental reaching the central nervous system during the peak placental transmission.

Antagonism to Neuromuscular Block by Germine Acetates. WERNER FLACKE, M.D., and MILTON H. ALPER, M.D., *Departments of Pharmacology and Anesthesia, Harvard Medical School, and Peter Bent Brigham Hospital, Boston.* Germine mono- and diacetate, semisynthetic ester alkaloids of the Veratrum family, markedly increase tension output of skeletal muscle in response to stimulation at subtetanic frequencies. Unlike previously investigated veratrum alkaloids, they do not cause bradycardia and hypotension in any dose. Their basic action is the conversion of the single muscle action potential normally elicited by a single conducted impulse into a brief period of tetanic firing. Since this also occurs in denervated muscle, the effect is, at least in part, located in the muscle proper and not at the neuromuscular junction (Flacke, W.: Arch. Exp. Path. Pharmakol. *240:* 396, 1961; J. Pharmacol. Exp. Ther. *141:* 230, 1963). *Methods:* The sciatic nerve was stimulated supramaximally in anesthetized cats at a basic rate of 0.1 second. Tension output of the gastrocnemius muscle was measured isometrically. Blood pressure, and in some experiments respiratory movements and inspiratory force, were also recorded. Drugs were given intravenously or intra-arterially. *Results:* When given during complete neuromuscular block, produced by d-tubocurarine, gallamine, decamethonium, or succinylcholine, the germine acetates had no effect on the muscle. However, when neuromuscular block was not complete, the injection of one of the germine acetates (1 to 3 mg./kg.) caused a prompt increase in tension output. The magnitude of the increase depended upon the magnitude of the block present. When one of the neuromuscular blocking agents was given as a single injection, subsequent administration of a germine acetate shortened the duration of the block and increased tension output to a level considerably higher than that existing during the control period. The duration of the block caused by a single injection of curare was shortened when curare was given in the pres-

ence of an effective dose of a germine ester. Inspiratory force, measured as intrapleural pressure change during tracheal occlusion, was increased markedly by the alkaloids. Rapid intravenous injection caused a transient small increase in blood pressure, and a brief period of apnea followed by deepened respiratory movements. Intermittent deep inspirations when absent during anesthesia were restored by the germine acetates. *Discussion:* The experiments present evidence that partial neuromuscular block can be overcome by agents which do not act primarily on neuromuscular transmission. The germine acetates increase tension output of those muscle fibers still reached by the nerve impulse in the presence of a submaximal dose of a blocking agent. This occurs regardless of the agent used and of the nature of the existing block. An effective dose of the alkaloids increased tension output during partial or waning neuromuscular block to a level much higher than that existing before the block. One of the esters, germine diacetate, has been used in patients with myasthenia gravis where it was found to be as effective as anticholinesterase medication and, so far, free of hazardous side effects (Flacke, and others: New Eng. J. Med., *275:* 1207, 1966). *Summary:* It has been shown in cats that germine mono- and diacetate are capable of markedly increasing the development of tension in skeletal muscle in response to nerve stimulation in the presence of drug-induced partial neuromuscular block. The effect occurs regardless of the nature of the block and is presumed to be due to a postsynaptic action of the agents.

Earliest Evidence of Phase II Myoneural Block. FELIX G. FREUND, M.D., and RUDOLPH H. DE JONG, M.D., *Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington.* In man and other mammalian species succinylcholine (Sch) and decamethonium (C10) are believed to produce an initial depolarization or Phase I neuromuscular block which subsequently changes to a non-depolarization or Phase II block (Zaimis, E. J.: J. Physiol. *122:* 238, 1953). While electromyographic studies suggested that in man the transition from Phase I to Phase II occurs only after rather large doses of Sch (Churchill-Davidson, H. C., Christie, T. H., and Wise, R. P.: ANESTHESIOLOGY *21:* 144, 1960) more recent studies, measuring muscle tension, indicated that this happens with considerably smaller doses (Katz, R. L., Wolf, C. E., and Papper, E. M.: ANESTHESIOLOGY *24:* 784, 1963). In view of this discrepancy we decided to re-examine the problem of simultaneous recording of the electrical and mechanical muscle responses to nerve stimulation. *Methods:* To determine drug dosage at which transition from Phase I to Phase II block occurs we studied 32 patients anesthetized with thiopental followed by nitrous-oxide-halothane. Muscle-relaxants were administered only during the study period. Subcutaneous electrodes delivered supramaximal stimuli of 0.3 msec. duration to the ulnar nerve at the wrist. Surface electrodes and a tension transducer were used to record respectively the electrical and mechanical responses of the adductor pollicis brevis which were displayed on an oscilloscope and photographed on moving film. Magnitude of myoneural block was determined by the ratio of experimental to control response to a single stimulus. Characterization of the block as depolarization on nondepolarization was based on the commonly used criteria of constant or declining ("fatigue") response during tetanic nerve stimulation (40 stimuli per second for 5 seconds) and absence or presence of post-tetanic facilitation. Drugs were given intravenously, Sch either in single doses or continuous infusion; C10 only in single doses. *Results:* Even the smallest dose of Sch (10 mg.) or C10 (2 mg.) that would produce a measurable degree of transmission depression, invariably resulted in a nondepolarization (curare-like) block characterized by a rapid fall of both electrical and mechanical responses during tetanization, and by post-tetanic facilitation. Although typical muscle fasciculations were often noticed after the first dose of Sch and occasionally after C10, no evidence of Phase I block was seen with either drug at any time. The results indicate that in anesthetized man Sch and C10 produce a neuromuscular block that from its very onset has electro-mechanical characteristics indistinguishable from those of a curare block. (This investigation was supported by University of