SPINAL CORD DEPRESSANT DRUGS*

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The pharmacology of drugs possessing a depressant action on the spinal cord received little attention in the past. The discovery of useful applications of curare in medicine and surgery directed attention to other substances capable of producing paralysis. The purpose of the present article is to summarize the pharmacological properties of various substances producing paralysis of skeletal muscles by a depressant action on the spinal cord. Because of the lack of suitable laboratory methods for the evaluation of the therapeutic potentialities of these substances, the clinical results obtained with some of them have also been briefly reviewed. The actions of local anesthetic drugs on the spinal cord were specifically omitted.

TRI-*O*-CRESYL PHOSPHATE

During the early part of 1930 a large number of people in the southwestern part of the United States developed a peculiar form of paralysis which appeared about 10 days after the consumption of an alcoholic beverage sold as "Fluid extract of Jamaica Ginger U.S.P." and often called "Jake." Smith *et al.* (113, 114) have shown that tri-*o*-cresyl phosphate, present as an adulterant in certain fluid extracts of Jamaica ginger, was the etiologic agent of the epidemic of ginger paralysis.

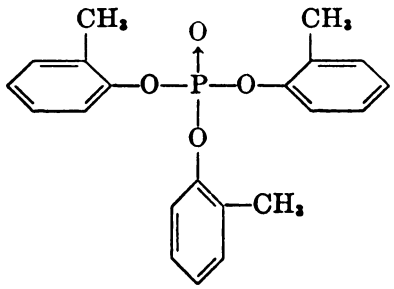

FIG. 1. Structural formula of tri-o-cresyl phosphate

Clinical course: The disability began with soreness of the leg muscles which was soon followed by bilateral foot drop. Bilateral wrist drop also developed in many cases but the disability in the hands was never as marked as in the feet. Paralysis was always bilateral and symmetrical. The clinical picture indicated an involvement of the lower motor neuron localized to the lower lumbar and lower cervical regions of the spinal cord.

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Effects in animals: Tri-*o*-cresyl phosphate administered orally to rabbits or guinea pigs in doses of 50–100 mg per kg caused at first a mild degree of hyperexcitability with generalized muscular tremor and incoordination. This state passed after hours or days, depending on the dose given, into a picture dominated by flaccid muscular asthenia and generalized flaccid paralysis. The rabbits did not show symptoms comparable to the characteristic wrist drop and foot drop observed in human beings after ingestion of adulterated ginger extract. The symptoms of tri-*o*-cresyl phosphate poisoning in the rabbit were, however, exactly the same as those observed after administration of adulterated ginger extracts to these animals.

Oral administration of tri-*o*-cresyl phosphate to dogs, cats and monkeys was without effect but subcutaneous or intramuscular injections produced motor paralysis of the hind limbs after an interval of 6 or more days. In calves and chickens, paralysis similar to that observed in humans could be produced by both oral and parenteral administration (113). Albino rats appeared wholly refractory to the effects of the poison by all routes of administration. Mice were relatively insensitive; flaccid paralysis of the hind legs occurred in some animals after large doses (68).

The site of action: The pharmacological examination of the neuromuscular apparatus in tri-*o*-cresyl phosphate poisoning in hens (115) indicated that neither the muscle fibres nor the motor end plates were affected. Histological examination of the nervous system in Jake paralysis in man and tri-*o*-cresyl poisoning in various animals showed degeneration of the myelin sheaths of the peripheral nerves and degenerative changes of the anterior horn cells throughout the spinal cord (116). Autonomic cells of the cord and dorsal root ganglia also showed definite abnormalities (76).

Effect on enzymes: Bloch (23) found that tri-*o*-cresyl phosphate had a marked inhibiting action on cholinesterase and serum lipase *in vitro* and *in vivo*. Tri-*m*-cresyl phosphate and tri-*p*-cresyl phosphate did not inhibit these enzymes. The action of the *o*-isomer was not due to the liberation of *o*-cresol in the animal body.

If acetylcholine plays an important role in the transmission of impulses in the spinal cord, a relationship between the anticholinesterase activity and the paralysing property of tri-*o*-cresyl phosphate might be expected. However, other substances possessing an inhibiting action on cholinesterase do not produce paralysis. It is possible that the action of tri-*o*-cresyl phosphate on other serum esterases may play an important part in the production of ginger paralysis.

Action of related compounds: Tri-*p*-cresyl phosphate and tri-*m*-cresyl phosphate were much less toxic than the *o*-isomer and failed to produce toxic effects in rabbits, chickens and cats in doses up to 3 grams per kg. Triphenyl phosphate, phenol and the three isomeric cresols were also considerably less toxic than tri-*o*-cresyl phosphate and differed from the latter by the production of symptoms soon after administration of toxic dose (114, 115). Tri-*o*-cresyl phosphite produced qualitatively similar symptoms as the phosphate in rabbits, chickens and rats. In cats, flaccid paralysis or marked extensor rigidity, particularly of the hind limbs, was

observed (115). The histological lesions produced by tri-*o*-cresyl phosphite consisted in a degeneration of the ascending spino-cerebellar tracts and the descending mesencephalic-pontine-cerebello-spinal tracts. In addition, there was also minor degeneration of the lower motor neuron characteristic of tri-*o*-cresyl phosphate (79).

Industrial and medicinal use of tri-o-cresyl phosphate: Tri-*o*-cresyl phosphate and mixtures of the three isomers are widely used in industry as plasticizers in the manufacture of celluloid, paints and varnishes and in tanning of leather. Hodge and Sterner (68) examined the skin absorption of tri-*o*-cresyl phosphate with the help of radioactive phosphorus. They found that absorption through the palmar skin of the hands may occur and may constitute a real hazard in industrial operations permitting repeated exposures to this compound.

Polyneuritis has followed the use of an abortifacient known as Apiol which contains tri-*o*-cresyl phosphate (72a). Certain cases of polyneuritis and of acute ascending paralysis of the Landry type may be due to tri-*o*-cresyl phosphate poisoning (76). Transient paresis of the legs in all members of a family which used a butter substitute and salad oil containing tri-*o*-cresyl phosphate has been described (58a).

DITHIOBIURET

During studies concerning the antithyroid activity of compounds related to thiourea, Astwood *et al.* (2) observed that the chronic administration of dithiobiuret to rats caused reversible paralysis of the skeletal muscles.

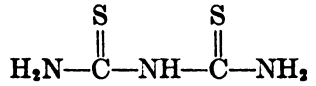

FIG. 2. Structural formula of dithiobiuret

Effect on animals: When dithiobiuret was given in a single dose, it either did not produce symptoms or caused death, the effect observed depending on the amount of the drug given. The lethal dose of the compound for an adult rat from a single injection was 20 to 50 mg. On chronic administration of the drug in drinking water in concentrations of 0.001 per cent to 0.002 per cent, corresponding to less than 0.5 mg of the drug per rat per day, profound muscular paresis was observed after 2 to 4 days. Paralysis appeared first in the hind legs and later ascended to affect all voluntary muscles of the body with the exception of those of respiration, the head and neck. Paralysis was not complete as the animals were able to feed and water themselves. Muscular paresis was maintained as long as the administration of the drug was continued. Animals which had been paralysed for some time lost weight and showed wasting and contractures of the paralysed muscles. Discontinuation of the drug resulted in complete recovery of muscle function in a few days. The chronic administration of slightly larger doses of dithiobiuret caused muscular paralysis and death by respiratory paralysis at the end of 5 to 6 days.

The site of action: The site of action of dithiobiuret is in the central nervous system. Faradic stimulation of motor nerves elicited muscular contraction in paralysed animals. The fact that strychnine failed to induce convulsions in paralysed animals suggests that dithiobiuret possesses a selective depressant action on the spinal cord (2). Altschul (1) did not observe any changes in the electroencephalograms of animals tested after acute or prolonged administration of dithiobiuret.

The anticonvulsant action: In rats, dithiobiuret raised the threshold to electrically induced convulsions and modified the form of convulsions. While normal animals showed tonic-clonic seizures, animals under the influence of dithiobiuret showed seizures of sustained tonic character followed by only minimal clonic movement (1). These observations are rather interesting in view of the findings of Toman *et al.* (121) who have shown that anticonvulsant drugs as a rule abolish the extensor tonic component of the maximal seizure pattern in doses which do not influence or even prolong the clonic phase. Dithiobiuret, therefore, appears to possess a qualitatively different anticonvulsant action. However, the anticonvulsant effect of dithiobiuret was well marked only in animals which were paralysed (1).

The mode of action: Histological examination of the central nervous system of animals paralysed with dithiobiuret did not disclose any structural damage. The acetylcholine and cholinesterase content of brains of paralysed rats was normal. Paralysis could not be counteracted by the administration of pilocarpine, neostigmine, atropine or epinephrine or by large doses of crude liver extract, thiamine, nicotinic acid, vitamin A, biotin, brewer's yeast or biuret (2). Astwood *et al.* (2) believe that dithiobiuret interferes with a hitherto unrecognized process essential to the transmission of impulses in the central nervous system, by blocking a component of some enzyme system.

BENZIMIDAZOLE

Goodman, Gilman and Hart (51, 49) in 1943 made the interesting observation that the simple chemical compound benzimidazole caused transient paralysis in various species of laboratory animals.

The paralysing action: An intraperitoneal injection of benzimidazole to mice or cats in doses of 200 to 300 mg per kg caused a profound decrease of muscle tone and loss of postural reflexes. After administration of the drug, the hind legs became affected first, the trunk and foreleg muscles next and the neck musculature was the last to show the effect of the drug. Large doses of the drug caused complete muscular paralysis which appeared in the order mentioned. During paralysis respiration remained adequate and was sometimes increased during the initial phase of action of the compound.

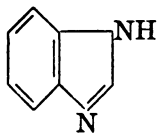

FIG. 3. Structural formula of benzimidazole

During paralysis, corneal and pupillary reflexes were normal and deep reflexes normal or exaggerated. There was little response to painful stimuli; but the impairment was probably secondary to the spinal cord deficit, since very painful stimuli caused dilatation of the pupil.

Paralysis lasted for about one hour and was followed by gradual recovery of muscular power. Recovery as a rule was complete about 4 hours after administration of the drug. Paralysis was not preceded by excitation and was not accompanied by a loss of consciousness. These observations indicate that benzimidazole can produce selective cord paralysis in doses which do not cause anesthesia.

Effect on vital functions and toxicity: Electrocardiographic studies showed that the heart was uninfluenced by larger doses of benzimidazole. The fall of blood pressure observed after rapid intravenous injection of the compound may have been due to vasodilatation.

Respiration remained adequate and the animals continued to breathe spontaneously even during complete paralysis of all voluntary muscles. Death from toxic doses was due to respiratory paralysis. In mice and probably also in other animals the mean lethal dose was more than twice as large as the mean paralysing dose. Benzimidazole, therefore, possessed an adequate margin of safety.

Chronic administration of benzimidazole for many weeks to rats and mice in doses which did not affect voluntary movements, did not influence the growth, behaviour or general appearance of the animals. No gross changes were observed in any organs after the animals were sacrificed.

Benzimidazole has been effectively administered by the intravenous, intraperitoneal, subcutaneous, and oral routes. The compound is apparently well absorbed. Data concerning the fate of the compound in the body are not available. It appears probable that it is rapidly inactivated in the body as cumulative toxicity did not develop. Administration continued over long periods of time did not increase the susceptibility of the animals to the effect of the drug.

Actions on the nervous system: Paralysing doses of benzimidazole did not exert any effect on peripheral nerves and did not affect transmission at the neuromuscular junction. Although full doses of benzimidazole did not cause loss of consciousness and did not affect the electroencephalographic patterns, the drug did elevate the thresholds for evoked cortical potentials and seizures. The loss of the postural reactions and the ascending type of paralysis are not incompatible with a depressant action of the drug on the midbrain and spinal cord (49). During paralysis the deep reflexes were exaggerated and clonus was sometimes present. The specific structure in the central nervous system on which this depressant action is exerted may well be the interneurons. This view is supported by the finding that benzimidazole has a depressant action on multineuron reflexes in the spinal cord, such as the flexor or crossed extensor reflexes, but has little effect on the knee jerk which is mediated by a two-neuron arc (53). The transient emesis sometimes observed after intravenous administration of benzimidazole may be due to a depressant action on inhibitory interneurons of the vomiting center.

The effect of benzimidazole in animals in which various ablations were carried out is of interest. In acute decerebrated cats, benzimidazole caused a disappear-

ance of extensor rigidity and of tonic neck and labyrinthine reflexes. In acute decorticate or hypothalamic preparations, sham rage was abolished and, in spinal cats, responses to nociceptive stimuli disappeared but myotatic reflexes were enhanced (49, 52). The spastic syndrome in a monkey with bilateral resection of cortical area 6 as well as bilateral removal of the caudate nucleus was improved by benzimidazole (51).

The anticonvulsant action: The effects of benzimidazole could be antagonized by nikethamide (52) and metrazol (49). Benzimidazole also decreased the incidence and severity of metrazol convulsions in mice. In animals in which multineuron reflexes have been depressed by benzimidazole, metrazol was less effective than nikethamide in antagonizing these effects on the cord (119). Benzimidazole possessed a powerful antagonistic effect to convulsions and death produced by strychnine and was in this respect at least equal and probably superior to myanesin (7).

Benzimidazole abolished the extensor tonic component of maximal electroshock seizures in rabbits, cats and rats (120). It shared this property with clinically effective antiepileptic drugs such as diphenylhydantoin and phenobarbital, but was considerably less specific in its action.

The diuretic action: Rats given daily doses of benzimidazole 200 mg per kg intraperitoneally exhibited marked polydipsia and polyuria. Polyuria was detectable after 3 days and persisted as long as benzimidazole was administered. Despite a 10 to 20 fold increase in urinary volume, young rats continued to grow and maintained chloride balance. There were no histopathologic changes in the hypothalamus, posterior pituitary, kidneys or other organs. Polyuria was not influenced by large doses of posterior pituitary hormone and was probably due to a specific inhibition of renal tubular reabsorption of water (52).

Other pharmacological properties: Benzimidazole was devoid of local anesthetic action. It had no spasmolytic effect on smooth muscle (49). Wooley (134a) found that benzimidazole in concentrations of 600 micrograms per cc. of medium completely inhibited the growth of *Saccharomyces cerevisiae*. Half maximum inhibition of growth with this organism, *E. coli* and *S. lactis R* was obtained with concentrations of 300 micrograms per cc., 370 micrograms per cc. and 725 micrograms per cc., respectively. Adenine (1000 micrograms per cc.) and guanine reversed inhibition but other purines had little or no effect. The paralyzing action of benzimidazole was not prevented by adenine.

Clinical use: Goodman (49) suggested that benzimidazole, because of its effect on skeletal muscle tone and its anticonvulsant action, may be of value in the treatment of spastic and convulsant disorders. He also considered the use of the drug as a supplemental agent in general anesthesia to increase muscular relaxation. As benzimidazole is readily soluble in water, it may be more suitable for this purpose than the relatively insoluble myanesin. Benzimidazole given intravenously in small dosage to a spastic patient caused a decrease of muscle tone, some nausea and evidence of early intercostal involvement (50). In another patient suffering from Little's disease temporary relaxation of skeletal muscle spasm was observed (52).

The mode of action: The mode of action of benzimidazole is not known. It appears probable that benzimidazole blocks an essential metabolite or enzyme necessary for the propagation of impulses through the interneurons. The action of benzimidazole is in some respects similar to that of myanesin and glyketal and it appears possible that all three drugs have a similar mode of action. Benzimidazole, however, differs from myanesin in affecting cortical mechanisms to a lesser extent (118a).

Related compounds: Goodman (49) examined a number of congeners of benzimidazole, including the methyl, phenyl and dibenzimidazole derivatives. None approached benzimidazole in potency and deviations from the parent structure resulted in loss of the characteristic pharmacodynamic properties.

MYANESIN AND OTHER GLYCEROL ETHERS

Gilbert and Descomps (47) in 1910 observed that 3-phenoxypropane-1,2-diol caused transient paralysis of skeletal muscles in guinea pigs and rabbits. They also noted the antipyretic and local anesthetic properties of this substance and recommended its use in humans as an analgesic and antipyretic. It became commercially available under the name of Antodyne (44). The findings of the French authors were soon confirmed and amplified by Filippi and Rodolico (42). Berger and Bradley (16) examined the pharmacological properties of numerous simple mono ethers of glycerol and found that most of these compounds had a qualitatively similar action. Myanesin, 3-(2′-methylphenoxy) propane-1,2-diol, one of the more potent compounds of the series, has since been the subject of numerous pharmacological and clinical studies and has been made commercially available under various names (Lissephen, Oranixon, Tolserol and Toloxyn in the United States, Myanesin in Great Britain and the British Commonwealth, Relaxar in France (77) and Glycresin in northern Europe (22)).

Short reviews on myanesin have been published (130, 40).

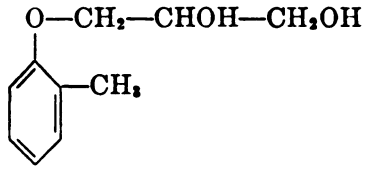

FIG. 4. Structural formula of myanesin

Physical and chemical properties: Myanesin is a white, crystalline solid, and has a melting point of 70–71°C. It is odorless, has a bitter taste and produces a sensation of numbness on the tongue. Solubility in water at 20°C is 1 in 85; in 10 per cent urethane solution, 1 in 40; and in 25 per cent urethane solution, 1 in 4.5. It is very soluble in ethyl alcohol, propylene glycol and aqueous solutions of urea and ethyl urea. Relatively stable supersaturated aqueous solutions can be obtained by cooling solutions prepared at higher temperatures. Solutions of the drug are stable and can be sterilized by heating, and are compatible and misci-

ble with solutions of sodium chloride, glucose, barbiturates and thiobarbiturates (16, 17).

A solution of 0.01 g of myanesin in 10 drops of concentrated sulphuric acid is slightly red; on addition of a drop of formaldehyde solution a deep red color appears (93).

The paralysing action: Small doses of antodyne or myanesin caused reduction of spontaneous activity and a decrease in muscle tone. Larger doses produced ataxia, flaccid paralysis and loss of the righting reflex. Muscular paralysis was always of the ascending type. The posterior limbs and the lower half of the body were affected first and remained paralysed longer than the anterior limbs and neck muscles (42, 16). Respiration was not embarrassed even during complete paralysis of skeletal muscles. During the initial phase of the drug action, respiration was sometimes increased in depth and rate. Paralysis was neither preceded nor followed by excitation or convulsions and was followed by complete recovery of muscular power.

Paralysis occurred within 2 minutes after administration of the drug. The depth and duration of paralysis depended on the amount of drug given. In mice after intraperitoneal administration of 250 mg of myanesin per kg, the righting reflex was lost for about 25 minutes. During paralysis the animals remained motionless and did not execute running movement usually observed after administration of small doses of barbiturates or other anesthetics. The animals were completely limp and lacked righting reflexes. They reacted with powerful and sustained muscular contractions to painful stimuli. The pupillary and corneal reflexes and the knee jerk were unchanged. There was no change in the size of the pupils.

During the peak of paralysis after large doses of the drug, the corneal reflex was lost, the pupils were somewhat dilated and reacted sluggishly to light. Nystagmus was observed for short periods of time during the peak of the drug action. There was some dilatation of the pupil in response to nociceptive stimuli but the withdrawal reflex was abolished. Large doses of myanesin caused salivation in rabbits and cats but vomiting was not observed.

Recovery from paralysis was usually rapid. There was some incoordination of movements for about one hour after muscular power was regained. Burke and Linegar (28) observed nausea and vomiting during recovery from paralysis in dogs.

Route of administration: Myanesin could be effectively administered to animals by the intravenous, intraperitoneal, intramuscular, subcutaneous, rectal and oral routes. The amount of drug producing paralysis varied greatly with the route of administration (Table 1). On intravenous administration, the effect obtained varied greatly with the speed of injection. In rabbits the largest tolerated dose on rapid injection was about 100 mg per kg whereas as much as 350 mg per kg could be tolerated if the injection was carried out very slowly (16).

Species sensitivity: Myanesin produces paralysis in most species of laboratory animals. When the amount of drug required for the production of paralysis was expressed in mg per kg body weight, smaller doses of myanesin were required for the production of paralysis in species of large animals than in species of small

animals. Thus the mean paralysing doses for mice, rats, rabbits and dogs on intravenous administration were approximately 150, 110, 50 and 30 mg per kg, respectively. This relation between the size of the dose and size of the animal species is not unusual and holds true for many drugs.

After rapid intravenous injection of myanesin to rabbits, transient rigidity was sometimes observed (9, 28). The rigidity was similar to that observed after decerebration and was probably caused by a "pharmacological transection" due to the depressant action of the drug on certain structures of the midbrain and not by a direct action on skeletal muscle. The rigidity was transient and was followed by complete flaccid paralysis.

Guinea pigs appeared somewhat less sensitive to the paralysing effect of myanesin than other species and frequently showed salivation, dyspnoea and ruffled fur following administration of the drug (7).

TABLE 1

Mean paralysing (PD_{50}) and mean lethal doses (LD_{50}) in mice and rats after administration of myanesin by various routes

ROUTE		MICE	RATS
Intravenous	PD_{50} mg/kg	150 ± 6	113 ± 10
	LD_{50} mg/kg	322 ± 11	195 ± 10
Intraperitoneal	PD_{50} mg/kg	178 ± 9	120 ± 10
	LD_{50} mg/kg	610 ± 10	430 ± 18
Subcutaneous	PD_{50} mg/kg	325 ± 20	
	LD_{50} mg/kg	1000 ± 56	
Oral	PD_{50} mg/kg		1330 ± 80
	LD_{50} mg/kg		2150 ± 148

In frogs (R. *temporaria*) flaccid paralysis and cessation of respiration were obtained after 3 to 10 mg of myanesin injected into the anterior lymph sac. In frogs myanesin also caused a loss of indirect excitability of the muscle (curare-like action) in doses which caused reversible paralysis. In this respect the action of the drug in frogs differed from that in mammals in which loss of indirect excitability of muscle after tolerated doses of myanesin was not observed (16).

The injection of myanesin into the cavity of marine bivalves caused prompt relaxation of the constrictor muscle and opening of the shell (7).

Acute toxicity: Death from toxic doses was due to respiratory paralysis. The heart continued beating for a short time after respiration had ceased. Table 1 gives the mean paralysing and mean lethal doses obtained after administration of myanesin by various routes to mice and rats. It shows that there is an adequate margin of safety between paralysing and lethal doses of the drug. The standard safety margin of myanesin calculated according to Foster (43) after intraperitoneal administration to mice was 113 per cent.

Post mortem examinations carried out in animals dying after large doses of myanesin showed moderate engorgement of the liver and spleen, subpleural hemorrhages in the lungs and distention of the right auricle with blood (7).

Chronic toxicity: Young growing rats fed for 9 weeks on a diet containing 2 per cent of myanesin did not gain weight as rapidly as the controls which were litter mates. This may have been due to lower food consumption, possibly because of the unpalatibility of the drug-containing diet. On post mortem examination, six out of 20 treated rats showed calculi in the bladder. Other organs did not show any macroscopical or microscopical changes (16).

In another chronic toxicity experiment (18), six young Wistar rats weighing 100 to 140 grams received a diet containing 2 per cent of myanesin while six other animals of similar weight and age served as controls. Each animal on the myanesin-containing diet consumed on the average 0.28 gram myanesin per day. The health of all animals was excellent throughout the period of the experiment. During the duration of the experiment, the urine was examined daily for abnormal constituents and the urea contents of the urine of each animal was estimated at frequent intervals.

One rat receiving the myanesin-containing diet passed dark brown urine from the 7th to the 13th and again from the 36th to the 55th day of the experiment. The urine contained protein but gave negative tests for blood and bile pigments. Another myanesin-fed animal passed discolored urine from the 30th to the 34th day. This urine did not contain protein, blood or bile. The urines of the remaining four test animals and of the six control rats did not contain abnormal constituents at any time during the course of the experiment.

The urea output varied greatly from day to day in both test and control animals, but on any one day the values of the controls were always close to those of the test animals. The animals receiving myanesin usually had a somewhat lower urea output and urine volume than the controls but the differences between the control and test values on any one day were smaller than the day-to-day variations of either the test or control animals. On the 78th and 160th day of the experiments, the red and white cells of all rats were counted and the hemoglobin content determined. The counts of the test animals did not differ significantly from those of the controls and were within the normal limits occurring in Wistar rats. On the 55th day of the experiment, three animals were killed; one control rat, one rat which was on the myanesin diet but did not show any symptoms, and the animal (No. 1) which showed dark urine and proteinuria on two occasions. All three animals were in good general health and there were no pathological findings found at post mortem examination. No organs, with the exception of the kidneys, showed histological changes. The only abnormality found was an increase of vacuolation of the glomeruli, which was somewhat more marked in rat No 1 (which had proteinuria and dark urine) than in the rat which tolerated the myanesin-containing diet without symptoms. Similar abnormalities were present in the kidneys of animals which were on the drug-containing diet for 164 days.

Effect on the cardiovascular system and respiration: Antodyne in doses of 100 to 400 mg per kg given intravenously to rabbits caused elevation of blood pressure and bradycardia. After larger doses, the rise of blood pressure was later followed by a fall. At the time of onset of paralysis, the blood pressure was usually elevated above the original value (42).

Myanesin injected intravenously to anesthetized rabbits or cats did not cause any alteration of blood pressure or respiration in doses of 10 mg per kg. Larger doses caused a transient fall of blood pressure, bradycardia and a decrease in rate and increase in depth of the respiratory movements. A rise of blood pressure after myanesin was never observed (16). Oostende (99) found in dogs that myanesin in doses which produced relaxation of abdominal muscles (15 mg per kg) did not depress the blood pressure or respiration and did not influence the homeostatic mechanism of blood pressure regulation. Larger doses caused a small and transient fall of blood pressure and slight inhibition of respiration but left the homeostatic mechanisms uninfluenced.

The blood pressure responses to epinephrine, acetylcholine and histamine were not altered even after large doses of myanesin. Myanesin did not influence the depressor effect and slowing of the heart produced by stimulation of the peripheral vagus nerve (7).

Action on the muscle: Myanesin in concentrations of 1 in 500 produced a slow contracture of the isolated rectus abdominis of the frog (R. temporaria). Higher dilutions of the drug were ineffective (9).

Contractures produced in the isolated rectus abdominis muscle of the frog by acetylcholine could not be prevented by myanesin in high dilutions (9).

Myanesin injected intravenously to cats in doses of 10 to 30 mg per kg did not cause any change in the muscle action potential of the tibialis anticus muscle. Doses of 50 mg per kg depressed and 70 mg per kg abolished the muscle action potentials (117).

The myoneural junction: Intravenous administration of myanesin in doses of 50 mg per kg to chloralosed or decerebrated cats did not influence the indirect excitability of the gastrocnemius muscle. In mice after very large doses of the order of 500 mg per kg there was no response to indirect stimulation but the threshold to direct stimulation was unchanged (9). This effect may have been due to either a depression of neuromuscular transmission or to direct action on the nerve (local anesthetic action). Because indirect excitability was not abolished after systemic administration of large doses of cocaine and procaine, it appears likely that myanesin in very large doses may produce a block at the myoneural junction. This curare-like effect, however, does not play any part in the production of reversible muscular paralysis in mammals because under such conditions paralysis to indirect stimulation is never observed.

The local anesthetic action: The local anesthetic activity of myanesin was similar to that of procaine when the rabbit's cornea or the motor or sensory nerves of the frog were used as test objects. When examined by the intracutaneous wheal method in guinea pigs, myanesin had only about two-thirds of the activity of procaine (9). As procaine does not produce paralysis on systemic administration, it appears unlikely that the paralysant action of myanesin would be due to its local action on the peripheral nerves. The opinion that the local anesthetic effect and the paralysing action are independent properties of the drug is further supported by the observation that the paralysing drug, benzimidazole, does not possess any local anesthetic action.

Effect on the peripheral nerve: Myanesin in doses of 30 mg per kg intravenously did not influence the nerve action potentials, the neuromuscular conduction time, or the nerve conduction velocity in cats. After doses of 50 mg per kg, there was marked depression of the nerve action potentials, and a definite prolongation of the nerve-muscle transmission time and the nerve conduction time (117). The rheobase, chronaxie, galvanic tetanus ratio and repetitive stimuli ratios were unchanged even after the administration of toxic doses (42a).

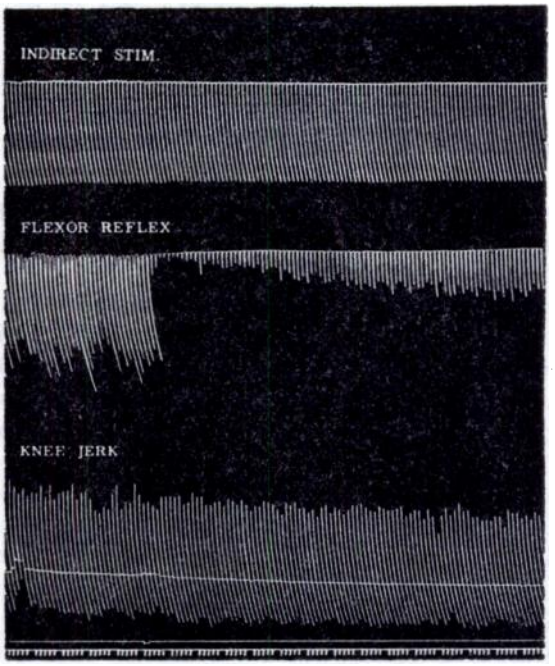

FIG. 5. The effect of myanesin on indirect excitability of skeletal muscle, the flexor reflex and the knee jerk. Cat 2.89 kg. Dial anesthesia.

Tracings from above downwards: 1) Stimulation of the carpal flexor muscles of the front leg through its nerve; 2) The flexor reflex; 3) The knee jerk; 4) Signal line and 5) Time in 10 second intervals. At the signal myanesin 40 mg. injected intravenously.

Effect on spinal reflexes: Myanesin had no effect on the normal knee jerk of cats and rabbits in doses which caused muscular relaxation and paralysis. The flexor and crossed extensor reflexes were depressed or abolished after small, non-paralysing doses of the drug. This effect is illustrated in Figure 5 which also shows the lack of curare-like action of myanesin. The depressant action of the drug on multineuron reflexes taken in conjunction with its lack of effect on two-neuron arc reflexes suggests that myanesin possesses a selective depressant action on the interneurons of the spinal cord. An equal degree of depression of the flexor reflex in an anesthetized cat weighing about 3 kg. was obtained after intravenous injections of 80 mg. benzimidazole, 40 mg. myanesin or 25 mg. glyketal (7).

Myanesin had a marked effect on exaggerated tendon reflexes. In lightly

anesthetized cats in which exaggerated knee jerks and tremors were produced by the administration of strychnine, myanesin in small doses abolished the tremor and reduced the knee jerk to its usual size (9). Myanesin also reduced to normal the hyperirritable spinal reflexes produced in monkeys by the injection of neostigmine or strychnine, but did not have any effect on normal reflexes (73).

Stephen and Chandy (117) examined the effect of myanesin on contralateral transmission through the spinal cord. When they stimulated one sciatic nerve and recorded the nerve action potentials from the other sciatic nerve, no changes from the normal were observed after injections of 40 mg per kg of myanesin. These findings are in disagreement with the results obtained by the reviewer who observed suppression of the crossed extensor reflex in both intact anesthetized and spinal cats after similar and even smaller doses of myanesin.

Effect on facilitatory and inhibitory systems: The loss of postural reflexes, the occurrence of nystagmus, and certain clinical observations in humans show that myanesin possesses a definite action on the basal ganglia and nuclei of the brain stem. This action was experimentally investigated by Henneman *et al.* (63). Working with cats, they found that the reduction of the knee jerk observed after stimulation of the suppressor centers in the reticular formation could be counteracted by the administration of myanesin. On the other hand, the increased knee jerk obtained after stimulation of the facilitatory centers of the reticular formation could be reduced by the administration of myanesin to the size present before stimulation. Thus, it appears that myanesin can counteract impulses originating in both the suppressor and excitatory nuclei of the reticular formation. These effects were obtained with small doses of myanesin which did not cause paralysis.

Inhibition and facilitation of the knee jerk resulting from cortical stimulation were abolished with still smaller doses of myanesin. This observation suggests that longer and more complex circuits, such as are usually involved in spasticity, are more vulnerable to myanesin. Purely spinal facilitatory and inhibitory reflex arcs examined in decapitate preparations were similarly influenced. From this type of evidence, and from electrical studies of segmental spinal reflexes, it appears that myanesin relieves spasticity by reducing tonic extrapyramidal fac litation of stretch reflexes, whatever its source. Because facilitation dominates inhibition in spasticity, it is presumably more affected by the drug (63).

Effects on cortical function: Electroencephalographic studies in humans did not show any evidence of significant alteration in the electrical activity of the cortex after large intravenous doses of myanesin (117, 46). In certain cases which showed increased nervous tension, there was an increase in normal alpha rhythm after myanesin but slow waves were not observed. Abnormal waves recorded from the base of the brain disappeared after myanesin (117). Everett and Toman (50) found definite electroencephalographic changes of the sleep type with myanesin but not with benzimidazole when doses were employed which just produced spinal cord effects.

Finkelman and Dobin (42b) stimulated the cortex of cats by application of strychnine and recorded potentials from the cortex and the pyramids. After

myanesin, 30 mg per kg intravenously, the cortical spikes continued but none could be observed at the pyramid. The synchronous movements of the extremity observed after application of strychnine disappeared after administration of myanesin. From these results it may be concluded that myanesin did not act on cortical cells but impeded transmission through subcortical efferent pathways.

The anticonvulsant action: Launoy observed in 1910 that guinea pigs treated with antodyne tolerated lethal doses of strychnine without ill effects (78). Myanesin also possessed a powerful antagonistic action to the effects of strychnine. On simultaneous intravenous administration, as little as one-thirtieth of the LD_{50} of myanesin protected mice from a minimal lethal dose of strychnine. Larger doses of strychnine could be antagonized by proportionally larger doses of myanesin. Myanesin antagonized both the lethal and the convulsant action of strychnine in small, non-paralysant doses and was, in this respect, much more effective than hexobarbital which possessed a protective action only in anesthetic doses (9). Orloff *et al.* (100), using timed intravenous infusions of strychnine, found myanesin more effective than trimethadione, phenurone and phenobarbital in elevating the threshold for convulsions and in protecting mice from death.

The antagonistic action of myanesin against metrazol was relatively weak. Large paralysing doses of myanesin were required to prevent convulsions from metrazol. Smaller doses of myanesin were effective in preventing death but had little effect on the incidence and severity of convulsions (8, 124).

Myanesin effectively antagonized the central convulsant effects of hexachlorocyclohexane in dogs (37).

Antodyne, myanesin and numerous related compounds elevated the threshold to electrically induced convulsions in rats and rabbits. In this respect, antodyne and myanesin were about equally effective as trimethadione (11). Unna *et al.* (124) have shown that myanesin prevented death from electroshock in mice and changed the pattern of the seizures. The tonic flexor-extensor phase was abolished and only clonic convulsions were observed. These were of a much more violent nature than in the controls. The effect of myanesin in rabbits undergoing electroshock was studied by Holt *et al.* (68b).

Myanesin antagonists: With the possible exception of strychnine, there is no other drug known at present which has an appreciable analeptic action in myanesin paralysis. The following drugs did not have any appreciable effect on the duration of paralysis in mice: epinephrine, amphetamine, atropine, nikethamide, ephedrine, metrazol, physostigmine, picrotoxin, neostigmine, and strychnine. The duration of paralysis in rabbits was shortened by strychnine if the drug was given intravenously immediately after myanesin was administered (8).

Synergistic effects: The simultaneous administration of ineffective doses of hexobarbital and myanesin to mice produced narcosis of 30 minutes duration. Small doses of myanesin also increased the depth and duration of hexobarbital anesthesia and suppressed prenarcotic excitement (16). On joint administration to mice, myanesin and pentobarbital produced an additive effect (128).

The joint action of d-tubocurarine administered with myanesin, as judged by the ability of the animals to maintain themselves on the rotating cylinder, was

less effective than would have been expected on the basis of simple summation of effects. When lethal doses were given, the combined effect of d-tubocurarine and myanesin was potentiated (20).

Antipyretic and analgesic action: Antodyne in a large dose had a marked but short-lasting hypothermic action in dogs (47). In guinea pigs made febrile by the injection of sputum of tuberculous patients, antodyne in doses of 100–150 mg per kg caused a marked but transient fall of temperature (42). Myanesin did not possess any analgesic action in rats, mice and rabbits in doses insufficient to cause paralysis (16).

Effect on urine flow: Antodyne had a prompt but short-lasting diuretic effect (42). With myanesin, a transient antidiuretic action was observed (18). In rats, doses of 350 mg per kg significantly reduced urine excretion for about 5 hours following administration of the drug but did not greatly influence the total amount of urine excreted within 20 hours.

Other properties: Myanesin in dilutions of 1 in 10,000 did not affect the tonus and contractions of the isolated rabbit duodenum. Contraction of the guinea pig ileum caused by histamine or acetylcholine could be partially relaxed by myanesin in a dilution of 1 in 5,000 (16).

Myanesin was unable to protect guinea pigs from dyspnoea and death produced by histamine or acetylcholine aerosols (7).

It was not possible to sensitize guinea pigs to antodyne or myanesin (79a, 7). The repeated cutaneous application of 10 ml per kg of a 5 per cent aqueous solution of antodyne discolored the skin of rats but did not cause irritation (79a). An exposure to antodyne mist for one hour produced slight temporary respiratory irritation in hamsters (79a).

Injected intravenously in rabbits, myanesin in doses of 110 mg per kg given on two successive days did not affect the blood sugar and blood urea levels. This dosage was also without effect on the number of red and white cells. The hemoglobin content of the blood was slightly lowered after injection of the drug but this decrease was not significant. There was also a slight relative neutropenia and lymphocytosis after administration of large doses of myanesin to rabbits (7).

Myanesin in large paralysing doses did not depress the tail response in morphinized mice (101). This reflex is regularly depressed after small doses of d-tubocurarine or β-erythroidine.

A marked delay in the onset of rigor mortis could be obtained in rabbits by the administration of 300 mg per kg of myanesin 30 minutes before the animal was sacrificed (4).

The antibacterial action: Myanesin possessed a bactericidal action on various gram-positive and gram-negative bacteria in concentrations from 0.2 to 1 per cent. The effective concentrations against *Streptococcus hemolyticus*, *Pseudomonas pyocyanea* and *Clostridium Welchii* were 0.2, 0.8 and 0.4 per cent, respectively. The bactericidal action of myanesin was not greatly inhibited in the presence of 10 per cent horse blood. Tests for inhibition of phagocytosis, carried out by the technic of Welch and Hunter (129) using artificially opsonized staphylococci,

showed that myanesin was significantly less toxic to leucocytes than was phenol in concentrations of 0.2 and 0.4 per cent. In higher concentrations, the toxicity of the two compounds was similar. Myanesin did not exert any chemotherapeutic activity in mice infected with hemolytic streptococci or *Ps. pyocyanea* (7).

Method of determination: Three methods for the determination of myanesin in blood and body fluids have been described. The method of Wyngaarden *et al.* (136) depends upon nitration of myanesin in aqueous solution and the development of a strong yellow-green color on addition of sodium hydroxide. Titus *et al.* (118) developed two methods of determination: one involves coupling of myanesin with diazotized 2,4-dinitroaniline, and the other a colorimetric determination of the formaldehyde resulting from periodate oxidation. The coupling method is most sensitive and permits the determination with accuracy of 2 micrograms per ml. The smallest amount of myanesin which can be measured by the other two methods is about 5 micrograms per ml.

Morch (93) described 2 methods suitable for the quantitative determination of myanesin in pharmaceutical preparation.

Metabolism of myanesin: Myanesin is quickly metabolized to a physiologically inactive compound in the body. Suitable extracts of the urine collected from rabbits or rats after large doses of myanesin did not cause paralysis in mice (16, 18). Chemical analysis showed that, in dogs, only 0.1 to 2 per cent of the administered dose was excreted as free myanesin (136, 118), while 32 to 42 per cent were excreted in conjugated form (136).

Further studies disclosed the presence of at least two different metabolic products of myanesin in the urine (54, 105). The metabolite excreted in large quantities was identified as β-(*o*-toloxy)-lactic acid. This compound melted at 146°C, was optically inactive, and had a neutral equivalent of 198. Because of its low toxicity, it appeared to be a true detoxification product. It was pharmacologically inert and did not possess any paralysing myanesin-like action in doses as high as 1200 mg per kg (105).

The other metabolic compound appearing in the urine after administration of myanesin gave a positive test with Ehrlich's diazo reaction (18). The diazo reaction observed conformed to the type B reaction of Hunter (69). The chemical structure of this compound has not yet been determined but it appears probable that it represents a further step in the degradation of myanesin. Although this metabolite was excreted in small quantities, it was present in the urine as early as 15 minutes after an oral dose of myanesin (21). The reaction was given by urine passed up to 8 hours after a single dose of myanesin. Rats fed for 2 months a diet containing 2 per cent of myanesin continued to excrete the metabolite for 2 days after myanesin has been discontinued. The intensity of the color in the urine was proportional to the amount of drug taken.

Phenolic constituents in urine: The excretion of phenols in urine after large doses of antodyne was unchanged (42). The phenolic constituents in the urine of rats which had been fed a diet containing 2 per cent of myanesin for 150 days were estimated by the method of Volterra (127). There was a small increase in free volatile phenols and a very marked increase of the conjugated phenols. The amount of

aromatic hydroxy acids and residual phenols was about twice as large in the test animals as in the controls. An aqueous solution of myanesin subjected to analysis by Volterra's method was quantitatively indicated in the residual phenol fraction (18).

The nature of the conjugated phenols excreted after the administration of myanesin has been further investigated. It was found that 59 per cent of the total conjugated phenols or 3.7 per cent of the total myanesin ingested was conjugated to glucuronic acid, and 14.4 per cent of the conjugated phenols or 0.13 per cent of the ingested dose of myanesin was excreted as a sulphuric acid conjugate (18).

Plasma levels: Wyngaarden *et al.* (136) correlated the plasma levels of myanesin with the effects observed in dogs. After intravenous administration of 50 mg per kg of myanesin, flaccid paralysis was observed with blood levels of about 5 mg per cent. Paralysis was very transient, but unsteadiness and muscular weakness persisted for about 20 minutes. During this time, the plasma levels were 2.4 mg per cent. The myanesin concentration dropped to about 0.8 mg per cent 40 minutes after administration of the drug. No free myanesin could be detected in the 90-minute plasma sample of any of the dogs.

Rate of disposition: The rate at which myanesin was detoxified in rabbits was determined. Myanesin was injected intravenously as a 10 per cent solution at a rate of 100 mg per minute. The mean lethal dose was 220 mg per kg. To obtain an indication of the rate of detoxification, it was assumed that death of the animal would occur when an amount of myanesin equivalent to the LD_{50} would be present in the body in unchanged form. The occurrence of death after injection of one half of the LD_{50} repeated at various intervals was therefore observed. The difference between the LD_{50} given in one dose and the lethal dose after fractional doses was taken to be equal to the amount of drug detoxified during the period of time elapsing between the administration of the first fractional dose and the death of the animal. When doses were given at 10-minute intervals, on the average 40 per cent of the LD_{50} (*i.e.*, 88 mg per kg) was detoxified in 21 minutes. Therefore, 4.2 mg per kg were detoxified each minute. The corresponding values obtained when myanesin was given at intervals of 15 and 20 minutes were 3.7 and 3.9 mg per kg per minute, respectively. Thus it appears that rabbits can dispose of about 4 mg myanesin per kg each minute (7). Cats tolerated the intravenous infusion of 4.5 mg of myanesin per minute per kg body weight for 3 or 4 hours (16).

Morrison *et al.* (95) examined the rate of disposal in dogs by a more direct method. They injected a priming dose of 60 mg per kg of myanesin intravenously and 5 minutes later started a continuous infusion of myanesin at a rate of 1 ml per minute. The concentration of the drug was adjusted so as to give each animal either 1 or 2 mg of myanesin per kg per minute. Blood samples for determination of plasma concentrations were taken at 30-minute intervals for 2 hours during the period of infusion and at hourly intervals thereafter. Infusion of 2 mg per kg per minute resulted in increasing plasma concentrations and 1 mg per kg was insufficient to maintain plasma levels.

Distribution in body fluids and tissues: Myanesin is widely distributed in the

body approximately according to the water content of each tissue. A notable exception to this was the brain in which the ratio of tissue to plasma was always more than unity and averaged about 2. The concentrations of myanesin in spinal fluid and saliva were consistently lower than in plasma (94, 95, 103). Data on the concentration of myanesin in the spinal cord have not been published.

Related compounds: Most ethers of glycerol of the structure R-O-CH_2-CHOH-CH_2OH produced transient paralysis qualitatively similar to that observed after antodyne or myanesin (24, 11, 80).

When R was an aliphatic radical, straight chain alkyls contributed more to the paralyzing activity than branched chain isomers or unsaturated radicals. The *n*-amyl ether was the most potent compound of the aliphatic series. It was about as active as antodyne and about one-third as active as myanesin.

The activity of compounds in which R was a substituted benzene nucleus varied with the position and kind of the substituent group. Compounds with a small alkyl or alkoxy group or chlorine in the ortho position possessed strongest paralysing action. Compounds with these radicals in meta or para position were less active than the ortho isomers. The presence of a hydroxy, amino, amido, ester or hydroxy-alkyl group or multiple substitution in the benzene ring with alkyls, halogens or both decreased paralysing activity (11).

Compounds with lower solubility than myanesin showed, for the most part, a slower onset and longer duration of action. The rather insoluble 3-(1'-methyl, 4'-isopropyl) propane-1,2-diol on oral administration to dogs produced more prolonged and constant blood levels than myanesin (29).

Stereochemical configuration did not appear to influence paralysing activity as judged by the similar activity of the levo and racemic guaiacol glycerol ethers (112).

The effect of substitutions in the glyceryl side-chain depended on the structure and position of the substituent group. Methyl substitution on the C_2 atom of the glyceryl side-chain did not materially alter paralysing activity but substitution on the C^1 atom decreased activity. Substitution in the hydroxyl groups decreased or destroyed paralysing activity.

An increase or decrease in the length of the glycerol chain caused a decrease or disappearance of paralysing properties as witnessed by the slight activity or inactivity of the glycol, erythritol and mannitol homologues (11).

Alpha substituted glycidyl ethers were generally more potent than the corresponding glycerol derivatives. Replacement of the hydroxy groups of C_1 and C_2 atoms by aliphatic groups decreased the potency (67).

The alpha thioethers and sulphones of glycerol also had paralysing activity but were more toxic than the oxygen ethers.

The 3-(2'-methoxyphenoxy)propane-1,2-diol which possesses paralysing properties of a similar order as myanesin has been sold for many years as an expectorant under the proprietary name of Resyl.

Myanesin acid succinate possessed pharmacological properties qualitatively similar to myanesin. It was less toxic and had a much weaker paralysing action. In doses not causing paralysis, it had a longer duration of action than myanesin.

Liver homogenates hydrolysed myanesin acid succinate into myanesin and succinic acid and the compound was dealt with in a similar way *in vivo* (106, 19).

Certain 2-substituted-1, 3-propanediols had a stronger anticonvulsant action and a weaker paralysing action than myanesin and similar compounds. 2,2-Diethyl-1, 3-propanediol, called DEP, the outstanding compound of the series was as active as phenobarbital in preventing convulsions and deaths from lethal doses of metrazol in mice. It was more effective than phenobarbital or myanesin in antagonizing the convulsant and lethal effects of strychnine. Suitable doses of DEP also prevented or modified electroshock seizures in mice and rabbits (14a).

The Clinical Use of Myanesin

Effect of administration in humans: The slow intravenous administration of 1 gram of myanesin to adults did not cause any effects (83). A similar dose given more rapidly caused a subjecive sense of warmth, relaxation and slight giddiness but no impairment of mental faculties. There was diminution of muscle tone without interference with voluntary muscle control. Strength measured on a dynamometer was not altered. Coarse nystagmus in all directions, loss of eye convergence and slurred speech were also observed. Rarely patients became faint when placed upright while under drug action. During or after administration, no apprehension was felt (83, 117, 46, 110).

After administration of somewhat larger doses (2 grams or 30 mg per kg), most patients complained of feeling "dopey" or relaxed. After completion of the injection, the depression disappeared within 2 to 3 minutes but the relaxed feeling persisted for about an hour (117). Baisi (2a) observed vomiting of central origin (which was not preceded by nausea) after parenteral administration of myanesin.

The oral administration of myanesin in 1 gram doses, as a rule, did not cause any symptoms provided that it was given after meals. A similar dose given on an empty stomach sometimes caused transient giddiness and a feeling of relaxation. A few patients experienced "heart burn" and nausea (21). Certain patients exibited a mild degree of euphoria for 1 to 2 hours following administration of the drug (117, 62, 7).

Use during anesthesia: For the performance of numerous surgical operations, adequate muscular relaxation is required. To obviate the risk concomitant to deep anesthesia, the use of curare with light anesthesia has been advocated (57). Curare used in this way produces paresis or paralysis of the skeletal muscles by blocking neuromuscular transmission. Myanesin is used in order to depress the reflex hyperexcitability present during light anesthesia. It is not used clinically for its paralytic action which requires amounts greater than those usually given to patients (10).

The effect of myanesin in anesthesia was described for the first time by Mallinson (83). He used the drug in 112 cases in conjunction with pentothal and nitrous oxide or cyclopropane and obtained excellent relaxation with doses ranging from 0.5 to 2 grams intravenously (about 7 to 28 mg per kg). Respiration and circulation were not impaired and no complications attributable to the drug were

encountered. The tone of the musculature of the intestinal tract was unchanged or slightly diminished (85, 90). The postoperative condition of patients given myanesin was better than that of patients receiving spinal or deep general anesthesia or curare. Mallinson stated that myanesin had advantages over curare because of the wider margin of safety, adequate abdominal relaxation without intercostal paralysis, the potentiation of barbiturate action and the absence of bronchospasm and salivation. The shock-like state which is sometimes observed after the administration of curare has not been noted after myanesin (84). These results were confirmed by Turnbull (123), Bistrom and Viikari (22) and Musgrove (96).

Lyall (82) obtained satisfactory results with myanesin in robust individuals who did not relax easily with ether. In very ill patients, and in thoracic surgery where controlled respiration is of advantage, curare seemed preferable. Ballantine (3), Marshall (89) and Macar (82a) also commended myanesin for producing satisfactory muscular relaxation without respiratory depression. Because of the occurrence of venous thrombosis after administration of a 10 per cent solution, they recommended the use of more dilute solutions which did not cause ill effects. Marston (90) and Carman (31) were impressed by the small amount of myanesin required to secure relaxation in many abdominal operations. Wilson and Gordon (134) and Davison (38) recommended myanesin as an aid to anesthesia in children.

Mallinson (86), in summarizing his experience of 1500 myanesin injections, stated that the principal field for myanesin was abdominal surgery, hemorrhoidectomy and colpoperineal repair. Used jointly with pentothal, myanesin was of little value in facilitating intubation. It abolished laryngeal spasm when used during deeper levels of anesthesia. Myanesin was also useful in tonsillectomy and Caesarean section, when gas and oxygen and pentothal were used as the anesthetic agents. Mallinson believes that relaxation with myanesin is as good as with curare. This view was contradicted by Gray (55) and Woolmer (135) who found myanesin ineffective in reasonable dosage. Dinnick (39) abandoned the use of the drug because the relaxant effect was not as pronounced as that produced by curare. Dale (35, 36) found the action of myanesin unpredictable. In some cases, relaxation was comparable to that associated with spinal analgesia, while in others relaxation was absent or poor. Because relaxation of skeletal and abdominal muscles in the absence of stimulation of the peritoneum was good, he used myanesin successfully in gynecology for examinations under anesthesia. Myanesin was also of value in orthopedic operations for manipulation of the spine (36).

The Use of Myanesin in Nervous Disease

The effects of myanesin on experimental animals suggested that the drug may be of value in certain nervous disease where spasticity, tremor and involuntary movements were a factor.

Paralysis agitans: Stephen and Chandy (117) were the first to show that the intravenous injection of myanesin in about 1 gram doses abolished the tremor

and rigidity of patients suffering from paralysis agitans. The symptoms remained in abeyance for 30 to 60 minutes and were less severe than usual for about 12 hours. Voluntary muscular power was not impaired. These results were confirmed and amplified by Schlesinger *et al.* (110) who thought that patients with rigidity have an unusual sensitivity to myanesin. Hunter and Waterfall (71) and others (70, 87, 46) also found myanesin effective in paralysis agitans on parenteral administration. Hay (62), treating paralysis agitans in psychotic patients, gained the impression that the remission of symptoms lasted the longer, the more recent the onset of the Parkinson syndrome.

Berger and Schwartz (21) found that myanesin administered orally was effective in certain cases of paralysis agitans. Although the effect of the drug on oral administration was not as spectacular as that observed after parenteral administration, it was of longer duration and did not cause side effects. Berger (7) treated 47 cases of paralysis agitans of various etiology with myanesin orally. Some decrease of rigidity and tremor was observed in 22 cases, 21 patients were unchanged and in four the tremor became temporarily worse. Cases of post-encephalitic, idiopathic and arteriosclerotic origin appeared to respond equally well. The oral efficacy of myanesin was recently confirmed by Gammon and Churchill (46).

Myanesin is said to have an unquestionably greater effect in cases of Parkinsonian rigidity and tremor than any other therapy short of narcosis (46). These results are of particular interest in view of the fact that myanesin differs from most other drugs recommended for the treatment of paralysis agitans in not possessing atropine-like action (14).

Involuntary movements: The efficacy of myanesin in suppressing or diminishing athetotic and chorea-like movements has repeatedly been shown (117, 110, 21, 46, 108). Athetoid movements in cerebral palsy sufferers, and those observed in bilateral athetosis and dystonia musculorum deformans, responded equally well. Senile tremor was also greatly improved but cases of Huntington's and congenital chorea were unaltered (46). Gammon and Churchill (46) observed an increase of the intention tremor in 2 cases of multiple sclerosis but the reviewer noted a favorable effect on intention tremor and head wagging in three out of 19 cases of multiple sclerosis. Myanesin was also found of considerable value for the amelioration of the jerking movements of the head observed in spasmodic torticollis (7). It proved of no value in four cases of hereditary intention tremor occurring without other neurological symptoms.

Spasticity: The status of myanesin in spasticity due to upper motor neuron lesion is not yet clearly defined. After intravenous administration of the drug, Stephen and Chandy (117) observed complete flaccidity in a congenital spastic child but did not note any change in the degree of spasticity in a case of spastic paraplegia due to a tuberculous lesion involving the thoracic vertebrae. Schlesinger *et al.* (110) have shown that myanesin in suitable dosage has a pronounced though evanescent effect upon the isolated or partly isolated spinal cord. Mather (91) reported immediate and pronounced relaxation of the spastic muscles of the lower limbs in cases of spastic hemiplegia, paraplegia, disseminated sclerosis and other upper motor neurons lesions after an intravenous injection of 1 gram of

myanesin. The effect lasted for 5 or 6 hours. After oral administration of myanesin to certain hemiplegic patients, a decrease of spasticity and recovery of some of the voluntary movements were observed (21). The effect of the drug manifested itself mainly by improvements of the physical performance of the patients. There was little or no change in the tendon reflexes and clonus.

Muscle spasm: Schlesinger *et al.* (109, 110) believe that acute muscle spasm constitutes the major indication for the use of the drug. Myanesin was particularly effective for the relief of muscle spasm due to acute low back and cervical spine syndromes. The drug also proved of value as an aid or substitute for traction (109, 36), for the reduction of major fractures in muscular males (36), for the evaluation of the reversibility of contractures and deformities, and for facilitation of physical therapy (110). Organic facial hemispasm or fasciculations in amytrophic lateral sclerosis did not show any alteration after myanesin (46).

Tetanus: All the symptoms of experimental tetanus in mice could be abolished by myanesin (9). Belfrage (6) used myanesin intramuscularly in 2 cases of tetanus and found it more effective than curare. The value of myanesin in tetanus has been confirmed by others (89, 109, 46, 77, 38a). Torrens *et al.* (122) reported a carefully studied severe case of tetanus in which myanesin gave much benefit. They found that the intravenous injection of 1 gram of the drug in a 5% solution abolished the spasms and enabled the patient to take nourishment. The reflexes remained brisk and clonus persisted. They advocate further clinical trials by the oral, intramuscular and intravenous routes.

Convulsive states: Hunter and Waterfall (71) tried the effect of myanesin in 3 cases of continuous epileptic attacks and observed immediate disappearance of the seizures after intravenous doses of 0.4 to 1.0 gram. Schlesinger (109) also found myanesin of value in status epilepticus. Gammon and Churchill (46) observed the disappearance of the characteristic spike and dome waves pattern in the electroencephalograms of six cases of true petit mal. Convulsive cases with focal lesions and two cases of petit mal associated with generalized seizures were unaffected.

Judged by animal experiments, myanesin should be the drug of choice in strychnine poisoning. The use of the drug for this purpose has not been reported. Myanesin was not of much value for the prevention of traumatic accidents during convulsive shock therapy (109). Doses of 30 mg per kg myanesin did not diminish the intensity or the duration of therapeutic electroshock convulsions (62) but shortened the period of apnea following the convulsions (Unna, personal communication). Holt *et al.* (68a) found that dilantin markedly enhanced the ability of myanesin to soften convulsive rigor.

Psychoses: Schlesinger (110) used myanesin in two cases of catatonia without benefit. Gammon and Churchill (46) observed improvement in a patient with reactive depression. A deteriorated negativistic schizophrenic became communicative for the first time in years and an agitated patient became calm and communicative under the action of the drug. Hay (62) observed pleasant relaxation or euphoria without other changes in the mental condition of four schizophrenics. Three deteriorated catatonics did not show any psychic effects and remained

mute. The changes in manic-depressive patients were minimal and of short duration.

Schlan and Unna (110b) found in patients with anxiety states that myanesin allayed anxiety without clouding consciousness. The drug also had a sedative action in manic depressive psychoses. In schizophrenic patients a sedative action was noted only when the environment was not disturbing.

Miscellaneous conditions: Myanesin was of no value in two cases of Friedreich's ataxia (7). In the treatment of various arthritic symptoms (21, 109), myanesin was sometimes helpful but it is not clear whether the effect of the drug in these conditions was due to its muscle relaxing effect, its antipyretic or analgesic action, or to other factors. A case of true gouty arthritis responded dramatically to the administration of the drug by mouth.

In patients addicted to morphine and heroine, myanesin abolished somatic symptoms of withdrawal such as yawning, nausea, vomiting and leg cramps but did not affect craving for the drug (110b). Myanesin also promptly abolished the tremor and anxiety of chronic alcoholics in abstinence (110b).

Stephen and Chandy have shown that myanesin is effective in suppressing intractable pain of thalamic origin (117). In tabes, spontaneous pain was abolished and the exaggerated second-pain in response to pinprick was reduced without loss of pinprick perception. Causalgic pain was relieved for a short time and improved for 24 hours. Phantom limb pain was unaffected (46). Brooks *et al.* (26) found that the painful limitations of movements in two cases of poliomyelitis were unaffected.

Toxic Effects and Complications

Hemolysis and hemoglobinuria: Pugh and Enderby (102) have shown that myanesin had hemolytic properties *in vitro* in concentration of 1 in 200. The hemolytic action of the drug was increased by the solvents used in the preparation of the commercially available solutions (64). The solvents used were ethanol and propylene glycol (56). Ogilvie *et al.* (98) showed that a 10 per cent commercial solution of myanesin caused flocculation of blood.

When myanesin solutions were injected into a vein at the wrist and blood samples withdrawn from a vein in the antecubital fossa were examined for the presence of hemolysis, the injection of 1.5 cc of a 5 per cent solution caused considerable lysis but a similar amount of a 1 per cent solution did not cause any change from the control. In these experiments, a commercially prepared solution of myanesin was used and no attempt was made to determine whether myanesin or the solvents were responsible for hemolysis (102). The occurrence of intravascular hemolysis without hemoglobinuria after intravenous myanesin has been observed by Lyall (82) and Wilson and Gordon (134). Pugh and Enderby (102) observed hemoglobinuria following the intravenous use of myanesin in three cases. Samples of urine voided soon after the injection were discolored and contained hemoglobin, but no hemoglobin was found in subsequent samples over a period of 2 days. Stephen and Chandy (117), Noble (97), Brooks *et al.* (26) and Marshall (89) noticed intense hemoglobinuria after administration of myanesin

in 10 per cent solution by the intravenous route. Pugh and Enderby believe that intravenous hemolysis occurs with every injection of strong solutions of myanesin. Because of the high threshold value of hemoglobin, hemoglobinuria is seen only occasionally. They consider preparations of myanesin, as constituted at present, unsatisfactory for intravenous use because of the danger of blockade of the kidney tubules with acid hematin crystals formed from the hemoglobin in acid urine. Wilson (133), Hay (62) and Enderby (41) felt that the solvent and not myanesin itself may be responsible for hemolysis.

Administration of more dilute solutions (5 per cent or less) did not cause hemoglobinuria or other untoward effects in large series of cases (110, 109, 46, 122, 89, 31, 96). According to Mallinson (86), fewer than 20 cases of hemoglobinuria have reported out of an estimated 10,000 administrations of myanesin. He believes that, in certain patients, the discolored urine may be due to an abnormal pigment and not to hemoglobin. Mallinson (86) and Wilson and Gordon (134) presented experimental evidence to show that myanesin increased the fragility of the red cells, but Torrens *et al.* (122) found a normal red cell fragility curve after 12 grams of myanesin had been given as a 5 per cent solution in divided doses. After oral administration of myanesin, hemoglobinuria has not been observed (41, 21).

Kidney damage and anuria: Hewer and Woolmer (65, 66), Dinnick (39) and Goodier and Goodhart (48) described cases of fatal anuria after the intravenous use of myanesin during anesthesia. The necropsy findings were similar to those observed after incompatible blood transfusions and may have been due to intravascular hemolysis followed by deposition of pigment in the renal tubules. The histological picture of the kidneys also suggested that myanesin may cause cortical ischemia. Mallinson (86) reported uremia in two patients who had myanesin during anesthesia. He believes that the uremia in these cases and in the case of Hewer and Woolmer was produced by the trauma of the operation and that it belongs to the "crush syndrome without crush injury" picture (85). He described the occurrence of fatal anuria of a similar type in a case anesthetized with thiopental and curare (88).

Venous thrombosis: Opinion varies as to the cause and frequency of this complication. Mallinson (84, 86) and Vartan (125) reported complete freedom from this complication and drew attention to the possibility of pentothal being the cause. Stephen and Chandy (117) recorded seven cases of localized thrombophlebitis in a series of 50 administrations. All patients recovered within 48 hours. Griffith and Cullen (56) had four cases of thrombophlebitis among 120 patients and Musgrove (96) observed this complication in 10 out of his 200 patients. Several authors reported single cases of venous thrombosis (126, 55, 134, 39).

Intra-arterial injection: Ogilvie *et al.* (98) described a case of gangrene of the hand and forearm after accidental injection of myanesin. Brooks *et al.* (26) observed hemolysis in the brachial vein after an injection of the drug into the brachial artery.

Circulatory effects: Hunter (70) saw a simultaneous failure of circulation and respiration of central origin after intravenous injection of 3 grams of myanesin. This was at once reversed by 5 cc of nikethamide intravenously. Lyall (82)

observed falls of the systolic and diastolic blood pressure varying as a rule between 10 and 25 mm. In elderly individuals, the falls were greater but never caused anxiety. Cowen (34) observed a partial heart-block shortly after administration of myanesin.

GLYKETAL AND OTHER 2,2-ALKYL-4-HYDROXYMETHYL-1,3-DIOXOLANES

It has recently been shown that certain 2-substituted-4-hydroxymethyl-1,3-dioxolanes caused effects on the central nervous system similar to those caused by alpha substituted ethers of glycerol (15, 12). Fifty compounds of this type have been examined and it was found that 2-methyl,2-*n*-amyl-4-hydroxymethyl-1,3-dioxolane, named glyketal, possessed the strongest paralysing activity. The pharmacological properties of glyketal have been investigated (13).

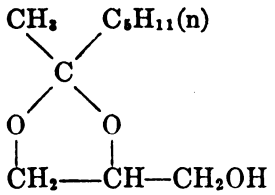

FIG. 6. Structural formula of glyketal

Physical and chemical properties: Glyketal is a colorless, viscid liquid with a faint fruity odor; it boils at 128–132°C at 10 mm pressure. Glyketal hydrolyses slowly on standing. It is only very slightly soluble in water but forms fairly stable emulsions.

Effect on animals: The action of glyketal in laboratory animals was very similar to that of myanesin. It caused muscular relaxation after small doses and paralysis with a loss of the righting reflex after larger doses. The drug was a somewhat more effective paralysing agent than myanesin and possessed a similar toxicity.

After intravenous administration of the compound to rabbits, the corneal reflex was lost during the peak of the drug action. During this time, some animals also showed nystagmus. Lethal doses caused death by respiratory paralysis. Paralysis was not preceded or followed by excitation. The lower segments of the spinal cord appeared to be affected first by the drug and were the last to recover from its effects.

Effect on circulation and respiration: In the intact animal, respiration during paralysis was not affected or was somewhat increased in rate and depth. In cats anesthetized with dial, intravenous injections of glyketal in doses of 5 mg per kg did not affect respiration but produced a slight and transient fall of blood pressure and a decrease in heart rate. Larger doses had a greater depressor effect. Atropine affected neither the fall of blood pressure nor the bradycardia produced by the drug.

Effect on the nervous system: Glyketal did not possess any action on the peripheral nerves. It did not influence neuromuscular transmission and did not have any curare-like action. It also did not affect two neuron arc reflexes such as the

knee and ankle jerks. Multineuron reflexes such as the flexor and crossed extensor reflexes were depressed with small doses of the drug. The crossed extensor reflex which is mediated by several interneurons was depressed with smaller doses of glyketal for longer periods of time than the flexor reflex which probably has a shorter intercalated pathway between the afferent and efferent parts of the reflex arc.

Glyketal was very effective in abolishing tremor and repetitive phenomena occurring spontaneously or induced by administration of strychnine. The effects on multineuron reflexes, tremor and repetitive phenomena were apparent after doses of the drug which did not cause paralysis.

The marked effect of the drug on multineuron reflexes and repetitive phenomena, taken in conjunction with its ineffectiveness in suppressing two neuron reflexes and the lack of analgesic action of the drug, suggests that glyketal acts by selectively depressing the interneurons. In this respect, it appeared more potent and selective than benzimidazole and myanesin.

Glyketal did not seem to affect cortical activity and did not influence the electroencephalogram.

Anticonvulsant action: Glyketal possessed some antagonistic action to the convulsant and lethal effects of strychnine, metrazol and picrotoxin. This antagonistic action was, however, weak and of a lower order than that of benzimidazole and myanesin.

Other pharmacological properties: Glyketal possessed a few other pharmacological actions than those described. It did not cause analgesia in doses not causing paralysis. The sensory impairment during paralysis was probably due to the motor deficit and was not complete. Glyketal had a local anesthetic action comparable to that of procaine.

Clinical use: The effect of glyketal in humans has not yet been investigated. It is likely to be of value in conditions in which abnormal impulses reverberate in closed interneuronal circuits such as may be the case in chorea, athetosis, and certain forms of tremor and muscle spasm. It may also be worth a trial in conditions in which the interneurons are in a state of irritation, as may be the case in acute poliomyelitis.

APO-β-ERYTHROIDINE

It has been suspected for some time that β-erythroidine, apart from its curare-like action, also possesses central depressant properties (30, 61). These two properties have been dissociated in apo-β-erythroidine which lacks the peripheral action but still retains the central depressant properties of β-erythroidine (107).

Apo-β-erythroidine was prepared by heating β-erythroidine to 120°C with either phosphoric or sulfuric acid. Apo-β-erythroidine isolated from the reaction mixture was a solid which, after crystallization from ethanol, melted at 132–132.5°C. It was insoluble in water but could be easily dissolved in dilute acid.

On intraperitoneal administration to mice in doses of 150 mg per kg, apo-β-erythroidine caused flaccid paralysis and loss of postural reflexes. The paralysing

effect of apo-β-erythroidine was similar to that observed after administration of benzimidazole, myanesin or glyketal but differed from these agents in producing paralysis of much longer duration.

Apo-β-erythroidine did not possess any curare-like action and did not affect two neuron reflexes but depressed selectively multineuron reflexes such as the flexor reflex. It appears that apo-β-erythroidine also possesses a selective depressant action on interneurons (107).

SPASMOLYTICS

It has been known for over 60 years that certain solanaceous drugs were effective in the treatment of paralysis agitans. The opinion has been expressed that the efficacy of these drugs in certain disorders of the extrapyramidal nervous system was more likely due to their central depressant action than to their inhibiting action on cholinergic nerve endings. With this idea in mind, Domenjoz (39a) examined the pharmacological properties of a number of spasmolytic drugs and recommended parpanit, the diethylaminoethylester of phenylcyclopentanecarbonic acid for clinical trials in hyperkinetic and dystonic conditions.

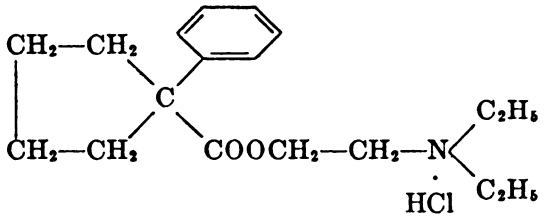

FIG. 7. Structural formula of Parpanit

Pharmacological properties: Parpanit injected in mice or rats in doses of 50 mg per kg caused an increase of spontaneous activity, similar to that observed after comparable doses of atropine. Larger doses of parpanit caused convulsions and death. Paralysis of skeletal muscles did not occur. Parpanit was about 13 times less effective than atropine in antagonizing the action of acetylcholine on the isolated rabbit duodenum but possessed in this respect an activity comparable to other synthetic spasmolytic drugs. Parpanit also had a considerably weaker mydriatic and salivation-inhibiting action than atropine (39a).

In dogs intravenous administration of 3 mg per kg did not markedly affect blood pressure and did not influence the vasodepressor and respiratory reflexes. Larger doses had a depressor effect on the blood pressure and stimulated respiration. Parpanit caused vasodilatation by a direct effect on the vessels and did not act directly on the vasomotor center (66a).

Parpanit did not affect neuromuscular conduction and did not alter excitability of skeletal muscles (66a). Fleisch and Baud (42c), using a quantitative method, found a decrease in the tonus of the adductor muscles of the hind leg of intact and spinal rabbits after parpanit in doses of 4 to 40 mg per kg. They also observed a

decrease of muscle tonus and an increase in the threshold for the patellar reflex in humans after doses of 100 mg. They believe that parpanit acts on the proprioceptive nerve endings of the muscles and joints. This effect is similar to that of procaine but is stronger and of longer duration.

Parpanit suppressed bradycardia, bronchospasm, hyperactivity of the gastrointestinal tract, convulsions and muscular fasciculations produced by di-isopropyl fluorophosphate (DFP). It also antagonized the convulsive action of strychnine in dogs (66a) but was ineffective in suppressing convulsions caused by niketh-amide in guinea pigs (45a).

Berger (7) examined the effect of parpanit on spinal reflexes in cats anesthetized with dial. Small doses of the drug of the order of 2 to 4 mg per kg depressed or abolished the multineuron reflexes, such as the flexor reflex, but did not affect two neuron reflexes such as the knee jerk. This depressant action on interneurons is of interest because parpanit is the only agent of this kind which does not possess paralysing properties. It may be inferred that the blocking action on interneurons and paralysing activity are independent properties of drugs, and that paralysing activity does not constitute a measure of the potential value of a drug as a blocking agent for interneurons.

Gruber *et al.* (59) have shown that several autonomic blocking agents inhibiting structures innervated by postganglionic cholinergic nerves also had a depressant action on the central nervous system. They found that parpanit, trasentin and syntropan injected intravenously relieved decerebrate rigidity in cats, and depressed reflexes caused by stimulation of the back and paws in spinal preparations. For these purposes the drugs were found superior to atropine and scopolamine.

Clinical use: Parpanit has been found of value in the treatment of paralysis agitans and of other dystonic and hyperkinetic conditions (60, 60b, 60c, 21a, 111a). Schwab and Leigh (110a) evaluated quantitatively the effect of parpanit in 50 cases of parkinsonism and found the drug superior to previous medication in 65 per cent of cases. The degree of improvement was usually around 25 per cent. Dunham and Edwards (39b) observed some improvement in 9 out of 19 patients suffering from paralysis agitans. They found the activity of parpanit comparable to that of the solanaceous drugs. Side-actions, in decreasing order of frequency, were giddiness, weakness, drowsiness, paresthesia and rarely hallucinosis. Dryness of the mouth and blurred vision were of lesser severity after parpanit than after atropine.

Parpanit given intravenously in doses of 20 to 30 mg softened the initial contraction and clonic phase of electroshock seizures in humans (60a).

The effect of parpanit on involuntary movements of extrapyramidal origin may be due to the depressant action of the drugs on interneurons. The decrease in rigidity and tremor obtained in certain cases of paralysis agitans is probably not due to the depressant action of the drug on interneurons, because atropine and thephorin (14), which are also of value in parkinsonism, do not affect multineuron reflexes.

CHOLINERGIC AGENTS

In view of the potential role played by acetylcholine in the transmission of impulses in the nervous system, its effects on the reflex activity of the spinal cord are of great interest.

Schweitzer and Wright (111) found that, in cats under chloralose anesthesia, an intravenous injection of acetylcholine depressed or abolished the knee jerk. This effect was due to a direct inhibitory action on the spinal cord and was only partially annulled by atropine. Neostigmine, carbachol and certain other drugs which prevent the destruction of acetylcholine by cholinesterase behaved similarly. Physostigmine had an opposite effect an caused a marked enhancement of the knee jerk.

Merlis and Lawson (92) investigated the action of physostigmine on spinal reflexes in dogs. They found that it depressed the knee jerk and augmented the flexion and crossed extension reflexes. Bülbring and Burn (27), using a preparation in which the lower part of the spinal cord and the hind legs were perfused by two different circuits of blood, found that both physostigmine and neostigmine depressed the knee jerk and augmented the flexor reflex. They interpreted their findings by assuming that, in the case of the knee jerk in which only a single synapse is involved, an accumulation of acetylcholine occurs which blocks transmission of the impulse. In the case of the multineuron reflexes, the accumulation of acetylcholine is not great enough to cause blockage at ordinary rates of stimulation, but the muscle fibres contract repeatedly to each single shock, so that a single twitch becomes a short tetanus. It appears that the knee jerk and flexor reflex are modified by eserine and neostigmine as might be expected if transmission at the synapse of the spinal cord would be affected by acetylcholine. This view is further supported by the observation that the effects of both physostigmine on the knee jerk and flexor reflex were prevented or abolished by atropine.

Wikler and Frank (132) studied the effect of neostigmine and physostigmine in chronic spinal dogs. Subcutaneous administration of neostigmine was followed by enhancement of all hindlimb reflexes and the appearance of irregular spontaneous movements of the hindlimbs. Eserine produced spontaneous hindlimb movements which were either irregular or rhythmic. The activity induced by eserine could be abolished by morphine or methadone. The depressant effect of the cholinergic drugs on the knee jerk may have been obscured in these experiments by their direct stimulant action on the muscle (104).

Clinical use: Neostigmine has had a fairly wide clinical use in neuromuscular dysfunctions in which muscle spasm is an important feature, such as hemiplegia, cerebral palsy, rheumatoid arthritis and subacromial bursitis (74, 33, 45). It has also been used in acute poliomyelitis to reduce pain and relax the muscles (75, 25, 32).

Neostigmine may be of value in these conditions for several reasons. The inhibiting action of the drug on cholinesterase may facilitate the passage of impulses from nerve to muscle by preserving the available acetylcholine at the nerve endings. It may also have a direct action on the synapses in the spinal cord as has

been assumed by Kabat (75), but this effect would be different from that observed by Bülbring and Burn (27) as it was not antagonized by atropine. Neostigmine also possessed a direct stimulant effect on the muscle. This stimulant action was apparent after the cholinesterase was destroyed by di-isopropyl fluorophosphate (104).

The value of neostigmine in spastic conditions is still under discussion and investigation.

MORPHINE AND OTHER ANALGESICS

Wikler (131), investigating the action of morphine on the central nervous system of cats, observed in acute and chronic spinal preparations a marked depression of the flexor and crossed extensor reflexes. The knee and ankle jerks were either not affected or were slightly augmented. In long surviving spinal dogs, single doses of morphine or methadone caused similar effects. Luckhardt and Johnson (81), using larger doses of morphine, observed a depressant effect of the drug on the knee jerk of spinal dogs.

It appears that morphine and methadone, in doses comparable to those used in humans, have little effect on two neurons arc reflexes but depress or abolish nociceptive multineuron reflexes. Wikler concluded that these effects may be due to a depressant action of morphine on the interneurons. In view of the strong analgesic action of these drugs, the abolition of responses to nociceptive stimuli may be due to a depressant action of morphine on pain perception. The ineffectiveness of morphine in abolishing reverberating nervous impulses also speaks against a direct action of the drugs on interneurons.

BARBITURATES

Beecher *et al.* (5) found that the flexor reflex in cats under light barbiturate anesthesia was not followed by an after-discharge. During ether anesthesia, a marked after-discharge was observed. From this they inferred that the long-circuiting of sensory impulses is much more seriously curtailed under barbiturate than under ether anesthesia. Wikler and Frank (132) observed that small doses of pentobarbital sodium of the order of 8 mg per kg abolished the flexor and crossed extensor reflexes in chronic spinal dogs and slightly depressed the knee jerk and ipsilateral extensor thrust. Larger doses of pentobarbital (15 mg per kg) had also a depressant action on the knee jerk and extensor thrust and after still larger doses all reflex activity disappeared.

The barbiturates and other anesthetics cause a progressive depression of all functions of the central nervous system. Eccles (39c) and Brooks and Eccles (25a) have shown that pentobarbital blocks synaptic transmission by so increasing the stability of the surface membrane of the motoneurones that the discharge of impulses is not initiated by normally effective synaptic potentials. Pentobarbital also diminishes the internuncial after-discharge set up by strong stimulation of the dorsal roots, and greatly prolongs the time constant of decay of the dorsal root potential set up by dorsal and ventral root volleys (39d). Although some depression of all components of the reflex pathway has been observed (25a),

it appears likely that anesthetics exert their action specifically on the synaptic region of the motoneurones just as curare does on the endplate region of the muscle (39c).

DISCUSSION AND SUMMARY

Most substances possessing a depressant effect on the spinal cord have the important common property of producing paralysis of the ascending type. Tri-*o*-cresyl phosphate, dithiobiuret, benzimidazole, myanesin and glyketal depress the lower segments of the cord in small doses. With larger doses, higher segments of the cord and the midbrain are also affected in an ascending order. The anesthetics differ from the spinal depressants by first depressing higher levels of the central nervous system and by producing paralysis at lower levels only after large doses. The vital functions of the medulla are spared by both the anesthetics and spinal depressants and are affected after toxic doses only.

Whether the spinal depressant action of these agents is direct or is secondary to their effects on certain structures of the midbrain is not known. Clinical observations and the experimental work of Henneman *et al.* speak in favor of an indirect action.

The available agents producing depressant effects on the spinal cord may be arbitrarily classified into 4 groups: 1) agents producing irreversible paralysis by damaging the anterior horn cells, such as tri-*o*-cresyl phosphate; 2) agents producing reversible paralysis on chronic administration such as dithiobiuret; 3) agents causing transient paralysis and possessing a selective depressant action on the interneurons, such as the benzimidazole, the glycerol ethers, the 2,2-alkyl-4-hydroxymethyl-1,3-dioxolanes, and apo-β-erythroidine; and 4) agents which depress interneurons but do not cause paralysis, such as parpanit.

It is of interest that four chemically different classes of compounds produce similar and highly selective effects on interneurons and postural reflexes. There is no indication that these compounds affect transmission of impulses mediated by acetylcholine. Their mode of action is unknown and when uncovered may bring to light new aspects concerning the transmission of impulses in the central nervous system.

The four families of chemicals blocking interneuronal transmission differ from each other in the intensity of this action and in their antagonism to the effects of strychnine, which to some extent is possessed by all. Glyketal, the most potent interneuronal blocking agent, possesses the weakest anti-strychnine action. Benzimidazole has the strongest antagonistic action to strychnine and the weakest action on interneurons. Myanesin possesses both interneuronal blocking action and anti-strychnine properties to a marked degree. Apo-β-erythroidine has a blocking action on interneurons of an order similar to myanesin. Its antagonistic action to strychnine has not yet been investigated.

Spinal depressants and interneuronal blocking agents are of potential therapeutic value in the treatment of muscle spasm, spasticity, tremor and involuntary movement. They may also be of value for the production of muscular relaxation during anesthesia. Up to the present, only myanesin has received adequate clini-

cal trials. Although it has produced remarkable effects in numerous cases, the value of the drug is limited. It is unsuitable for routine intravenous use because of the low solubility and the hemolytic action of the drug. The intravenous use of dilute solutions of myanesin during emergencies such as tetanus, strychnine poisoning or status epilepticus may be justified, but intramuscular administration which should be equally effective and less dangerous would be preferable. The oral use of myanesin is impeded by the low potency and rapid inactivation of the drug.

In the past, the activity and potential clinical usefulness of spinal depressants has been evaluated in terms of their paralysing potency. This criterion of activity is unsuitable because it is not intended to use these agents clinically for the production of paralysis. It appears probable that the interneuronal blocking action or the antagonistic action to strychnine would be a better criterion for assessing the clinical potentialities of these drugs; however, it is not known which of these two unrelated properties is the more important one. This question may be answered by clinical trials of benzimidazole and glyketal, the results of which may indicate new approaches toward the development of more effective agents of this type.

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