THE CORRELATION BETWEEN ANIMAL TESTING PROCEDURES AND CLINICAL EFFECTIVENESS OF CENTRALLY ACTING MUSCLE RELAXANTS OF THE MEPHENESIN TYPE*

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Since Berger and Bradley (1946) described the unique skeletal-muscle relaxant properties of mephenesin, this agent has been used in the symptomatic treatment of a heterogeneous group of human ailments. These include such conditions as skeletal muscle spasm of rheumatoid (Smith, R. T., 1949; Jacqueline, 1950; Hermann and Smith, 1951) or traumatic origin (Schlesinger and Stinchfield, 1951; Mead, 1951), certain psychiatric disturbances (Schlan and Unna, 1949; Dixon *et al.*, 1950; Herman and Effron, 1951), tetanus (Torrens *et al.*, 1948; Godman, 1951; Boles and Smith, 1951; Biehl and Helm, 1951), and various neurological hyperkinetic states (Stephen and Chandy, 1947; Berger and Schwartz, 1948; Schlesinger *et al.*, 1948; Effron and Schultz, 1951; Libet and Rubin, 1952). Although reports have appeared on the ineffectiveness of mephenesin in some of these conditions, it is agreed generally that this drug is of some value in patients with skeletal-muscle hypertonus and symptoms of spasm or spasticity.

The unique skeletal-muscle relaxant properties of mephenesin are thought to be due to its depressant action on certain polysynaptic pathways principally in the spinal cord (Berger, 1947, 1949a; Henneman *et al.*, 1949; Smith, W. K. *et al.*, 1949; Traverner, 1952). This view does not take into account the observations that mephenesin also depresses certain polysynaptic arcs at supraspinal levels. The linguomandibular reflex mediated over intercalated neurons of the lower brainstem is depressed by this agent (King and Unna, 1954). Conduction of strychnine-induced activity from the motor cortex to the pyramids is prevented by mephenesin (Finkelman and Dobin, 1949). The polysynaptic circuits of the thalamo-cortico-thalamic system (Kaada, 1950; King, 1954, 1956; Domino, 1955) and the cerebellum (Kaada, 1950; Goldman and Snider, 1955) also are depressed by this agent. It is to be emphasized that mephenesin does not depress all polysynaptic pathways in the central nervous system. The polysynaptic arcs involved in the activating system, for example, are unaffected (King, 1954, 1956) unless overwhelming toxic doses are given (Domino, 1955).

Mephenesin does not necessarily produce skeletal muscle relaxation as a result of depressing neuronal transmission only in polysynaptic arcs. Recently this agent in relatively small doses has been shown to affect certain types of transmission in various monosynaptic arcs (Latimer, 1955).

The short duration of action and low order of potency of mephenesin when given orally have prompted an intensive search for more effective agents in the last ten years. Many different chemicals have been screened for mephenesin-

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like activity by many different investigators. As a result of animal screening methods several substances have been found that have been or are presently being evaluated clinically in man. This paper will attempt to review the animal screening techniques that have been used generally and will present a summary of the results of clinical trials with some of the newer compounds.* An attempt will be made to discuss critically the correlation between clinical effectiveness and the adequacy of animal testing procedures that have been used in the light of present-day concepts of the pathophysiology of spasticity in man.

Animal-Testing Procedures

Initial Screening Methods

Physical examination of intact animals. Organic chemists can provide us with hundreds of thousands of chemicals, some of which are potentially useful therapeutic agents in man. Pharmacologists have the unique privilege and important function of developing accurate screening methods to find potential drugs. Fortunately, by careful physical examination of various laboratory animals, centrally acting muscle relaxants such as mephenesin can be distinguished readily from other types of central nervous system depressants. Rodents, especially the mouse, rat, and hamster, have been used in the preliminary screening because of their small size, ease of handling, availability, and comparatively small cost. The chemicals tested have been given by the oral or parenteral route. Because an orally effective agent is desired for use in man, the oral route in animals has been preferred, although there is no assurance that compounds effective by this route in rodents will be necessarily orally effective in man. For example, agents that cause emesis in man may be retained orally in rodents, because these animals have poorly developed vomiting mechanisms. Also, there are no data available regarding the similarities or differences in absorption of chemical substances in man and subhuman forms. In the absence of such data, screening for therapeutic agents by oral administration to animals is empirical.

Prior to and after the administration of the test agent, the animal is observed for signs of stupor and behavioral changes and is given a careful physical examination. Systematic observations of respiratory changes, color of the mucous membranes and paws as an index of oxygenation, salivation, ataxia, ability to walk a tightrope, ability to hang on an inclined screen, and sensory perception are evaluated. Various neurological reflexes mediated over polysynaptic arcs such as the righting reflex and withdrawal reflex, are determined. Goodsell *et al.*, 1954, have shown that selective depression of the pinneal reflex, relative absence of pawing movements, and abdominal relaxation are additional criteria of mephenesinlike activity. These changes, along with the presence of an ascending reversible hind-limb weakness (hind drop), paraplegia, loss of the righting reflex, good respiratory exchange, and absence of stupor, provide presumptive evidence of a central skeletal muscle-relaxant action. Periph-

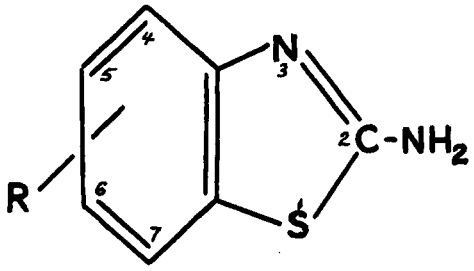
* Reports of clinical trials with some of these agents have not been published. It is through the kindness of the clinical investigators and scientific directors of the respective pharmaceutical companies involved that these reports have been made available.

erally acting skeletal-muscle relaxants such as *d*-tubocurarine are readily distinguished from the centrally acting muscle relaxants by the presence of a head drop, complete muscle flaccidity, and respiratory embarrassment.

After a preliminary survey of the action of a compound in rodents, its actions are determined by similar physical examinations of larger laboratory animals such as the rabbit, cat, and dog. Within these species considerable variation in response may exist. One class of centrally-acting muscle relaxants, the benzazoles, serves to emphasize this point (Domino *et al.*, 1952).

In a select series of substituted 2-aminobenzothiazoles, the order of potency was determined for oral and/or intravenous administration to mice, rabbits, and dogs (Domino, 1951). Inasmuch as it is difficult to determine the precise potency on the basis of impressions from physical examination and determination of the median loss of righting-reflex dose, the data must be regarded as approximate. As shown in FIGURE 1, the substituted 2-aminobenzothiazoles are arranged in order of potency on oral and intravenous administration to albino mice, oral administration to albino rabbits, and intravenous administration to mongrel dogs. The rank-difference coefficient of correlation was determined for the potency of the benzazoles given by the intravenous route in mice (column *A*) versus the oral route in mice (column *B*) versus the oral route in rabbits (column *C*), and the intravenous route in mice (column *A*) versus the intravenous route in dogs (column *D*). The calculation was made according to the formula $r_s = 1 - \frac{6Sd^2}{n(n^2 - 1)}$ as given by Spearman (quoted by Snedecor, 1946). The correlation (rank-difference) of $A - B$ was $+0.39$, $B - C$ was $+0.33$, and $A - D$ was $+0.68$. The correlation (mice versus dogs) was greatest ($+0.68$) when the intravenous route was used. This was much greater than when the oral and intravenous routes were used in one species (mouse), or when the oral route was used in two species.

All of the substituted 2-aminobenzothiazoles mentioned produced a typical pattern of mephenesinlike effects in mice. Rabbits had, in general, a flaccid paralysis when given the 5- or 6-methyl or chloro derivatives. The 4-methyl, methoxy, or chloro derivatives of 2-aminobenzothiazole tended to produce stimulation in the rabbit. In dogs a methyl or chloro group in position 4 or 7 of 2-aminobenzothiazole also produced signs of central nervous system stimulation. This was especially true of a chloro group in position 7. A methyl or chloro group in position 5 formed a compound with more depressant than stimulant properties. In position 6 the methyl and chloro substitutions formed agents with purely depressant effects. It is apparent that considerable variability, both qualitatively and quantitatively, exists among subhuman species. There is no reason to expect man not to react with similar variability. It is surprising that useful agents that act on the central nervous system of man are found as frequently as they are on the basis of screening methods using subhuman forms. Obviously we probably discard many potentially useful drugs simply by choosing the most potent member of a series of compounds tested in a limited number of different subhuman species. Until better screening methods are developed using species that react in the same way that man does in



A	B	C	D
Mice intravenous	Mice oral	Rabbit oral	Dog intravenous
4 - Cl	4 - CH_3	6 - CH_3	7 - Cl
4 - OCH_3	7 - Cl	6 - Cl	4 - CH_3
4 - CH_3	4 - OCH_3	4 - CH_3	4 - Cl
7 - Cl	6 - Cl	2 - NH_2	4 - CH_2CH_3
4 - CH_2CH_3	5 - CH_3	4 - Cl	6 - Cl
5 - CH_3	4 - CH_2CH_3	4 - OCH_3	6 - CH_3
6 - CH_3	6 - CH_3	5 - CH_3	2 - NH_2
2 - NH_2	2 - NH_2	5 - Cl	5 - Cl
6 - Cl	4 - Cl		5 - CH_3
5 - Cl	5 - Cl		

FIGURE 1. Descending order of potency of some substituted 2-aminobenzothiazoles given by different routes to various species (Domino, 1951, and Domino *et al.*, 1952).

response to the type of pharmacological agent desired, we shall probably continue to discard important compounds.

Screening with anticonvulsant tests. Since mephenesin has anticonvulsant actions against strychnine, pentylenetetrazol, and electroshock, these convulsants have been used in tests with rodents to find more potent analogues. Mephenesin is more effective against strychnine convulsions and the tonic phase of electroshock than against pentylenetetrazol (Orloff *et al.*, 1949; Unna and Kaplan, 1949). Berger (1949a) has summarized the antistrychnine effects of mephenesin, 2-methyl, 2-n-amyl-4-hydroxymethyl-1,3-dioxolane and benzimidazole, and he has concluded that the antistrychnine effects of these drugs do not parallel their ability to depress transmission over some spinal

interneurons. This is further substantiated by the known effects of trimethadione and diphenylhydantoin on polysynaptic transmission in the spinal cord. Trimethadione depresses the polysynaptic flexor reflex with little effect on the patellar reflex (Goodman *et al.*, 1946). Thus, if antistrychnine effects parallel spinal interneuron depression, one would expect trimethadione to be more effective against strychnine and the tonic phase of electroshock than against pentylenetetrazol; but this is not true. Similarly, since diphenylhydantoin has little effect on the patellar and flexor reflexes (van Harreveld and Feigen, 1950), it should be less effective against strychnine and the tonic phase of electroshock. On the contrary, it is very effective against electroshock, and it has some antistrychnine effects.

The substituted 2-aminobenzothiazoles have afforded another opportunity to compare anticonvulsant actions (Domino *et al.*, 1951) with their known depressant actions on certain spinal interneurons. Petersen, R., 1952, has shown that the substituted 2-aminobenzothiazoles were effective in abolishing strychnine and electrically induced seizures according to the following position of substitution 6 > 5 > 4 or 7. Funderburk *et al.*, 1953a, reported that the 4- or 7-position-substituted 2-aminobenzothiazoles were the most potent as spinal interneuron depressants. These investigators have emphasized that while the predominant actions of these compounds were on spinal interneurons, the 4- and 7-position compounds produced stimulation of higher centers while the 6-position derivatives did not (Funderburk *et al.*, 1953b). Within this series of compounds it appears that there is better correlation between anticonvulsant properties and actions on higher centers than on the spinal cord. The conclusion that depression of spinal interneurons and anticonvulsant properties are independent seems justified.

Site of Action Testing Methods

Action on spinal cord monosynaptic and polysynaptic arcs. Because of their convenient size and availability, cats and dogs have been used most frequently to obtain data as to the site of action of a test compound. Since mephenesin increases the effects of anesthetics such as barbiturates (Berger and Bradley, 1946; Walker *et al.*, 1948; Lang *et al.*, 1951) the use of animal preparations relatively free of anesthesia is preferred. For acute experiments high spinal preparations performed under ethyl ether anesthesia have been used frequently. High spinal sections in cats are technically simpler to perform than in dogs, where hemorrhage may be severe unless great care is taken. When the cord is severed under deep anesthesia, spinal shock appears to be minimal. The patellar reflex is relatively normal shortly after transection when the ether is blown off by artificial respiration. Some degree of spinal shock is present (Liddell, 1934) and therefore is another source of variability. Cats after spinal transection show considerable variability in the stimulating voltage necessary to elicit threshold or consistent reproducible responses. The mean blood pressure of such preparations even with minimal blood loss during surgery may vary from 50 to 90 mm. of mercury (Kissel and Domino, 1956). Presumably these variations in mean arterial pressure are the result of varying degrees of spinal shock. Cats and dogs with a chronic spinal condition have been used

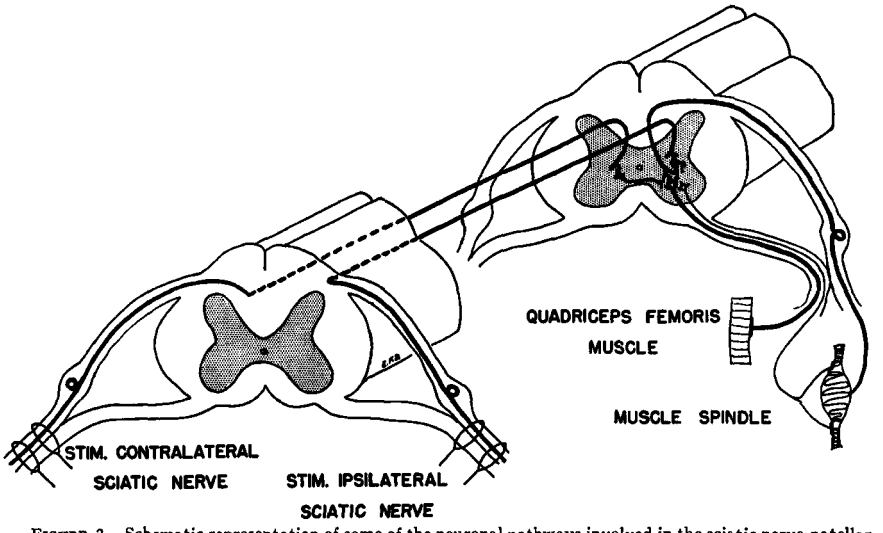


FIGURE 2. Schematic representation of some of the neuronal pathways involved in the sciatic nerve-patellar reflex preparation.

(De Bodo and McC. Brooks, 1937; Wikler, 1950) with the obvious advantages of lack of anesthesia and no spinal shock. In such animals sensitization of neurons by denervation occurs and must be kept in mind in any interpretation of drug effects.

After the animal has been prepared it is placed in a suitable recording apparatus, and the patellar reflex (monosynaptic) and various polysynaptic reflexes (flexor, crossed-extensor, Phillipson's, extensor thrust, and others) are elicited. One preparation commonly used determines the action of the test agent on the modification of the effects of sciatic nerve stimulation on the patellar reflex. The neuronal circuits involved are shown diagrammatically in FIGURE 2. The patellar tendon is tapped by means of a mechanical hammer that stretches transiently the muscle spindles, causing them to discharge. The elicited reflex of the quadriceps muscle is recorded. This reflex is thought to be monosynaptic (Lloyd, 1944). The effects of stimulation of the contralateral sciatic nerve result in facilitation, inhibition, or crossed extension, depending upon the electrical parameters, and are mediated over polysynaptic arcs (Lloyd, 1944). Stimulation of the ipsilateral sciatic nerve results in an inhibition of the patellar reflex. This pathway for reciprocal inhibition has been considered to be monosynaptic (Lloyd, 1944) although recent evidence suggests a possible polysynaptic mechanism (Eccles *et al.*, 1956). Mephenesinlike agents abolish the effects of contralateral sciatic nerve stimulation, but they leave the patellar reflex intact. The inhibitory effects of ipsilateral sciatic nerve stimulation are not modified.

By means of electrophysiological techniques the efferent activity of the ventral root due to afferent stimulation of the dorsal root can be recorded using the classical dorsal root-ventral root preparation (Renshaw, 1940; Lloyd,

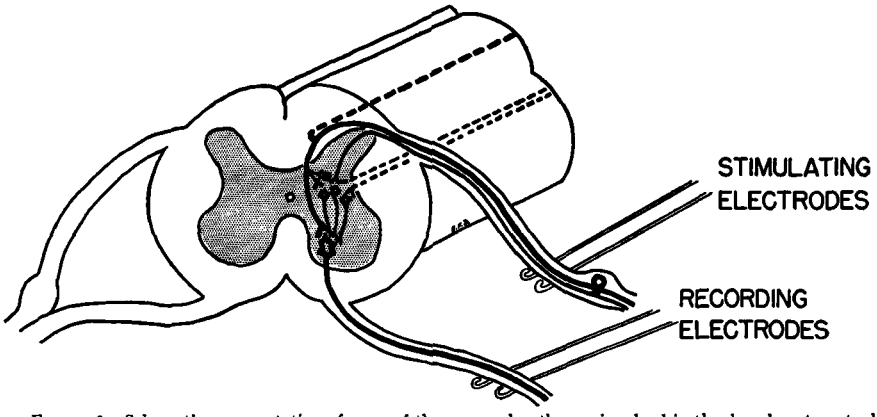


FIGURE 3. Schematic representation of some of the neuronal pathways involved in the dorsal root-ventral root preparation.

1941b). This preparation has the advantage of eliminating peripheral afferent (muscle spindle) and efferent (neuromuscular junction and skeletal muscle) structures, thus obtaining data directly from spinal cord structures. A schematic diagram of the neuronal circuits involved in this preparation is shown in FIGURE 3. Both monosynaptic and polysynaptic arcs are present. An electrical impulse entering the spinal cord through a dorsal root gives rise to a characteristic discharge potential from the ventral root of the same segment that can be amplified and seen on an oscilloscope. After a latency of about 1 msec., a prominent initial spike appears, followed by an irregular elevation of about 10 msec. duration. The initial spike represents an impulse traversing the monosynaptic arc, and the subsequent irregular potentials represent discharge across polysynaptic arcs. In appropriate doses, mephenesinlike agents reduce the polysynaptic discharge, leaving the monosynaptic potential intact.

Results obtained from the sciatic nerve-patellar reflex preparation and the dorsal-ventral root preparation are complementary. Both methods should be used for proper evaluation of a test compound because somewhat different information is obtained with each method. As shown in TABLE 1, many central nervous system depressants besides mephenesinlike drugs have been reported to affect the polysynaptic arcs involved in these spinal reflexes. The dose-response curves for depression of monosynaptic and polysynaptic pathways with each of these agents probably vary considerably. As yet no systematic dose-response curves have been reported with any of these agents. In appropriate amounts each drug listed in TABLE 1 has been reported to depress polysynaptic transmission at a time when monosynaptic transmission is relatively intact. Ethyl alcohol and procaine in the dorsal-ventral root preparation show no selectivity in depressing spinal interneurons, but a low order of selectivity can be shown with the flexor reflex-patellar reflex or sciatic nerve-patellar reflex preparations. These differences may be due to the fact that the flexor or crossed-extensor reflex is elicited electrically at a level closer to threshold than the mechanically elicited patellar reflex.

TABLE 1

MISCELLANEOUS CENTRAL NERVOUS SYSTEM DEPRESSANTS THAT IN SMALL DOSES HAVE BEEN REPORTED TO SHOW SOME SELECTIVITY IN DEPRESSING CERTAIN SPINAL-CORD INTERNEURONS

Drug	Preparation	Reference
Pentobarbital	Flexor reflex—Patellar reflex	van Harreveld, 1947
	Dorsal root—Ventral root	Funderburk *et al.*, 1951
	Sciatic nerve—Patellar reflex	Domino *et al.*, 1955
Diallylbarbituric acid	Peripheral afferents—Ventral root	Hagbarth & Naess, 1950
	Dorsal root—Peripheral efferents	Petersen, I., 1952
Chloral hydrate	Sciatic nerve—Patellar reflex	Chen *et al.*, 1956
Chloralurethane	Sciatic nerve—Patellar reflex	Chen *et al.*, 1956
Urethane	Sciatic nerve—Patellar reflex	Kissel & Domino, 1956
α-Chloralose	Sciatic nerve—Patellar reflex	Kissel & Domino, 1956
Ethyl alcohol	Peripheral afferents—Ventral root*	Kolmodin, 1953
	Sciatic nerve—Patellar reflex	Kissel & Domino, 1956
Morphine and other narcotic analgesics	Flexor, crossed extensor, Patellar reflex	De Bodo & McC. Brooks, 1937
	Dorsal root—Ventral root	Wikler, 1950
		Wikler, 1945, 1950
		Takagi *et al.*, 1955
	Flexor reflex—Patellar reflex	Cook & Bonnycastle, 1953
	Sciatic nerve—Patellar reflex	Kissel & Domino, 1956
Procaine	Dorsal root—Ventral root*	Peterson, C. G., 1955
	Flexor reflex—Patellar reflex	Peterson, C. G., 1955
	Sciatic nerve—Patellar reflex*	Kissel & Domino, 1956
Trimethadione	Flexor reflex—Patellar reflex	Goodman *et al.*, 1946
Atrolactamide	Sciatic nerve—Patellar reflex	King, 1953
		King & Unna, 1954
Panparnit	Flexor reflex—Patellar reflex	Berger, 1949a
Apo-β-erythroidine	Flexor reflex—Patellar reflex	Sauvage *et al.*, 1949
		Megirian, 1954*

* No differential sensitivity on monosynaptic and polysynaptic pathways was obtained.

Although small doses of many central nervous system depressants inhibit the polysynaptic crossed-extensor and flexor reflexes without affecting the patellar reflex, the over-all actions of these compounds on the central nervous system are quite different. Since most neuronal arcs of the nervous system are polysynaptic, there must be enormous differences in the sensitivity of these agents on most polysynaptic circuits. Many examples of this are known. At cord levels the polysynaptic extensor thrust reflex of the chronic spinal dog is enhanced by morphine but depressed by mephenesin (Wikler, 1950). At brain-stem levels the polysynaptic circuits of the activating system are relatively unaffected by mephenesin (King, 1954, 1956; Domino, 1955), but markedly depressed by anesthetic agents including pentobarbital (Arduini and Arduini, 1954; King, 1954; Domino, 1955). Morphine shortens the duration and decreases the frequency of EEG arousal, but does not prevent it (Domino, 1956c). On the other hand, mephenesin depresses threshold recruiting responses that are mediated over polysynaptic arcs, while pentobarbital in small doses enhances these responses (King, 1954, 1956; Domino, 1955). Obviously what distinguishes mephenesinlike compounds from other central nervous depressants is not so much the degree of selectivity in depressing crossed-extensor and flexor reflexes of the spinal cord as the different degrees of depression of the hundreds of thousands of neuronal arcs of the higher cerebral centers.

Depression of the interneurons involved in the flexor or crossed-extensor reflexes is not necessarily related to skeletal muscle relaxation. Panparnit is an example of an agent that selectively depresses the flexor reflex, but does not produce skeletal muscle relaxation (Berger, 1949a). Presumably the skeletal muscle relaxation produced by mephenesin is related to its depressant actions on the intercalated neurons involved in extrapyramidal and pyramidal influences on the motor anterior horn cells. For this reason it is essential to use testing procedures that will determine such drug actions.

Action on the extrapyramidal system. There are many methods available for studying the effects of drugs on extrapyramidal influences on the motor anterior horn cells. One procedure used frequently is to determine the effects of drugs on the influence of various areas of the brainstem that modify spinal cord reflex activity. Electrical stimulation of the ventromedial bulbar reticular formation produces inhibition of the patellar reflex (Magoun and Rhines, 1946). Stimulation of more lateral and rostral bulbar areas produces facilitation of the patellar reflex (Magoun and Rhines, 1947). The influences of both systems are mediated primarily over polysynaptic arcs (Lloyd, 1941a; Lettvin, 1948). These are shown diagrammatically for the cat in FIGURE 4. Both brainstem and spinal crossings are present in facilitatory reticulospinal paths, but only spinal crossings exist for inhibition. The reticulospinal pathways are widely distributed in the lateral and ventral funiculi of the spinal cord. Facilitatory influences pass through the dorsal portions, and inhibitory influences through ventral portions of the spinal cord, but there is some overlap (Niemer and Magoun, 1947). The bulbar reticular areas are not necessarily purely facilitatory or inhibitory for all motor activity. Frequently reciprocal effects on various reflexes can be shown (Gernandt and Thulin, 1955; King *et al.*, 1955). The administration of mephenesinlike agents depresses the effects of bulboreticular stimulation on the patellar reflex (Henneman *et al.*, 1949; Kaada, 1950; Funderburk *et al.*, 1953a). Bulboreticular facilitation appears to be somewhat more sensitive to depression by mephenesinlike drugs than bulboreticular inhibition. It is of interest that procaine produces the opposite effects, that is, bulboreticular inhibition is more selectively depressed (Peterson, C. G., 1955). Many other extrapyramidal structures are known to modify reflex motor activity. These include the anterior and paramedian cerebellar cortex and fastigial nucleus; basal ganglia, especially the caudate nucleus; and portions of the forebrain, as well as the cerebral cortex (see FIGURE 4). The final common pathways for many of the facilitatory and inhibitory influences that can be elicited from these areas are presumably mediated in part via the brainstem reticular formation (Snider *et al.*, 1947; Lindsley *et al.*, 1949; Hodes *et al.*, 1951, 1954; Peacock and Hodes, 1951; Lindsley, 1952). In any detailed study of the site of action of a test agent, effects on these structures should be determined. Important differences between drugs are known to exist. For example, atrolactamide is more selective than mephenesin in depressing the inhibitory influences from the caudate nucleus (King and Unna, 1954).

Actions on the pyramidal system. Very little is known about the effects of centrally acting skeletal muscle relaxants on pyramidal tract influences on

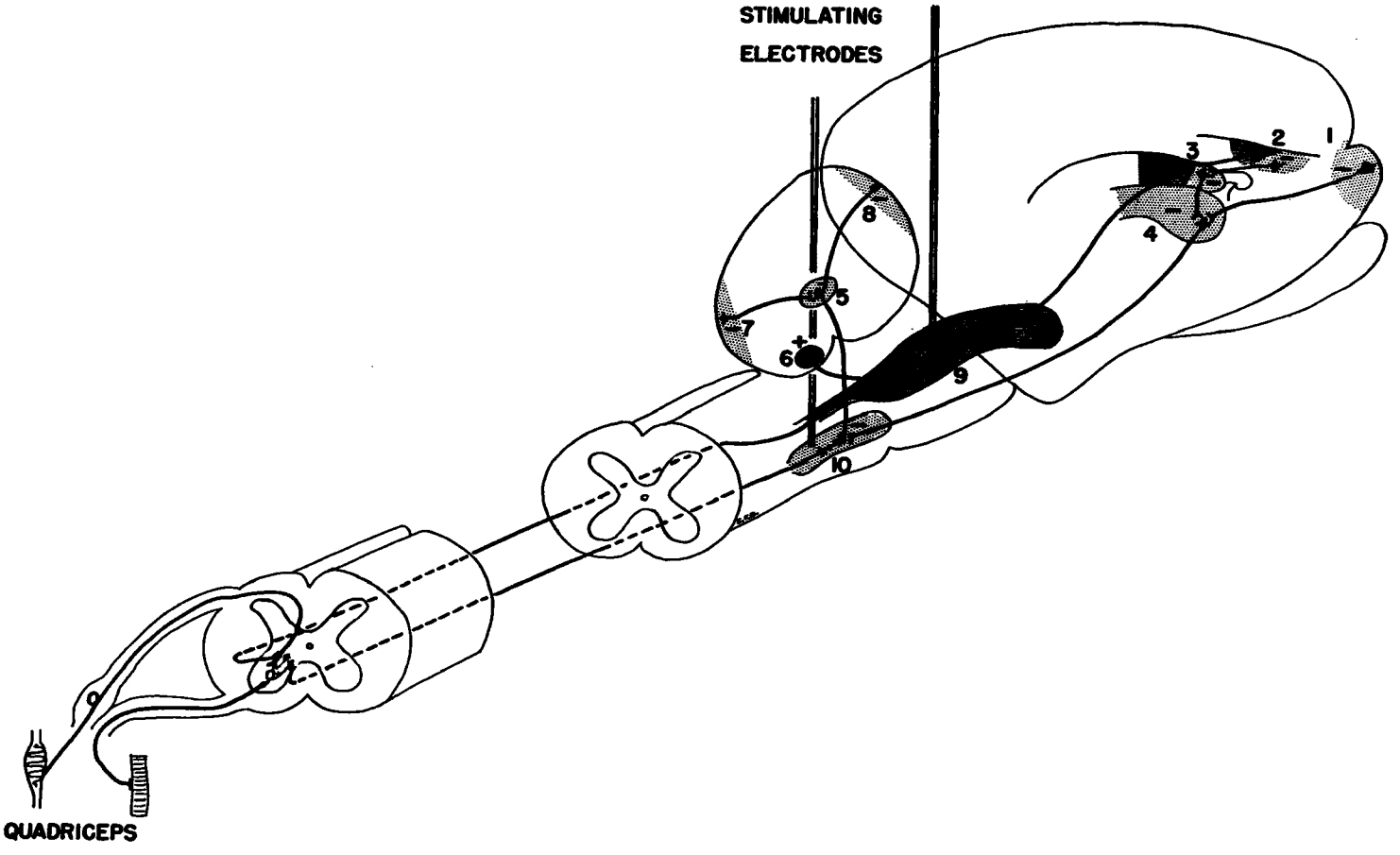


FIGURE 4. Schematic representation of some extrapyramidal structures that facilitate or inhibit the patellar reflex: 1, pericruciate cerebral cortex; 2, cingulate gyrus; 3, medial thalamic and septal nuclei; 4, caudate nucleus; 5, fastigial nucleus; 6, vestibular nucleus; 7, paramedian cerebellar cortex; 8, anterior cerebellar cortex; 9, lateral reticular formation; and 10, medial reticular formation (modified from Lindsley, Schreiner, and Magoun 1949)

anterior horn cells. This is surprising in view of the large number of intercalated neurons involved (Lloyd, 1944). Inasmuch as marked species differences exist in the percentage of pyramidal tract fibers ending via intercalated neurons on anterior horn cells, this subject will be discussed later.

Actions on brainstem activating system and cerebral cortex. As previously mentioned, mephenesinlike compounds differ from other central nervous system depressants in their relative lack of effects on the brainstem activating system and cerebral cortex. It is becoming more apparent that many central nervous system depressants in small doses show some selectivity in depressing interneurons involved in the flexor and crossed-extensor reflexes (see TABLE 1). Barbiturates are obviously not useful skeletal muscle relaxants because doses that depress interneurons of the spinal cord cause marked depression of the brainstem activating system (French *et al.*, 1953; Arduini and Arduini, 1954; King, 1954, 1956; Domino, 1955) and cerebral cortex (Domino, 1956a, b). For these reasons any experimental evaluation of a skeletal muscle relaxant must include appropriate electroencephalographic studies of spontaneous and elicited cerebral activity.

As shown diagrammatically in FIGURE 5 the brainstem reticular formation and the diffusely projecting thalamic nuclei constitute a second afferent system for sensory impulses to reach the cerebral cortex. These polysynaptic neuronal systems are involved in wakefulness and sleep (Delafresnaye *et al.*, 1954), and therefore they are of considerable importance in understanding differential drug effects. Compounds that abolish EEG arousal resulting from electrical stimulation of the activating system are of little clinical value as centrally acting skeletal muscle relaxants even though they may appear promising on the basis of other animal-testing procedures.

Therapeutic Action Testing Methods

A rational approach in finding new therapeutic agents for man is to reproduce the human disease in animals and then test potential drugs on such preparations. Several operative procedures are known that produce in animals symptoms of exaggerated postural reflexes that resemble in many respects spasticity in man. This does not imply that the same neural mechanisms that produce spasticity in animals are necessarily present in human patients. Nevertheless such testing methods are of some value in predicting the clinical efficacy of new drugs. Invariably electromyograms are taken to record skeletal muscle tone. Centrally acting muscle relaxants such as mephenesin will reduce the exaggerated muscle tone in such experimental preparations.

Spasticity resulting from temporary spinal cord asphyxia. Localized asphyxia of the spinal cord produces hind limb spasticity due to selective internuncial neuron damage. The asphyxia is produced by interfering with spinal cord circulation by compression of the descending aorta (Tureen, 1936; Kabat and Knapp, 1944) or by raising the intradural pressure above arterial pressure through a lumbar puncture in the isolated lumbosacral cord (van Harreveld and Marmont, 1939; van Harreveld, 1940). An appropriate interval of asphyxia differentially injures spinal cord neural elements so that preparations

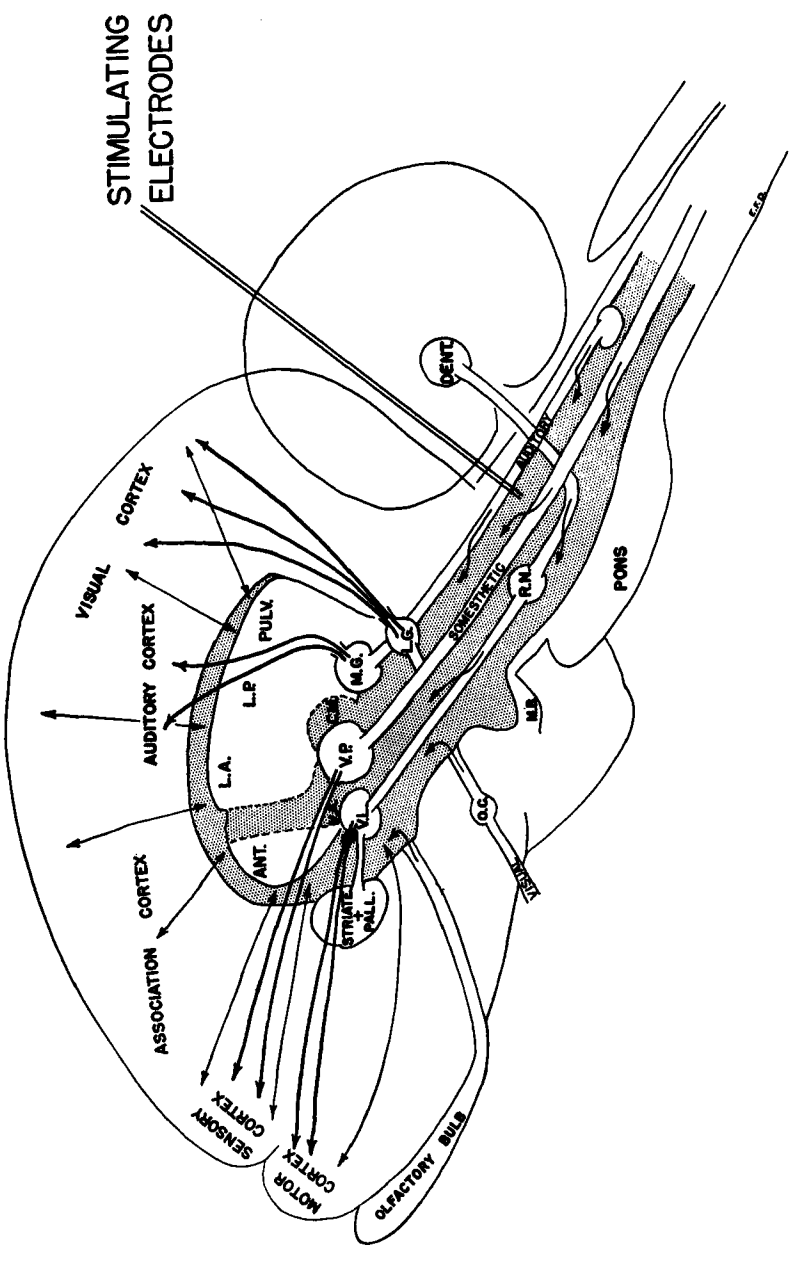


FIGURE 5. Schematic representation of the brain of a cat showing the primary afferents, and the secondary sensory system (stippled) consisting of some neurons of the brainstem reticular formation and diffusely projecting thalamic nuclei.

can be obtained in which the anterior horn cells and their muscle afferents (stretch reflex) are intact, while certain intercalated neurons are destroyed. Animals that have been subjected to such a procedure (cats and monkeys) show markedly exaggerated stretch reflexes and clonus that offer a convenient means for testing drugs.

Decerebrate rigidity. Transection of the brainstem at midcollicular levels produces a state of exaggerated posture that Sherrington in 1898 called decerebrate rigidity. Laboratory animals such as guinea pigs, rabbits, cats, dogs, and monkeys readily show this phenomenon (Fulton, 1949). Technical operative difficulties such as blood loss result in less constant preparations that tend to deteriorate and therefore have been thought to make this particular method of decerebration less satisfactory for drug studies (Funderburk *et al.*, 1953a). Ischemic decerebration produced by ligation of both common carotids and the basilar artery (Pollock and Davis, 1930, 1931) has been considered more satisfactory in this regard. Overtly both techniques produce a similar picture of decerebrate rigidity. Classical Sherringtonian decerebrate rigidity, however, is dissolved by section of the dorsal roots, while ischemic decerebrate rigidity is unaffected. Despite overt similarities the 2 types of decerebration are fundamentally different (Stella, 1944a, b). It is now known that Sherringtonian decerebration is dependent largely upon an intense inflow of excitatory impulses from the peripheral skeletal muscle spindle due to activity of the central γ efferents. On the other hand, ischemic decerebration involves primarily α-efferent excitation to skeletal muscle cells by-passing the muscle spindle mechanism. The cerebellum appears essential in regulating the proportion of α- or γ-efferent excitation (Granit, 1955; Granit *et al.*, 1955). Both forms of decerebrate rigidity involve transmission over intercalated neurons but of different types. In spite of the different neural mechanisms involved in producing the exaggerated skeletal muscle tone, both forms of decerebrate rigidity are relieved by mephenesinlike drugs. To date, no data are available on the differential sensitivity, if any, of the two preparations to mephenesinlike compounds. Recently in the rabbit, γ-efferent excitation of the muscle spindle has been shown to be depressed centrally by small doses (20 mg./kg., intravenously) of mephenesin (Granit and Holmgren, 1955).

Spasticity in chronic animal preparations. Since the time of Jackson, lesions of neural components normally suppressing postural reflexes have been recognized as producing symptoms of spasticity. Chronic spastic animals can be obtained readily by effecting surgical lesions of areas that normally inhibit postural reflexes (Magoun and Rhines, 1947). These include lesions of certain cerebral cortical areas (Hines, 1936, 1937; Fulton, 1937; Mettler, 1944; Welch and Kennard, 1944; Wagley, 1945), the caudate nucleus, bulbar inhibitory areas in the brainstem, anterior lobe and paramedian lobules of the cerebellum and fastigial nucleus (Schreiner *et al.*, 1949, and Lindsley *et al.*, 1949). Without exception the spasticity of such cat preparations is reduced by small amounts of mephenesin (Henneman and Scherrer, 1949). The spasticity of monkeys is similarly reduced, but no detailed comparative data are available in primates correlating the site of the lesion and differential drug efficacy.

Clinical Evaluation of Some Centrally Acting Skeletal Muscle Relaxants

As a result of our present animal-testing procedures, a number of centrally acting skeletal muscle relaxants have been found. Some are listed in TABLE 2. Several are or have been evaluated clinically in man with varying results. It is important to realize that it is exceedingly difficult to evaluate relief of spasticity in man. Few if any reliable methods are available to measure spasticity objectively. Electromyograms are useful but of limited value. Clinical impressions are the usual criteria of effectiveness. Minor relief of spasticity, even if real, may be overlooked in the spirit of objectivity. The sedative or tranquilizing actions of an agent may produce skeletal muscular relaxation secondarily and add difficulties in interpretation. Beneficial or toxic manifestations of placebo therapy are well known, and they complicate further any drug evaluation, especially in regard to the psychiatric uses of skeletal muscle relaxants (Wolf and Pinsky, 1954). Occasionally clinical reports appear claiming that certain pharmacological agents that have minimal muscle relaxant effects in some experimental animal preparations produce dramatic relief of spasticity in man. Chlorpromazine given intravenously is an example (Basmajian and Szatmari, 1955).

It is apparent from a casual observation of TABLE 2 that while there is a positive correlation between a compound's clinical effectiveness and its muscle relaxant properties in animals, the clinical effectiveness of any specific test substance cannot be predicted beforehand. Even in man considerable differences in effectiveness are observed. Mephenesin may be strikingly effective in some human cases of spasticity and completely ineffective in others. Until more is known about the central nervous system we are at a loss to explain such effects. There are numerous examples of a poor correlation between the effectiveness of a compound as determined by animal-testing procedures and clinical efficacy in man. 2-methyl,2-n-amyl-4-hydroxymethyl-1,3-dioxalane appears more effective than mephenesin on the basis of animal-testing procedures, but it is less effective in man. 2-2-diethyl-1,3-propanediol (DEP) is quite ineffective in man, yet 2-methyl-2-n-propyl-1,3-propanediol (meprobamate) is apparently as useful as oral mephenesin. Of some interest are the enthusiastic but preliminary reports of a tranquilizing action of meprobamate in man (Borrus, 1955; Selling, 1955). Some of these effects were observed in the early animal studies (Berger, 1954).

The benzazole derivatives furnish an interesting contrast in clinical effectiveness even though animal-testing procedures show similar sites of action. 2-amino-6-methylbenzothiazole and 2-amino-6-chlorobenzothiazole have been found in preliminary clinical trials with oral doses of 1 gm. or less to be relatively ineffective in relieving spasticity in man. When hypertonus is relieved, clonus appears increased. This latter action is reminiscent of the effects of small doses of mephenesin in decerebrate cat preparations (Henneman and Scherrer, 1949). Further clinical research using larger doses of these benzazoles would be informative. Another benzazole 2-amino-5-chlorobenzoxazole appears in preliminary trials to be more effective in man (TABLE 2). It is of considerable

TABLE 2

CLINICAL EFFECTIVENESS OF SOME CENTRALLY ACTING SKELETAL MUSCLE RELAXANTS

Agent	Pharmacological investigators	ffectiveness in human spasticity*	Clinical investigators
Mephenesin 3-(2′-methylphenoxy propane 1,2-diol	Berger & Bradley, 1946 Henneman *et al.*, 1949 Smith, W. K. *et al.*, 1949 Kaada, 1950 Traverner, 1952	++	Stephen & Chandy, 1947 Schlesinger *et al.*, 1948 Berger & Schwartz, 1948 Effron & Schultz, 1951 Libet & Rubin, 1952
3-(2′-methoxyphen-oxy) propane 1,2-diol	Schneider & Earl, 1954	+ †	Ginzel & Tschabitscher, 1951
1-ethoxy-3-isopropoxy 2-propanol	Hine *et al.*, 1949 Davis *et al.*, 1952 Goodsell *et al.*, 1954	+ †	Smith, R. T., 1953
2-methyl-2-n-amyl-4-hydroxymethyl-1,3-dioxalane	Berger *et al.*, 1948 Berger, 1949b	0 to + †	Berger, 1955b
2,2-diisopropyl-4-methanol-1,3-dioxalane	Berger *et al.*, 1948 Dietrich, 1955	? ‡	—
DEP 2,2-diethyl-1,3-propanediol	Lott, 1948 Berger & Ludwig, 1950 Slater *et al.*, 1950 Funderburk & Unna, 195	0 to + †	Denhoff *et al.*, 1951
Meprobamate 2-methyl,2-n-propy 1,3-propanediol d carbamate	Berger, 1954, 1955a Hendley *et al.*, 1954, 195.	++ †· ‡	Drew, 1955
Benzimidazole	Goodman, 1943 Goodman *et al.*, 1943 Goodman & Hart, 1944	+ †	Goodman, 1955
2-amino-6-methylbenzothiazole and 2-amino-6-chlorobenzothiazole	Domino *et al.*, 1952 Funderburk *et al.*, 1953a, l	) to + †· ‡	Amols, 1955 Friend, 1955 Glaser, 1956
Zoxazolamine 2-amino-5-chlorober zoxazole	Funderburk & Woodcock 1955 Kamijo & Koelle, 1955a, Marsh, 1955	++ to +++ †· ‡	Abrahamsen & Baird, 1956 Amols, 1956 Gomez *et al.*, 1956 Smith, R. T. *et al.*, 1956
1,2,4-Triazine derivatives	Mantegazza *et al.*, 1953	?	—
Dihydrobenzo-1-4-thiazine	Longo, 1952	?	—
1-phenyl-γ-(2-pyridyl)-propyl ketone	O'Leary *et al.*, 1951 Slater *et al.*, 1951	?	—
4-Alkoxy-β-(1-piperidyl)-propiophenone:	Abreu *et al.*, 1955	?	—

* The clinical effectiveness rating for skeletal muscle relax: is empirical ar approximate with a variation of one plus more or less. It is an opinion of this author only a ɔt necessarily t t of the clinical investigators. The effectiveness of mephenesin is arbitrarily designated as +

† Preliminary data.

‡ Further clinical trials are indicated.

interest that this compound may be more beneficial in spasticity of spinal origin than of cerebral origin (Gomez *et al.*, 1956). Spasticity of cerebral origin may have quite different pathophysiological mechanisms from spasticity resulting from spinal cord lesions.

Perspective

It is obvious that in the last 10 years, using our present animal-testing procedures, no centrally acting skeletal muscle relaxants have been found that on oral administration produce *dramatic* relief of spasticity in man. Perhaps none will ever be found, irrespective of the animal-testing methods used, but there is no reason for pessimism. Until our knowledge of comparative neuropharmacology is more adequate there are several empirical approaches for finding newer therapeutic agents. It is apparent that we should select animals with nervous systems similar to those of men. The tractable primates appear most suitable. Most initial screening has been in animals that have a normal central nervous system. Thus neural phenomena secondary to denervation are not present as they are in the diseased central nervous system of human patients. Perhaps our initial screening should be conducted directly in chronic spastic animal preparations. Even with more satisfactory animal-testing procedures, the chemical compounds screened have been selected purely on an empirical basis. In order to obtain clues as to compounds to be screened a knowledge of the mechanism of action of our present skeletal muscle relaxants is essential. The benzazoles, in particular, because of their structural similarity to purines and known antagonistic actions in bacteria and viruses (Woolley, 1944; Tamm, 1956), as well as being substrates in the molecules of vitamin B_{12} (Bonnett *et al.*, 1955; Hodgkin *et al.*, 1955) and serotonin (Erspamer, 1954) offer important leads. To date there is no evidence to suggest that these incidental observations are in any way related to the production of skeletal muscle relaxation.

Since our present animal-testing procedures have given us compounds that are mildly clinically effective, we can conclude that our current methods, in general, are correct but need to be subjected to a critical review. In order to obtain more effective therapeutic agents at least three aspects of the problem must be reconsidered. These include: (1) neurobiochemical similarities and differences between man and subhuman species used in the pharmacological screen, (2) neuroanatomical and neurophysiological similarities and differences between man and laboratory animals, and (3) pathophysiological mechanisms of spasticity in man and laboratory animals.

Comparative neurobiochemistry. An enormous vacuum of knowledge exists with regard to the neurobiochemistry of even one animal species. There is desperate need for research in this area. Surely there are important biochemical differences in the central nervous systems of animals and man. Until such data are available, there is little to be gained from speculation.

Comparative neuroanatomy and neurophysiology. A study of the comparative neuroanatomy of vertebrates reveals structural differences at all levels of the central nervous system (Arieïs Kappers *et al.*, 1936). Morphologically both pyramidal and extrapyramidal motor systems change considerably as one

TABLE 3

COMPOSITION OF THE PYRAMIDAL TRACT OF SOME LABORATORY ANIMALS AND MAN

Animal	Number of axons (Lassek, 1954)	Caliber of axons		Direct corticospinal component
		Small	Large	
Mouse	32,300	All	None	None
Cat	186,000	Almost all	Few	Minimal to none
Dog	285,300	Almost all	Few	Probably similar to cat
Monkey	554,000	Most	Increasing	Increasingly important
Chimpanzee	807,000	Most	↓	↓
Man	1,200,000	Most		

ascends the vertebrate scale. For example, there is a marked variation in the pyramids, in the size of the pallidum versus the striatum, of the olives, of the magnocellular and parvocellular portions of the red nucleus as well as the length of the rubrospinal tract. Presumably neurophysiological mechanisms vary accordingly. Throughout phylogeny there is progressive encephalization of nervous function culminating in man. This is reflected in the extent of incapacity resulting from cerebral cortical lesions. The carnivores function surprisingly well without much cerebral cortex, as demonstrated by the famous Goltz dog. At the same International Medical Congress of 1881 in London where Goltz demonstrated his decorticate dog, Ferrier and Yeo (Schäfer, 1882) showed, on the contrary, that removal of the motor cortex and surrounding area in the monkey resulted in a severe contralateral motor disability that decreased with time. Similar cortical lesions have been produced in other primates, including the chimpanzee and man, that result in even more severe motor disability (Fulton, 1949). Man differs considerably from even other primates by the importance of his cerebral cortex.

Perhaps the most obvious development of the motor system of primates is the pyramidal tract (Lassek, 1954). Inasmuch as this system may be of neurological importance in human spasticity (see below) the changing composition of the pyramidal tract will be discussed in detail as an example of the type of comparative study needed for other portions of the central nervous system involved in motor activity.

Many investigators have clearly demonstrated that the pyramidal tract changes considerably throughout phylogeny. Some of these differences are listed in TABLE 3. The number of axons comprising the pyramidal tract increases progressively and is largest in man (Lassek, 1954). This is not related to the size of the animal, for members within a species have a similar axon content. The axons of the pyramidal tract of lower vertebrates such as the mouse are very thin. In the cat and the dog, most of the axons are of small caliber with a few large axons. In ascending the primate scale, the large myelinated fibers of the pyramidal tract become increasingly important, although the absolute percentage is still small. In the mouse, the pyramidal tract terminates primarily on intercalated neurons. Many intercalated neurons also are present in the pyramidal system of man, but the corticospinal component, terminating directly on motor anterior horn cells, is substantial.

The degeneration studies of the boutons terminaux by Hoff, 1932, suggest that no more than 15 per cent of the pyramidal tract of the cat terminates directly on the anterior horn cells. A much smaller figure is suggested by the anatomical studies of Szentágothai-Schimert, 1941. The neurophysiological studies of Lloyd, 1941b, and Bernhard and Bohm, 1954, also suggest that most of the cat's pyramidal tract terminates primarily on intercalated neurons. Studies on degeneration of the boutons terminaux in the monkey by Hoff, 1932, and Hoff and Hoff, 1934, show that about 40 per cent of the pyramidal tract terminates directly on motor anterior horn cells. Bernhard *et al.*, 1953, in their neurophysiological studies stress the functional importance of the direct corticospinal component in the monkey. In ascending the primate scale, the direct corticospinal component of the pyramidal tract appears to increase proportionately, although there are no systematic studies elaborating the details. There is much circumstantial evidence present in the literature, however, to suggest its increasing importance in monkey, baboon, chimpanzee, ape, and man (Sherrington, 1889; Schäfer, 1899a, b; Leyton and Sherrington, 1917; Hoff, 1932, 1933; Hoff and Hoff, 1934; Levin, 1936; Levin and Bradford, 1938; Bernhard and Bohm, 1954).

Pathophysiological mechanisms of spasticity in man and animals. Much evidence based primarily on studies in lower animals supports the hypothesis that spasticity as characterized by hyperactive stretch reflexes, clasp-knife resistance to passive movements and clonus is due to involvement of extrapyramidal structures (Magoun and Rhines, 1947). Years ago Hughlings Jackson suggested at least two mechanisms for spasticity in man: (1) release of lower centers from higher neural control, and (2) an influx mechanism "from an unopposed one of a pair of amicably antagonistic neural systems." Most of the evidence is in favor of the latter theory. Thus spasticity is usually considered the result of diminished inhibitory influences when facilitatory motor influences are normal or exaggerated. Experimental spasticity in animals (see earlier discussion) can be produced readily as a result of damage to motor inhibitory areas of the central nervous system.

The results of most experimental studies on the pyramidal system agree with the concept of spasticity as a syndrome of extrapyramidal involvement. Thus, discrete removal of area 4 of the cerebral cortex in monkeys and chimpanzees (Fulton and Kennard, 1934) or section of the pyramids (Tower, 1940) produces skeletal muscle flaccidity. Few investigators have challenged this view. Denny-Brown, 1950, however, refers to unpublished data on the production of spasticity in a monkey with a pure pyramidal lesion. This report, as well as others (Meyers *et al.*, 1954) on the failure to confirm the existence of cortical suppressor strips (Garol and Bucy, 1944) have prompted Clark, 1952, to reject the notion that spasticity is purely an extrapyramidal syndrome, as suggested by Magoun and Rhines, 1947. Obviously many more data are necessary, especially as regards higher primates, to clarify the role of the pyramidal system. Until such neurophysiological data are available investigators interested in centrally acting skeletal muscle relaxants should keep in mind the possibility that human pyramidal tract disease might give rise to a spasticity that may be mediated in part over direct corticospinal components. Obviously

in such a condition, drugs such as mephenesin that depress interneurons predominantly should not be expected to be effective. Perhaps the observation of Gomez *et al.*, 1956, that human spasticity of spinal origin is more easily relieved by zoxazolamine than spasticity of cerebral origin may be explained on this basis.

Summary

Numerous experimental methods have been utilized for screening chemicals in animals in an attempt to find clinically effective, centrally acting, skeletal-muscle relaxants. These procedures invariably involve a careful physical examination of laboratory animals for evidence of a reversible paralysis of the hind extremities, and a study of the effects of the agents on various polysynaptic reflexes. In spite of intensive efforts of many investigators, few if any centrally acting muscle relaxants have been found to produce dramatic therapeutic relief of spasticity in man. It is apparent that our present animal screening procedures may be inadequate. Various testing methods are discussed in the light of present knowledge of the pathophysiology of spasticity in man.

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