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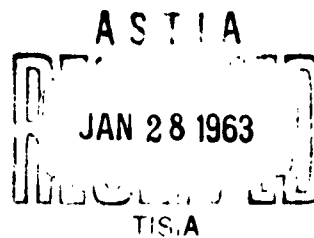PROSERINE, ESERINE, AND DIBAZOL AND THEIR
ADMINISTRATION IN NEUROPATHOLOGY
(SELECTED CHAPTERS)

By

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English Pages: 84

SOURCE: Prozerin, Ezerin, Dibazol i Ikh Primenenie
v Nevropatologii, Library of Practical
Medicine, Medgiz, Leningrad, 1956, pp. 7-33,
50-81, 102-108, 177-196.

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CHAPTER I

GENERAL PHARMACOLOGICAL CHARACTERISTICS OF PROSERINE, ESERINE, AND DIBAZOL

Very extensive literature is available on proserine and eserine and a number of works are devoted to a pharmacological evaluation of dibazol. While citing information on these preparations, particular attention will be devoted to facts pertaining to therapy of diseases of the nervous system. Only the most necessary information will be given on the remaining properties of these substances; however, in certain sections of the book, citations are made of appropriate literature sources in which the reader will find additional information on problems of interest to him concerning the pharmacology of proserine, eserine, and dibazol.

Since the mechanism of the action of proserine and eserine is associated with the interference of these substances in the processes of the chemical transmission of a nerve impulse, accomplished with the participation of acetylcholine, a brief summary and analysis of the present-day concepts of the possibility of pharmacologically interfering with these processes will preface this account of the pharmacologic data.

Possibilities of Pharmacologic Intervention in the Chemical Transmission of a Nerve Impulse Accomplished with Participation of Acetylcholine

Many investigators have attempted to explain chemical transformations occurring in nervous tissue. The importance of such quests is completely understandable because, knowing the chemical nature of nerve processes, it would be possible to undertake attempts for a purposeful action on these processes in order to control them. "One can hardly dispute that only a study of the physicochemical process occurring in nervous tissue will give us a true theory of all nervous phenomena," wrote I. P. Pavlov in 1926.

In 1921 the study of O. Loewi was published; he found that on stimulation of the vegetative nerves of isolated frog heart, a substance appeared in it which, being transferred to another isolated heart, caused in the latter the same changes as stimulation of the vegetative nerves in the first heart. Later development of these observations made it possible to establish an important fact: on transmission of a nerve impulse from the end of a vegetative nerve to a working organ, a chemical substance is released which was named a mediator.

In 1925 the important work of A. F. Samoylov was published; he found, by studying the effect of temperature on the rate of transmission of a nerve impulse from the ending of a motor nerve to striated muscle, that "at the boundary between the muscle and the nerve there is a mechanism whose rate of work depends on the temperature, just as the velocity of chemical reactions." These observations permitted the author to hypothesize that on transmission of an impulse from a motor ending to striated muscle a substance is released on the endings of the latter which plays the role of a chemical mediator. On the same basis

A. F. Samoylov considered that, in the nervous system itself the transmission of a nerve impulse is accomplished by chemical mediators. This hypothesis was soon confirmed by many experimental investigations which showed the existence of chemical transmission of a nerve impulse when it travels from the motor ending to a muscle, in the ganglia of the vegetative division of the nervous system, and in the central nervous system itself (A. G. Ginetsinskiy and N. I. Mikhel'son, 1945, 1948; K. M. Bykov, 1948; Kh. S. Koshtoyants, 1950; Burn, 1953;. Fulton, 1953; etc.).

It is necessary to note in particular the great services of our scientists in solving the problem of the chemical transmission of nerve impulses, in particular the works of A. F. Samoylov, A. V. Kibyakov, K. M. Bykov, L. A. Orbeli, etc.

At present we can consider established, the existence of two chemical mediators of the nerve impulse: acetylcholine and adrenaline.

$$H_3C \diagdown \overset{OH^-}{\underset{|}{N^+}}—CH_3—CH_2—O—\overset{O}{\overset{\|}{C}}—CH_3 \quad H\overset{OH}{\underset{|}{C}}—CH_2—NH—CH_3$$
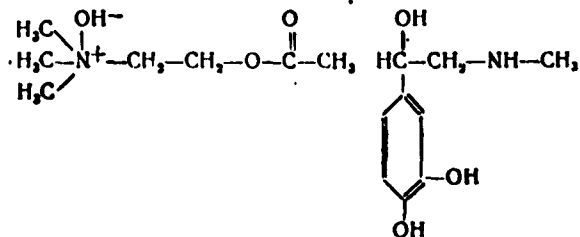
Acetylcholine   Adrenaline

Nerve fibers, on the endings of which acetylcholine is released as a mediator in the transmission of an impulse, are collectively called cholinergic fibers. To them belong the motor nerves running to the skeletal musculature, the preganglionic fibers of the parasympathetic and sympathetic divisions of the nervous system, the parasympathetic postganglionic fibers, sympathetic postganglionic fibers innervating the sweat glands; the synapses of the central nervous system are also cholinergic. New fibers on whose endings adrenaline is released are called adrenergic fibers. These include the sympathetic

postganglionic fibers except those of the sweat glands. It is necessary to note that at the endings of the adrenergic nerves a substance is liberated in certain cases along with adrenaline, which is very similar to the latter in chemical composition--noradrenaline; in a number of cases it is possible to detect other substances very similar to adrenaline in structure (A. M. Utevskiy, 1954). The performance of the "mediator" role is clearly demonstrated on analysis of the propagation of a single nerve impulse along a motor nerve toward striated muscle. At the neuromuscular junction, the impulse, together with electrical changes, induces a number of chemical transformations, as a result of which acetylcholine is liberated.* The latter affects the region of the skeletal muscle situated in the area of the neuromuscular junction. This region of the muscle, not different morphologically from others, is distinguished by its ability to react to acetylcholine, which is possibly due to the presence in it of a special biochemical system which is stimulated by acetylcholine; this system is called the cholinoreaction system. Stimulation of the cholinoreaction system, arising as a result of its interaction with acetylcholine, leads to a contraction of the muscle.

The action of acetylcholine, demonstrated as a result of a single nerve impulse, lasts no more than 0.002 sec because it is destroyed by cholinesterase. The latter is detected in many tissues of the organism; it is contained in the largest amount in the nervous tissue. This scheme of the transmission of a nerve impulse by means of acetylcholine can equally pertain to other cholinergic fibers.

In order to enhance the activity of an organ innervated by a cholinergic nerve we can present, by starting from the cited scheme,

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* Data exist which support the fact that propagation of an impulse along a nerve is also accomplished with participation of acetylcholine (D. Nachmanson, 1948).

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at least three possible variants of interference in the process of impulse transmission.

The first variant is the injection of acetylcholine into an organism (some authors call such acetylcholine "pharmacologic" in contrast to "physiologic" which is liberated in the appropriate nerve structures during impulse transmission). The injection of acetylcholine into an organism leads to the occurrence of a violent reaction to it in all cholinoreaction systems. This reaction is short-lived since the acetylcholine is rapidly destroyed by cholinesterase. It is evident that such a variant is of little practical value.

The second variant is a reduction of inhibition of the activity of the cholinesterase destroying the acetylcholine, and thus the creation of conditions under which it will be destroyed more slowly. In this case the action of each "portion" of physiologic acetylcholine lasts longer, and consequently the effect which it causes is more intensive. It was possible to find substances which reduce the activity of cholinesterase over a long period of time; this makes it possible to intensify the action of physiologic acetylcholine on the cholinoreaction systems for a determined period. Such a means of pharmacological action on the process of impulse transmission is of undoubted practical importance. The substances inhibiting the activity of cholinesterase are called anticholinesterases.

The third variant is the attempt to inject into an organism substances which would excite the cholinereaction systems like acetylcholine, but would not be destroyed by cholinesterase. It is possible to attain a sufficiently prolonged and, to some extent, expressed excitation of the cholinoreaction systems by the injection of such substances in definite doses. It was found, however, that between the cholinoreaction systems of different organs there is a very substantial difference

when, being sensitive to acetylcholine, they react dissimilarly to acetylcholinelike-acting substances.

As a result of a special study it was necessary to divide the cholinoreaction systems into two groups. The cholinoreaction systems of the first group react to muscarine in addition to acetylcholine. They received the name muscarine-sensitive cholinoreaction systems, or in short M-cholinoreaction systems. These systems have been detected in the internal organs, glands, and in the central nervous system. Substances capable of exciting the cholinoreaction systems of the first group received the name muscarinomimetic.

The cholinoreaction systems of the second group, in addition to acetylcholine, react to nicotine. They received the name nicotine-sensitive cholinoreaction systems, or, abbreviated, N-cholinoreaction systems. The latter are found in skeletal muscles, in ganglia of the vegetative division of the nervous system, in the adrenal cortices, in the central nervous system (it has presently been established that they are present in the spinal cord and in the hypophysis). Finally, N-cholinoreaction systems are found in the glomus caroticum.

Substances exciting the N-cholinoreaction systems are called nico-tinomimetic. The first studied representative of this group, nicotine, was at first tested on the vegetative ganglia, whereby its character-istic effect in the form of initial excitation and subsequent depres-sion of the functions of vegetative ganglia was detected. Since other types of action of nicotine were not known for a long time, it and allied substances were separated into a group of ganglionic poisons. The group of nicotinomimetic substances is even now often found in the pharmacological literature under this name, although the term "ganglionic poisons" no longer defines the essence of the action of the group of substances under consideration.

The hypothesis of the existance of two types of cholinoreaction systems was first expressed by S. V. Anichkov and M. A. Grebenkina (1946); they introduced the above-indicated classification of cholinoreaction systems and proposed the terms. S. V. Anichkov and co-workers also gathered important data on the potentiality of the pharmacologic action of the cholinoreaction systems (S. V. Anichkov, 1947, 1951; M. A. Grebenkina, 1948; S. V. Anichkov and A. A. Petropavlovskaya, 1949; A. A. Beolus, 1950; S. V. Anichkov and M. L. Belen'kiy, 1952).

All agents acting similarly to acetylcholine (acetylcholinesterase, muscarino- and nicotinomimetic substances and, finally, acetylcholine itself) are combined into a group of choline-positive or cholinomimetic substances.* A group of pharmacologic substances exists which prevent the action of acetylcholine and cholinomimetic agents; the substances · in this group are called cholinonegative or cholinolytic. The mechanism of action of cholinolytic agents lies in the ability of these compounds to make cholinoreaction systems insensitive to acetylcholine and to substances analogous to it in action.

In conformity with the division of the cholinoreactive systems, the cholinolytic substances are divided into two groups: agents blocking the N-cholinoreaction systems--antinicotinic substances (S. V. Anichkov and M. L. Belen'kiy, 1953).

During experimental investigations and practical administration of the antinicotinic substances, substantial differences were determined between individual representatives of this group. It turned out that some preparations initially block the cholinoreaction systems of

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* Strictly speaking these terms cannot be considered as being different. The term cholinopositive substances is broader than the designation of substances as cholinomimetic and includes the latter term. For example: acetylcholine is, of course, cholinopositive, but is not a cholinolytic substance.

Diagram of the Interrelation Between Cholinomimetic and Cholinolytic Substances

Cholinesterase

Cholinomimetic substances

Destroys acetylcholine ←——— Anticholinesterase ——— { Proserine, Eserine, Phosphacol, Galanthamine

——→ Acetylcholine
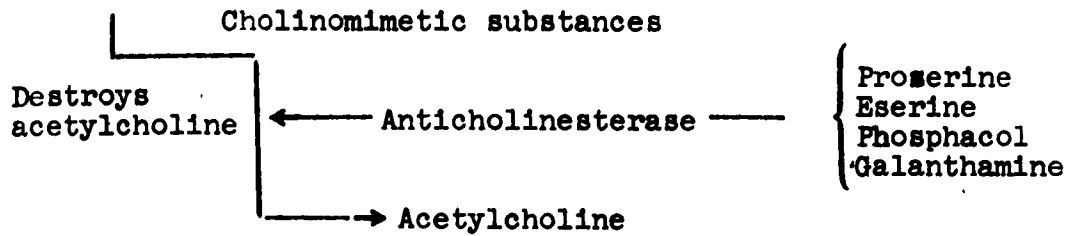
Muscarinomimetic substances

Muscarine, Pilocarpine, Furamon

Carbachol

Nicotinomimetic substances

Nicotine, Lobeline, Cytisine

Block M-cholinoreaction systems

Block N-cholinoreaction systems

M-cholinoreaction systems	N-cholinoreaction systems
Internal organs Glands	Skeletal muscles Vegetative ganglia Adrenal cortex Vascular chemoreceptors
Central nervous system	

Cholinolytic substances

—— Antimuscarinic   Antinicotinic ——

Atropine	Ganglion-blocking	Curareform
Scopolamine	Tetamon	d-tubocurarine
Tropacin	Diphacil	Diplacine
Platyphylline	Pachycarpine	Pirolaxon
Pentaphene	Gangleron	Ditilin

the vegetative ganglia--these substances are called ganglion-blocking;
others, on the other hand, mainly block the cholinoreaction systems of
striated muscles--this group of antinicotinic compounds received the
name curareform agents, on the basis of the preparation in which the
indicated properties were first detected--curare.

It is necessary to note the interest which is presently shown by
many investigators and clinicians in the group of antinicotinic sub-
stances. For example, substances of curareform action are used in
surgery as agents relaxing the musculature during an operation, and
are especially used widely in surgery on thoracic organs.

Ganglion-blocking agents are also used in surgery owing to the
capacity to lower the body temperature. In this case the sensitivity
of the central nervous system to hypoxia is lowered, which makes it
possible to perform long surgical manipulations on the heart and large
vessels.

Investigations of recent years have established that distinct
differences are noted in the series of curareform agents, thus giving
basis for a further refinement of the cited classification (Galibois,
1953; Paton, 1953, etc.).

In order to depict graphically the interrelation between the
individual groups of substances within the cited classification, a
diagram is proposed in which the most commonly used Soviet drugs be-
longing to the corresponding groups are shown additionally.

This diagram can conclude the account of the general interrelations
between the choline-positive and choline-negative substances, since a
detailed pharmacologic evaluation of each of the named substances in
the diagram is not the purpose of the present article. It is necessary
to report additional information on carbachol--a preparation which does
not participate in any of the previously mentioned groups. The reason

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for the special position of carbachol in the diagram is because of its structural similarity to acetylcholine, owing to which it acts on both types of cholinoreaction systems but is not destroyed by cholinesterase.

In conclusion it is necessary to point out the well-known tentativeness of the diagram. For example, it does not reflect the information that antimuscarinic substances in large doses demonstrate an antinicotinic action, that nicotine in small doses is a nicotinomimetic substance, but in large doses is a nicotinolytic substance, that carbachol in large doses has curareform action, etc.

The simplified diagram illustrates the interrelation between the choline-positive and the cholinolytic substances when they are used in therapeutic doses, and is given for a general orientation in problems of the pharmacologic action on processes of acetylcholine transmission of the nerve impulse.

General Information on Eserine, Proserine, and Dibazol

Eserine (physostigmine) is contained in bean seeds of a perennial vine (Physostigma venenosum) growing in tropical Africa. The beans of this plant are called Calabar after the place where they grow, and the local inhabitants call them "esere." Calabar beans became known in Europe in the 1850-1860's. Persons who brought them back from Africa reported that the population of the locale where these beans grow used them at that time for performing "trials by ordeal", from which the beans received still another name--ordeal beans.*

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* When one of the natives was accused of a crime, he was forced to eat a certain amount of the beans or to drink a potion made of them. If the accused remained alive he was considered not guilty and was released, if he died he was considered guilty and justly punished for his crime (V. I. Dybkovskiy, 1878).

According to the chemical structure, eserine is a methylated ester of carbamic acid and a nitrogen-containing aromatic alcohol:
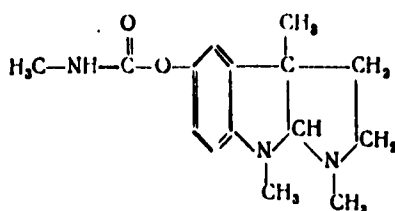
Eserine

In medical practice the salicylate of eserine (Eserinum salicylicum) is usually used--a colorless crystalline substance of bitter taste, soluble in 75 parts water or in 12 parts alcohol. The preparation rapidly decomposes in light and air and acquires a brown-red color. Eserine solutions are unstable in storage and therefore are made immediately before use. Solutions cannot be sterilized by boiling. The preparation must be stored in a well-closed vessel in a dark place, and its solutions in a light-resistant container with a ground stopper. Eserine solutions are prone to redden on decomposition.

Discovery of the chemical structure of eserine was the cause for a number of investigations, directed toward revealing the bond between the structure of eserine proper and also of synthetic substances similar to it in structure, and their physiological action. It turned out that the acetylcholinesterase action of these substances is associated with the presence of an ester bond between the carbamic acid and phenol hydroxyl, and also with the presence of amino nitrogen bound to the phenyl radical. On the basis of these investigations, a number of substances were obtained which had eserinelike action, among which proserine has received the greatest use.

According to the chemical structure, proserine (prostigmine, neostigmine) is (m-hydroxyphenyl)trimethylammonium methylsulfate dimethylcarbamate.

-10-

$$CH_3SO_4^-$$
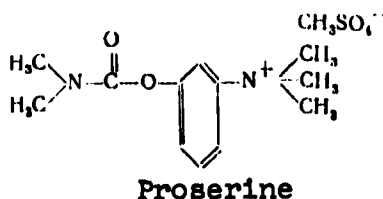
Proserine

The preparation is white or slightly yellow crystalline powder, of bitter taste, odorless, readily soluble in water, worse in alcohol. Aqueous solutions of proserine are stable and are not decomposed on boiling.

While eserine and proserine are similar in chemical structure, dibazol is a representative of a completely different class of compounds. The preparation is 2-benzylbenzimidazol hydrochloride. It is a white crystalline powder of bitter taste. A 1% solution is obtained on dissolving the substance in water, and more concentrated solutions are produced by heating; the solutions are stable and can be boiled. The preparation precipitates in an alkali solution.
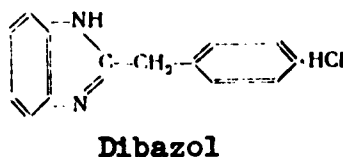
Dibazol

Dibazol was first synthesized in the Soviet Union and has been used since 1948. It was obtained from other benzimidazol derivatives by B. A. Poray-Koshits, L. S. Efros, and O. F. Ginzburg (1947). Pharmacologic investigation of these compounds was carried out in two laboratories. The action of benzimidazol derivatives on the central nervous system was studied in the laboratory directed by N. V. Lazarev. M. A. Rozin, having discovered the action of dibazol on the central nervous system of laboratory animals, and then its stimulating action on the performance of healthy people, transferred the study of the

preparation to the clinic for nervous diseases.* Later, in this same laboratory, basic information was obtained concerning the therapeutic properties of dibazol and its mechanism of therapeutic action (N. V. Lazarev and M. A. Rozin, 1951, 1954).

In the laboratory directed by S. V. Anichkov, this drug was sub-jected to an experimental investigation in connection with S. V. Anichkov's hypothesis concerning the presence of vasodilative and spasmolytic properties in different heterocyclic compounds bound with the benzyl radical. D. S. Paskov, who tested the preparation, dis-covered experimentally its hypotensive and spasmolytic properties and transferred a further study of the preparation to the clinic.

Effect of Proserine, Eserine, and Dibazol on the
Central Nervous System

The effect of proserine, eserine, and dibazol on the central nerv-ous system was investigated both in experiments on different laboratory animals and in a subsequent study of these substances in healthy per-sons in the clinic.

M. Ya. Mikhel'son, Ye. K. Rozhkova, and N. V. Savateyev (1954) observed the action of proserine on conditioned reflexes of dogs in whom food-initiated conditioned motor reflexes were developed by the method of free selection of feed. It turned out that proserine in a dose of 0.03 mg/kg as an intravenous injection did not have any effect on conditioned reflex activity of the animals. At the same time it was found that by using this previously nonactivating dose of proserine

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* Approval of the drug was carried out in the clinics directed by A. V. Triumov, G. D. Aronovich, and N. A. Kryshova. During this period considerable work was done at the G. I. Turner Leningrad Insti-tute.

in conditioned reflex disorders caused by pre-injection of atropine it was possible to achieve complete or partial restoration of reflexes (Table 1).

N. V. Sateyev (1953), while studying food conditioned motor reflexes in rats, established that proserine in a dose of 0.05 mg/kg had no noticeable effect on higher nervous activity of animals. The action of these and even smaller doses of proserine on higher nervous activity of rats was revealed in the case where a preliminary injection of atropine caused a disorder of conditioned reflexes in animals. These experiments were set up by M. N. Linyuchev and N. V. Savatev (1954) on white rats in which the ability to find the shortest exit from Khotin's labyrinth was developed. An hour after a subcutaneous injection of atropine in a dose of 5 mg/kg, the time the rats remained in the labyrinth was extended, the animals frequently made errors (went down dead-ends), and sometimes didn't find the exit at all. If proserine in a dose of 0.01-0.05 mg/kg is injected subcutaneously at the same time with atropine, these disorders of the higher nervous system in animals did not occur.

The already noted work of M. Ya. Mikhel'son, Ye. K. Rozhkova, and N. V. Savateyev also reported on the antagonism of pentaphen (a substance of antimuscarinic action) and proserine when studying their action on human higher nervous activity. After a subcutaneous injection of pentaphen or its ingestion a number of phenomena are developed which, reaching its maximum in about 40-45 min, are expressed in inarticulate speech, in the inability to answer simple questions, to recall a number of words and figures, to do simple addition, to read a text. Sometimes visual hallucinations occurred. At the same time disorders of walking are observed. Proserine in a dose of 0.02 mg/kg,

which does not usually render a noticeable effect on a healthy person, removed these disorders.

Therefore, proserine doses under ordinary circumstances inadequate for rendering a noticeable effect on higher nervous activity, demonstrated a distinct therapeutic action in disorders affiliated with impairment of acetylcholine transmission of a nerve impulse which arose as a result of using cholinolytic antimuscarinic agents--atropine and pentaphen.

According to the data of Bradley and Elkes (1953), a 0.5-1 mg/kg injection of eserine in cats, in which the electrical activity of various regions of the cerebral cortex was studied by implanted electrodes, induced the appearance of persistant low-amplitude waves. An eserine injection causing characteristic changes of the electrical activity of the brain had no effect on the over-all behavior of the animals. Proserine also had no noticeable effect on the brain electrical activity.

The effect of dibazol on conditioned reflexes of dogs was studied by Ts. Ordzhnikidze (1953). It was shown that with a daily injection of 5 mg of dibazol for 6-12 days, hypnotic phases disappeared in one of the animals by the second day of the experiment, and the disordered relation between the strength of the conditioned reflex stimulus and the magnitude of the response was restored. An abatement of hypnotic phenomena was noted in the second dog. After increasing the dibazol dose to 10 mg per day, differential disinhibition was noted in all three dogs, whereby in two of them there simultaneously occurred a considerable increase of positive conditioned reflexes.

In the second series of experiments the action of dibazol administered to animals for 20-25 days in larger doses, 100-200 mg, was determined. It turned out that a multi-day administration of the

TABLE 1

Effect of Proserine, Atropine, and Combination of These Substances on Conditioned Reflexes of the Dog Zor'ka

(Table Compiled from the Data Cited in the Study of M. Ya. Mikhel'son, Ye. K. Rozhkova, and N. V. Savateyev, 1954)

Date (1953)	Preparation and dose in mg/kg	Conditioned stimulus	No. of combination	Time of experiment	Conditioned food motor response — Latent period (in sec)	Conditioned food motor response — Correctness of seeking of feed trough	Comments
26/II		Metronome	105	10 hr 51 min	1	++++	Ate well
		Buzzer	43	10.56	1	+	. . . . .
		Metronome	106	11.02	1	+	. . . . .
		Metronome	107	11.07	2	+	. . . . .
		Buzzer	14	11.13	2	+	. . . . .
27/II	Atropine 0.17	Metronome	108	12.27	4	+	Didn't Eat
		Buzzer	15	12.17	Didn't approach trough		. . .
				12.55	same		. . .
21/IV	Proserine 0,03	Metronome	109	13.00	1	++++	Ate well
		Buzzer	46	13.05	2	+++	. . . .
		Metronome	110	13.10	1	+	. . . .
		Metronome	162	12.50		+++++	
		Buzzer	163	13.10			
		Metronome	80	13.15			
		Buzzer	164	13.20			
		Metronome	81	13.25			
24/IV	Atropine 0,17 } Proserine 0,03	Metronome	168	10.15	2	++	Didn't Eat
		Buzzer	84	10.35	1	++++	. . . .
		Metronome	169	10.40	2	+++	. . . .
		Buzzer	85	10.45	Didn't approach trough		
		Metronome	170	10.55			

preparation in these doses leads to suppression of conditioned reflex activity, which passes without a trace 2 days after administration of the drug stops.

M. K. Mikushkin and M. A. Rozin (1955) in experiments on 3 dogs observed the effect of dibazol in a dose of 10 mg with its single injection a half an hour before studying conditioned reflexes. A certain suppression of positive conditioned reflexes was noted on the day of administering the preparation; on the following day these disorders were not detected. Neither on the day of administration nor on the following day was it possible to establish any disorders of differential responses. Here we note the following fact: after injection of dibazol it became impossible to cause in the experimental animals a protective inhibition by the action of a strong sound stimulus. This unique phenomenon took place not just on the day of administration but also during the next two days; even 8 days after a single administration of dibazol, a protective inhibition was expressed very weakly.

The effect of dibazol on human higher nervous activity was specially investigated by Ye. Ye. Belenkiy (1952). It is known that the type of food or setting in which the person eats causes in the latter a conditioned reflex food reaction along with other reactions. Ye. Ye. Belenskiy established that the per cent of leukocytes at the moment of this reaction increases to 122 (with 100% taken as the number of leukocytes in the same persons on an empty stomach).

After administration of 0.005 g of dibazol, the per cent of leukocytes in the peripheral blood during the conditioned reflex food reaction increased to 142. An analysis of this action of dibazol showed the ability of the preparation to weaken the inhibitory process in the cerebral cortices. Thus, after administration of sodium bromide (0.6 g), which enhances the inhibitory process, the magnitude

of the conditioned reflex food leukocytic reaction is practically the same (121%); with the simultaneous administration of 0.005 g dibazol and 0.06 g sodium bromide, the stimulating effect of dibazol was, as a whole, removed (increase in the number of leukocytes to 115%).

P. T. Volkov and P. O. Makarov (1952), using the method of adequate optical chronaxy, noted that after administration of dibazol in doses of 0.005-0.01 g, chronaxy decreased for 3 and more hours in the persons they investigated. The decrease of the rheobase was less constant. On the basis of their observations the authors concluded that small doses of dibazol increase excitability of the cortical division of the visual analyzer.

Therefore the ability of the preparation to weaken the inhibitory process in the cerebral cortex was established by determining the effect of dibazol on higher nervous activity. It is possible that the simultaneous increase of excitability of the cerebral cortex, which was noted by the authors, is a consequence of this disinhibiting effect.

A sharp increase in the dibazol dose led to suppression to conditioned reflex activity of dogs. The depressing action of large doses of the preparation on higher divisions of the central nervous system is markedly shown in the experiments of M. A. Rozin (1949), who studied the action of dibazol on motor activity of white mice by means of a special instrument, an actometer.*

Dibazol was studied in doses of 125, 25, and 5 mg/kg of weight. It turned out that the preparation in these doses demonstrates a distinct depressing action on motor activity of mice; in a dose of 5 mg/kg

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* The instrument is a small spring-suspended cage in which the mouse is placed during the experiment. Any movement of the mouse in the cage is recorded by a special counter.

it caused in some experiments a noticeable suppression of motor activity, and in others, undoubtedly excited it.

Special experiments determined the action of dibazol in combination with caffeine which, as is known from the data of a number of authors (Triendl, 1939; D. K. Chervyakov, 1940; Scott, R. Andersen and Chen, 1946; M. A. Rozin, 1949; et al.), considerably enhances motor activity of white mice. It was shown that dibazol in a dose of 5 mg/kg did not in itself have a permanent effect on motor activity; together with caffeine it weakened the stimulating effect of the latter, especially during the first hour of the experiment. In a dose of 1 mg/kg dibazol did not change the action of caffeine. The results of these experiments are shown in Table 2.

On the basis of these data concerning the effect of dibazol on the higher divisions of the central nervous system, we can conclude that two unequal effects dependent on the dose are identified in the action of the preparation.

When using small doses of the preparation, a weakening of the in-process (first phase of action) is noted, however with an increase of dose a simultaneous weakening and excitory process (second phase of action) apparently begins. The conclusion of the existence and special characteristics of the second phase of action follows not only from the data on the weakening of positive conditioned reflex reactions by large doses of dibazol and their suppression of animal motor activity, but also from the fact that the preparation weakens the effect of caffeine which enhances the excitation process in the cerebral cortex. The fact that dibazol can weaken the excitation process in higher divisions of the central nervous system is indicated by the experiments of Yu. D. Zil'ber (1953), who found that this preparation in a dose of 10 and 100 mg/kg inhibits the development of corazol convulsions in frogs.

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TABLE 2

Effect of Dibasol, Caffeine, and a Combination of these Substances on Motor Activity of White Mice

Name of substance	Dose in mg/kg	Mean magnitude of motor activity at different intervals (in min) after administration.									$\frac{A}{B}$
		30	60	90	120	150	180	210	240		
Dibasol	125	56	10	1	9	16	6	2	11	A	
Physiological solution		71	-10	19	27	36	19	8	5	B	0,54
Dibazol	25	18	8	3	2	8	2	7	8	A	
Physiological solution		57	22	0	0	1	1	0	6	B	0,66
Dibasol	5	107	48	29	15	24	26	25	19	A	
Physiological solution		95	44	13	29	20	11	23	26	B	1,12
Caffeine	125	304	266	266	216	177	160	176	147	A	
Physiological solution		81	47	32	28	50	28	10	8	B	6,04
Caffeine Dibazol	125 5	82	128	141	118	96	94	98	76	A	
Physiological solution		114	48	15	35	23	12	27	31	B	2,72
Caffeine Dibasol	125 1	110	62	43	37	38	27	24	12	A	
Physiological solution		31	5	5	1	1	7	6	4	B	5,9

Comment. Each graph of the table shows results obtained in tests of the indicated substance or in corresponding control experiments. The conditions of the experiment were the same in all cases, but in different mice the nature of the motor activity was different. This is evident on comparing the data shown in the table for individual series of control experiments. The magnitude of motor activity is expressed in hypothetical units of the readings of the actometer counter. The physiological solution was always administered in an amount of 0.25 ml.

It is known that the summation of subliminal impulses, which are needed to evoke an unconditioned reflex of an animal, occurs mainly in the centers of the interbrain and midbrain (V. V. Zakusov, 1948, 1953).

The action of eserine, proserine, and dibazol on the summation of subliminal impulses in white mice was studied by M. A. Rozin (1954). The experiments were as follows: Electrodes wrapped with wet gauze were installed on both hind extremities of a mouse, held by the experimenter's hand in a vertical position. Electrical impulses at a frequency of 120 per minute were fed to the electrodes. A count of the

impulses causing withdrawal of one of the paws was made. An intra-
peritoneal injection of proserine (0.05 mg/kg), eserine (0.05 mg/kg),
and dibazol (10 mg/kg) did not cause any shifts in the summation of
impulses in the mice.

O. D. Kozlov (1952), while studying the effect of dibazol on se-
cretory activity of the isolated loop of dog intestine established that
the preparation, by exciting the appropriate centers of the stem por-
tion of the brain, causes hypersecretion. The same author established
the direct exciting action of dibazol on the respiratory center.

When determining the effect of proserine and eserine on the reflex
activity of the spinal cord it was revealed that the changes of the re-
flex activity of the animals which were observed in the experiment de-
pend on a number of factors, mainly on the dose of the drug, the method
of its administration, and on the characteristics of the reflex being
recorded. Therefore it is convenient to begin an account of the ex-
perimental material with the data of V. V. Zakusov and A. V. Valdman,
who for a number of years studied the effect of proserine and eserine
on various reflex reactions. The experiments of these authors were
set up on rabbits; injection of the substances was always done intra-
venously, and in all cases one and the same index was recorded--the
latent period of the reflexes (V. V. Zakusov, 1948, 1953; A. V. Valdman,
1950, 1952).

The phenomena found by these authors can be defined as follows:
proserine and eserine in small doses excite, and in large doses depress
reflex activity (Table 3).

The data in Table 3 show that in order to constrict the influence
of proserine or eserine on reflexes it is not sufficient to use any one
dose of the substance.

TABLE 3

Effect of Eserine and Proserine on the Latent Period of
Ipsilateral Flexor and Crossed Extensor Reflexes
(A. V. Valdman, 1952)

Substance	Doses in mg/kg, causing			
	decrease of	increase of	decrease of	increase of
	latent period of ipsilateral flexor reflex		latent period of crossed extensor reflex	
Eserine	0.02	0.1	0.02	0.04
Proserine . .	0.01	0.02	0.005	0.01

A. V. Valdman obtained data in experiments where both reflexes
were caused by stimulation of one and the same receptor field, i.e.,
the afferent part of both reflex arcs was common; consequently, dif-
ferences in the nature of the observed reactions occurred during trans-
fer of the impulse from the afferent to the efferent portion of the
arc and in the efferent portion itself. It is known that when deter-
mining the action of proserine and eserine on the activity of the spinal
cord, the pathway along which excitation is transmitted to the motor
cells of the cord is of importance. A. V. Valdman induced flexor move-
ments of the hind extremity of rabbits by stimulating either the appro-
priate afferent nerves or the pyramidal tracts.

A. V. Valdman, determining the dose of proserine and eserine in-
ducing complete suppression of motor reactions, established that for
suppression of reflexes stimulated by an afferent nerve the doses are
considerably smaller than for suppression of reactions evoked by stim-
ulating the pyramidal tracts.

Among the numerous investigations of the action of proserine and
eserine on spinal reflexes, the work of Bulbring and Burn (1941) is
especially distinguished. The authors set up experiments on a dog
with an artificial, separate, isolated blood supply of the spinal cord

and hind extremity (the muscles and nerves were separated for recording the reflexes). By this method a direct action of the preparation on the spinal centers is attained by injecting the substance into the arteries supplying the spinal cord. This precludes the possibility of an effect on the peripheral apparatus of the reflex arc, since the investigated extremity had an independent blood supply. It was established that proserine and eserine in small doses enhanced, and in large doses suppressed the flexor reflex.

Data of other authors who studied the action of proserine and eserine on the flexor reflex depend on the doses they used. Small doses caused only stimulation of reflexes, and their suppression ensued with injection of large doses. Investigators who studied the action of proserine and eserine in various doses observed the exciting action of eserine and the depressing action of proserine. This is understandable if we take into account (see Table 3) that proserine begins to demonstrate a depressing action on the flexor reflex at considerably smaller doses than eserine (Lefevre and Minz, 1936; Schweitzer and Wright, 1940; McKail, Obrador, and Wilson, 1941; G. N. Sorokhtin and F. Ye. Pozdnyakov, 1948; D. Taverner, 1954).

The data on the effect of eserine and proserine on the knee-jerk reflex are contradictory. Bulbring and Burn in experiments on dogs injected eserine and proserine into the isolated blood-supply system of the cord and observed a depressing action of both substances. Merlis and Lawson, having injected an eserine solution into the subarachnoid space of dogs noted either suppression, or enhancement of the reflex. Schweitzer and Wright, in experiments on cats with an intravenous injection of eserine, most often observed an enhancement of the reflex, and its depression with an injection of proserine. Calma and Wright (1944, 1947) noted an increase of the knee-jerk reflex in cats that

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received eserine either intravenously or in the subarachnoid space.
In experiments on rabbits, A. V. Valdman (1952) found that with an
intravenous injection of proserine and eserine, both preparations en-
hance the knee-jerk reflex, and that this action could be observed even
when injected in doses dangerous to the life of the animal.

We can assume that the divergence of the data on the effect of
proserine and eserine on the knee-jerk reflex is because the experiments
were set up with different species of laboratory animals, using dif-
ferent ways to administer the substances.

The action of dibazol on spinal reflexes was studied in experiments
on decerebrated cats (M. A. Rozin, 1949, 1951). It turned out that an
intravenous injection of the preparation enhances the flexor reflex
(Fig. 1).

On multiple injection of small doses of the preparation, and some-
times after a large dose, depression of the reflexes follows a short
period of stimulation; this depression can be eliminated by an intra-
venous injection of a sodium bromide solution. S. M. Vishnyakov (1955)
under the same experimental conditions noted that an injection of diba-
zol can stimulate the reflex activity of extensors. O. D. Kozlov
(1952), while determining the latent period of the flexor reflex, noted
that the latent period of the reflex is lengthened after a shortening
period as a result of the preparation.

Ye. I. Lyublina (1949), using the method she developed to deter-
mine the action of drugs on the knee-jerk reflex in man, established
that the injection of dibazol causes a distinct stimulation of this
reflex.

The irritability of the spinal cord can be lowered by injection of
large doses of dibazol; this is indicated not only by the fact of sup-
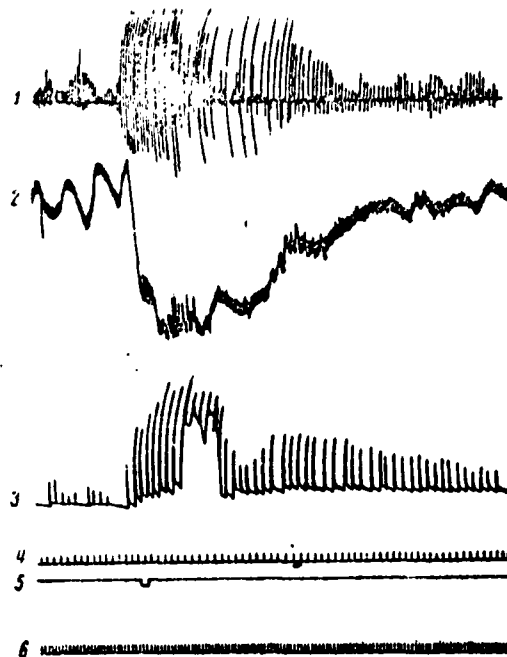pression of the flexor reflex. In 1953 Yu. D. Zil'ber noted also that

Fig. 1. Effect of dibazol on re-
flex activity, blood pressure, and
respiration of decerebrated cat.
1) recording of respiration; 2)
blood pressure recording in the
common carotid artery; 3) registra-
tion of the reflex contraction of
the semitendinosus muscle in response
to electrical stimulation of the
tibial nerve; 4) marking of the elec-
trical stimulations of the nerve;
5) marking of intravenous injection
of dibazol solution; 6) time markings.

in large doses the preparation inhibits the advent of strychnine con-
vulsions in frogs whereas in small doses it has the opposite effect.
The effect of proserine when administered in comparatively large doses
on the course of strychnine convulsions is expressed by their suppres-
sion (Schweitzer and Wright, 1937; G. N. Sorokhtin and M. S. Reyzen).

A comparison of the experimental data permits us to note certain
differences in the action of dibazol and proserine. For example, the
effect of dibazol on higher nervous activity was expressed in weakening
of the inhibitory process; proserine did not have the same effect.

Differences between proserine and eserine were noted relative to their effect on the electrical activity of cat brains.

There are especially great differences between these substances when administered in large doses: eserine enhances and proserine weakens strychnine convulsions; in toxic doses eserine, as is known, causes convulsions, and proserine produces a state resembling narcosis (M. Ya. Mikhel'son, 1948; G. N. Sorokhtin, 1950).

It is assumed that the differences in the action of proserine and eserine depend on the particular features of the physicochemical properties of these substances. In particular we have in mind data that eserine is dissolved well in lipoids, whereas proserine does not possess such property (Schweitzer, Stedmen, and Wright, 1939); therefore eserine affects only extracellular formations, particularly the synapse.

The hypotheses that differences in action of pharmacologically similar drugs can depend on the characteristics of their physicochemical properties now appear to be completely probable, and in certain cases proved experimentally (N. V. Lazarev, 1944). For instance, Ye. I. Lyublina (1955) showed that, evident differences in pharmacological action of narcotics are in accord with the characteristics of the physicochemical properties of these substances.

Other Types of Action of Proserine, Eserine, and Dibazol as
Possible Sources of Side-Effects Occurring in Treatment of
Diseases of the Nervous System

In addition to the effect on nervous system activity, proserine, eserine, and dibazol directly or indirectly change the functional state of many organs and systems. This action, sometimes being of independent interest and applicable for particular therapeutic purposes, is a side-effect in the treatment of neuropathy.

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When anticholinesterases are administered to an organism, a number of developments occurs that are affiliated with the action of these substances on the cholinergic structure of the parasympathetic nervous system. The tonus of the smooth musculature of internal organs is increased: esophagus, stomach, gut, bronchi, spleen, urinary bladder, ureter, uterus, etc. An abrupt enhancement of the secretion of various organs occurs: sweat, glands of the G.I. tract, bronchial, and the activity of endocrine glands, particularly of the adrenal cortex is increased. These phenomena, to some extent already expressed when therapeutic doses of anticholinesterases are administered, increase with the dose.* The occurrence of these side-effects is eliminated by administration of atropine.

The effect of a anticholinesterases on the work of the heart, vascular tonus, and blood pressure is very complex. Along with acetylcholine accumulating at the terminals of parasympathetic nerves, adrenalin, which is liberally released by the adrenal cortices, goes into action. While the former causes dilation of the peripheral vessels, weakening of cardiac contractions, a decrease of their rhythm and, as a result, a fall of blood pressure, the latter has the opposite effect. Under the effect of eserine the activity of adrenalin sometimes predominates and a slight increase of blood pressure is developed; with the use of proserine, the effect of acetylcholine, demonstrated by a drop of blood pressure, is frequently more expressed.

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* The properties of the indicated preparations to render a parasympathetic effect is sometimes used for therapeutic purposes. For example, in surgery clinics postoperative atonia of the gut and bladder can be removed by the use of acetylcholinesterases. On the suggestion of M. Ya. Mikhel'son (1952), proserine is used in obstetrics to eliminate inertia uteri.

The action of anticholinesterases on the eyes, which is especially evident on injection of solutions of the substances into the conjunctival sac, is expressed by stenocoriasis, decrease of intra-ocular pressure, and spasm of accommodation. These changes can be eliminated with atropine.

Under the action of toxic doses of these substances, all the named disorders acquire a sharply expressed character. Convulsions can occur simultaneously with eserine poisoning, and a sharp suppression of the CNS with proserine poisoning. In this case, combinations of two or several cholinolytic agents can be used for therapeutic purposes. This combination should include one antimuscarinic preparation and one anti-nicotinic preparation. Having blocked by means of these substances both the M- and the N-cholinoreaction systems of the organism, it is possible to stop the toxic action of acetylcholine which accumulated in cholinergic structures as a consequence of the inhibition of cholinesterase.

Dibazol has a definite effect on the musculature of smooth-muscle organs; it is demonstrated in relaxation of the muscles of the G.I. tract, bronchi, and in dilation of the vessel lumens (D. S. Paskov, 1948). In experiments on excised human heart (the heart was excised 1 $^1/_2$ - 2 hrs after death and perfused by Anitschkoff-Krawkoff's method), dibazol in concentrations close to therapeutic cause dilation of the lumens of the coronary vessels, and in experiments on isolated heart heart of frog, dibazol in similar concentrations reduces the force of the cardiac contractions and slows their rhythm. The effect of dibazol on the cardiovascular system is expressed by a drop of blood pressure. The hypotensive action of dibazol was confirmed in experiments on animals with experimentally induced hypertonia (A. I. Mokhnacheva, 1950; A. A. Belous, 1954). These properties of the preparation permitted

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us to propose it as a spasmolytic agent (to eliminate spasms of the vessels, musculature of the stomach, gut, etc.), and also for the treatment of hypertension (N. N. Savitskiy, 1953; V. I. Kuznetsov, 1953; Ye. N. Pavlova, O. N. Liberman, and S. V. Petrov, 1953; N. A. Tolubeyeva and S. A. Tseytlin, 1953).

In experiments on isolated cornu uteri of the rat, D. S. Paskov found that dibazol relaxes the musculature of the isolated uterus. However, Ye. A. Vyaz'menskaya (1952) later established that the injection of dibazol in cats, especially gravid cats, increased the uterine tonus and its rhythmical contractions. The same author then showed that dibazol can be used in inertia uteri in obstetric clinics.

These phenomena begin to arise at doses exceeding those prescribed for treatment of diseases of the nervous system. On a sharp increase of the dibazol dose, the blood pressure can drop and the patient experiences dizziness and nausea. These side-effects (quite short-lived) pass if the patient is put to bed.

Dibazol in large doses causes convulsions in experimental animals.[*] It is necessary to note however that therapeutic or convulsive doses of the preparation differ from each other. For example, the minimum dibazol dose causing convulsions in white mice is 100 mg/kg, and a therapeutic effect in experimental damage of the nervous system in the same animals is at a dose of 0.1 mg/kg, which approximately corresponds to the dose used in the treatment of diseases of the nervous system in the clinic (M. A. Rozin, 1949). When convulsions occur as a result of dibazol overdosing, the usual narcotics and anticonvulsive agents should be administered. Extreme overdosing is improbable in practice.

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[*] The convulsive action of the preparation was observed in experiments of cats, rabbits, and white mice. Dibazol does not cause convulsions in frogs; a narcotic state is developed on injection of large doses of dibazol (A. P. Sandovich, 1955).

CHAPTER III

EFFECT OF PROSERINE, ESSERINE, AND DIBAZOL ON THE INHIBITORY PROCESS

As early as 1903, N. S. Semenov established that parabiotic inhibition occurs in a nerve when it is mechanically compressed. Later this problem was the subject of many investigations (a summary of this problem is cited by D. G. Kvasov, 1948). In 1948 the works of O. P. Minut-Sorokhtina and G. N. Sorokhtin appeared which gave the results of experiments on the action of eserine and proserine on isolated nerve with their direct application and on the effect of eserine on a nerve altered by mechanical compression.*

The experiments were set up on a nerve-muscle preparation (gastrocnemius muscle--sciatic nerve). The nerve was compressed by a special device, as a result of which irritability and conductivity of the nerve at first was lowered and then completely disrupted. The application of an eserine solution to the area of the compressed nerve led to a temporary restoration of irritability and conductivity.

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* When examining data on the effect of any factors on altered isolated nerve it is necessary to take into account that, with an intact organism the parabiotic state of a damaged nerve has a number of special characteristics (M. P. Berezina, 1947, etc.).

Ye. Ye. Belenkiy (1951), who experimented on a nerve-muscle prep-
aration of frog (gastrocnemius muscle--sciatic nerve), disrupted con-
ductivity of a nerve area by applying Dieffenbach's arterial clamp.
Several minutes after clamping, electrodes placed close to the muscle
at the damaged place were able to cause tetanic contractions of the
muscle in response to a 15-second stimulation by an electric current;
at the same time the same stimulation of the nerve area lying beyond
the damaged place did not cause muscular contractions. Immersion of
the damaged nerve area into a dibazol solution after removal of the
clamp restored the conductivity of the nerve, which was again disrupted
after taking the damaged nerve from the dibazol solution and placing
it in an isotonic saline solution. Dibazol has an effect in very
great dilutions. For instance, a distinct effect was obtained when
the solution was used in a dilution of 1 : 10,000,000 (Fig. 8). Immer-
sion of the damaged nerve section in a dibazol solution when the clamp
was still on the nerve was not generally accompanied by restoration of
conductivity.

In 1863 I. M. Sechenov found that on stimulation of certain divi-
sions of frog brain, especially a brain section made along the line of
the thalami optici, an abrupt suppression of reflex activity occurs.
The latter is determined by the time from the instant of immersion of
the hind foot into acid to the instant of its reflex withdrawal. "Stim-
ulation with fused salt of a cross section of the thalami optici pro-
duces a severe suppression of the reflexes, whereby in an animal at
complete rest it is earlier than movements and convulsions caused by
this stimulation" (I. M. Sechenov, 1863). A further study of this
phenomenon, made at first by I. M. Sechenov himself, then by him and
V. V. Pashutin, and finally by V. V. Pashutin alone (1865) and by many
other Russian and foreign authors, showed that it is possible to suppress

reflexes not just by applying a salt crystal to the brain section, but also by stimulating the section with an electric current, with certain substances, and even with frog blood. This phenomenon of inhibition, first discovered in the CNS, was named Sechenov inhibition.
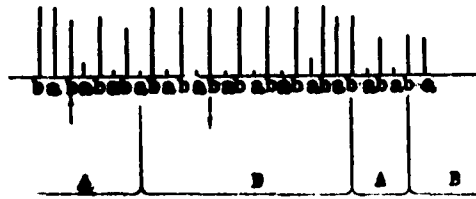

Fig. 8. Effect of dibazol on the conductivity of a nerve disrupted by mechanical compression (experiment on a nerve-muscle preparation, sciatic nerve--gastrocnemius muscle) (after Ye. Ye. Belenkiy, 1951). The vertical lines denote the height of muscular contraction on electrical stimulation of the area located above (a) and below (b) where the clamp is applied. The upward pointing arrow indicates the instant of applying the clamp on the nerve; the downward pointing arrow indicates the instant of removing the clamp. A) is the period the damaged area of the nerve was in an isotonic saline solution; B) the period the damaged area was in a dibazol solution (dilution 1 : 10,000,000).

A detailed study of the mechanism of Sechenov inhibition showed that it is accomplished by impulses sent to the spinal cord from the stimulated area of the central nervous system along two pathways: along the cerebrospinal and along the sympathetic pathways (A. V. Tonkikh, 1927, 1930; B. D. Stefantsev, 1939; P. A. Kiselev, 1948, 1950; V. V. Zakusov, 1948; V. A. Cherkes, 1954). Individual features of Sechenov inhibition were studied by A. M. Magnitskiy (1933, 1938),

G. A. Levitna (1948, 1953), S. A. Palatnik (1938), S. Ye. Rudashevskiy and F. T. Nekrylov (1952), and others.

At various times individual authors have attempted to test the action of a number of drugs on Sechenov inhibition (F. Matkevich, 1864; V. V. Zakusov, 1945, 1948; V. M. Chernov and N. A. Kudryavina, 1947). Here it was found that only ethanol in very large doses (F. Matkevich) and morphine (V. V. Zakusov) cause substantial weakening of the inhibition.

The action of proserine on the course of Sechenov inhibition was first described by L. B. Perel'man (1946) and later by L. B. Perel'man, N. V. Rayeva, and R. A. Stavitskaya (1949). The reflex activity of frogs was determined by the latent period of reflex on immersion of the hind foot into an acid solution. Sechenov inhibition was at first evoked and then, upon restoration of the reflexes, 1 ml of a 1 : 200,000 proserine solution was injected into the dorsal lymph sac, and after a certain time an attempt was again made to evoke inhibition. As a rule it was not successful: the injection of proserine prevented the occurrence of Sechenov inhibition.

A. A. Zubkov (1940), after sectioning the brain at the level necessary to cause Sechenov inhibition and after removing the overlying brain divisions, injected one drop of eserine solution, 1 : 10,000 or 1 : 30,000, into the spinal canal. As the solution descended along the spinal canal the effect of the solution began to be demonstrated by a lengthening of the time of the latent period of the reflex induced by electrical stimulation of one of the hind legs. The attempt to cause Sechenov inhibition at this period of the experiment led to a shortening of the latent period of reflex. The data of L. B. Perel'man and A. A. Zubkov was later confirmed by M. A. Rozin (1953), who found that

30 min after injecting doses of 0.05-0.1 mg/kg of proserine and eserine
solutions into the ventral lymph sac of frogs, Sechenov inhibition
could not be evoked in a considerable proportion of the experiments.
It is important to note that in these experiments, proserine and
eserine were injected in doses insufficient to change the reflex activ-
ity of frogs.

The action of dibazol on Sechenov inhibition was studied by Ye. Ye.
Belenkiy (1951), who found that 30 min after injecting dibazol in a
dose of 10 mg/kg into the ventral lymph sac, Sechenov inhibition was
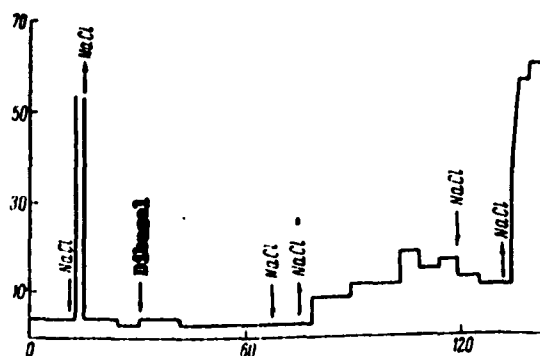not induced in most of the experimental animals (Fig. 9).

Fig. 9. Effect of dibazol on
Sechenov inhibition (Ye. Ye.
Belenkiy, 1951). Along the vert-
ical axis is the latent period of
flexor reflex of frogs in seconds.
Along the horizontal axis is the
time of the experiment in minutes.
↓ NaCl is the moment of applying
a crystal of fused salt on a sec-
tion of the thalami optic, ↑ NaCl
is the moment of removing the crys-
tal, ↓ dibazol is the moment of in-
jecting the preparation in a dose
of 10 mg/kg under the skin of the
animal.

As Ye. Ye. Belenkiy later showed, this effect is manifested when
the most diverse doses of dibazol are used. Testing of 0.0001, 0.001,
0.01, 0.1, 1.0, 10, and 100 mg/kg, he found all doses except the

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smallest and the largest retard inhibition; the greatest effect was with a dose of 1 mg/kg. This fact, as well as the removal of Sechenov inhibition by dibazol, was later confirmed by a number of authors (A. Ye. Uglov, 1953; S. M. Vishnyakov, 1955; etc.).

We already mentioned above, experiments in which disruption of reflex activity of both an uninjured and injured frog leg was caused by the passage of a strong electrical current. An analysis of the nature of the observed disorders of the reflex activity showed that, as a result of the trauma persistant inhibition occurs in the frog spinal cord which apparently determines the impairment of reflex activity in the uninjured leg. The presence of such inhibition was indicated by an experiment in which the latent period of the flexor reflex of the hind leg when immersed in a sulfuric acid solution of two concentrations (0.5 and 0.1%) was measured to determine the reflex activity of the animals. The first solution could be considered as a strong stimulus and the second as a weak stiumlus. After inflicting the damage it was possible to detect compensating and paradoxical reactions. The injection of dibazol restored the normal relation between the reactions to strong and weak stimuli, i.e., eliminated the signs of the inhibitory process (M. A. Pozin, 1952) (Table 5).

In a number of experiments the effect of proserine, eserine, and dibazol was determined on animals which had received a strong painful stimulus that caused suppression of impulse summation. The experiments were set up on mice (M. A. Rozin, 1954) and the number of subliminal impulses inducing withdrawal of one of the hind extremities was determined. Determinations of the impulse summation were made at three minute intervals; solutions of the test substances were injected intraperitoneally and the painful stimulation was caused by applying a strong clamp on the right ear of the mouse for two minutes.

TABLE 5

Change of the Latent Period of the Flexor Reflex of Undamaged
Leg of Frogs which Experienced Electric Trauma of the Symmetrical
Hind Leg Under the Effect of Dibazol

Time of observation	Frog № 19		Frog № 24	
	Latent period of flexor reflex in sec under the effect of 0.5 or 0.1% sulfuric acid solutions			
	0.5	0.1	0.5	0.1
Before damage	4	12	2	15
24 hr after damage	13	9	2,5	2
72 hr after damage	7	10	5	6

Both frogs injected with 10 mg/kg of dibazol

6 hr after damage	4	13	2	10

TABLE 6

Effect of Proserine, Eserine, and Dibazol on the Summation of Impulses in Mice Upon Application of a Painful Stimulus (average number of impulses before application of clamp is taken as unity)

Substance	Dose, mg/kg	Number of impulses causing motor reaction of mouse (in hypothetical units)	
		before painful stimulus	after painful stimulus
Physiological solution	0.1 ml per 10 g	1,0	2.7
Eserine	0.05	1,0	0.97
Proserine	0.05	1,0	1,84
Dibazol	10,0	1,0	1,87

It is known that suppression of impulse summation arising after application of a strong painful stimulus is the consequence of the process of inhibition developing in certain centers of the diencephalon and mesencephalon (V. V. Zakusov, 1948). The results of these experiments are shown in Table 6.

Of particular interest are the experiments of S. M. Vishnyakov (1954) who, by passing a strong electric current through one of the hind extremities of a rabbit, caused a sharp suppression of summation of the subliminal impulses addressed to the symmetrical hind extremity needed to evoke flexion of the latter. Before the painful stimulus,

flexion of the symmetrical hind extremity was evoked by applying a stimulus through needle electrodes (5-13 electrical impulses) implanted under the skin of the shin; after application of the painful stimulus for 50-60 minutes, contraction of this extremity could not be evoked by a 100 and more electrical impulses. An intravenous injection of dibazol in a dose of 10 mg/kg several minutes after this state led to renewal of the summation ability of the central nervous system.
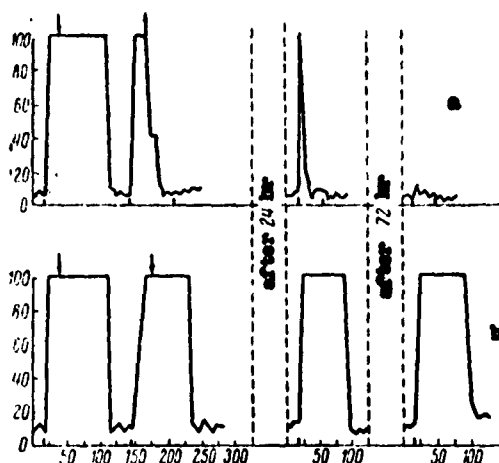

Fig. 10. Effect of dibazol on suppression of impulse summation induced in rabbits by applying a strong painful stimulus (S. M. Vishnyakov, 1954). a) Experiment with use of dibazol; b) result of control experiment. Along the vertical axis is the number of subliminal impulses causing the flexor reflex, and along the horizontal axis is the time of the experiment in minutes. The downward pointing arrow is the moment of the intravenous injection of a physiological solution; the upward pointing arrow is the moment of the intravenous injection of dibazol in a dose of 10 mg/kg.

S. M. Vishnyakov established another fact in these same experiments: repeated attempts to cause new suppression of the summation of impulses by an additional application of a painful stimulus, always successful

in control experiments, were either generally unsuccessful after injection of dibazol or caused a slight and brief suppression of the summation of impulses (Fig. 10).

V. V. Zakusov (1948) reported on the experiments of Bauman (1946) in which it was found that eserine in doses of 0.005-0.1 mg/kg attenuates inhibition of the central nervous system induced in rabbits by strong stimulation of afferent nerves. In doses of 0.1-0.2 mg/kg, eserine enhanced this inhibition.

The data on the effect of proserine, eserine, and dibazol on the course of spinal shock in animals deserves special attention.

It is known that after separation of the brain from the spinal cord, a temporary suppression of the activity of the spinal cord develops; Marshall Hall in 1850 defined this condition by the term shock. It was later learned that shock arises on sectioning the spinal cord at different levels and this phenomenon itself received the more accurate name of spinal shock.

An attempt to explain the mechanism of spinal shock led to setting up a series of special experiments. Goltz hypothesized that underlying this phenomenon is the inhibition of the spinal centers, occurring as a consequence of sectioning the spinal cord. Sherrington countered this theory. On the basis of considerable experimental material, he and his followers established that in animals, especially in higher mammals, "...spinal shock is not founded on stimulation resulting from trauma and moreover is not in the main a phenomenon of inhibition. The phenomenon of shock is apparently based on sectioning some descending conducting pathways" (Sherrington, 1906, 1935). The higher the degree of development of the animal, the greater importance are the supraspinal impulses for activity of its spinal cord and the deeper the demonstration of shock.

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At the same time there are facts, appreciably reinforced in recent years, that do not fit into Sherrington's system on the nature of spinal shock. For example, in certain birds decapitation does not lead to the phenomenon of spinal shock (I. Tarkhanov, 1895); phenomena resembling spinal shock develop after sectioning the posterior columns of the spinal cord (single and repeated) although there are almost no efferent fibers in them (E. A. Asratyan, 1940, 1947; M. G. Durmish'yan, 1954); signs of an inhibitory state of the spinal centers could be detected during the period shock developed (D. A. Lapitskiy, 1948; V. N. Drozdova, 1948, 1950). New data compel us once again to analyze the phenomena of spinal shock and to attempt to reveal in its mechanism new links supplementing what is already known.

We must assume, for example, that the mechanism of spinal shock varies relative to the developmental level of the end-brain. In animals with a low development of the end-brain, for example in frogs, the phenomena of spinal shock are transient, but are again reproduced on resectioning of the cord at a lower level; suppression of the reflex activity of frogs, occurring after sectioning the spinal cord, is re-moved, like Sechenov's inhibition, by the application of an a-c anode on the spinal cord (D. A. Lapitskiy, 1948). Apparently inhibition of the spinal cord serves as a decisive factor in the phenomena of spinal shock in frogs. Spinal shock is demonstrated in a different way in animals with a more developed end-brain. In them, first and foremost appear the after-effects of the dissociation of the spinal cord and the overlying divisions of the central nervous system. However, there are grounds to assume that in the given case the phenomena of inhibition are associated with different kinds of disorders occurring as a result of sectioning the spinal cord.

A study of the effect of proserine, eserine, and dibazol on the course of spinal shock was started by G. N. Sorokhtin (1945). He investigated the effect of eserine on spinal shock of dogs. Eserine salicylate was injected subcutaneously in a dose of 0.2-0.3 mg/kg, 5-15 minutes before sectioning the spinal cord at the D_{VIII}-D_X level or 24 hours after the operation. It turned out that the injection of eserine, especially the preventive injection, removes the phenomena of shock; this is expressed in the preservation of the stretch reflex, support reflex, Philippson's reflex, crossed extensor reflex, extensor impulse, and muscle tone. Later, in experiments on cats, G. N. Sorokhtin and O. P. Minut-Sorokhtina (1948) observed the action of eserine injected in a dose of 0.6-0.8 mg, 5-10 min before transection of the spinal cord. In the control animals the blood pressure dropped to 45% of the preoperative level 60 minutes after sectioning the cord, and in animals which preliminarily received eserine the blood pressure dropped an average of 70% in comparison with the preoperative level. Stimulation of the central end of the peroneal nerve with an electric current led to a rise of blood pressure in the control animals by 6-10 mm Hg and in the animals that received eserine, by 10-20 mm.

The authors of these investigations when evaluating the obtained experimental data proceeded from the concepts of shock as the result of elimination of the supraspinal impulses. The deficit of these impulses (i.e., the deficit of acetylcholine by means of which these impulses are accomplished with the corresponding fibers of the descending pathways) led to a decrease of the working tone of the nerve centers of the spinal cord and to their "atony" (according to Sorokhtin's terminology). By using eserine, owing to its anticholinesterase action, it is possible to create an accumulation of acetylcholine at the terminations of other nerve fibers approaching the spinal centers, to

enhance the action proceeding from these conductors and, thus, not permit the occurrance of "atony" and prevent the development of spinal shock.

The action of dibazol was studied under conditions similar to those just described. M. A. Rozin (1949) caused spinal shock in cats by cutting the spinal cord at its boundary with the medulla oblongata (all divisions of the central nervous system lying above the section were removed; the cat was given artificial respiration). An intravenous injection of the substance in a dose of 20 mg/kg evoked a very slight and brief stimulation of the flexor reflex of the hind extremity.

A comparative assay of the action of proserine, eserine, and dibazol on the course of spinal shock was done in experiments on frogs (M. A. Rozin, 1954). Solutions of the investigated substances were injected into the thickness of thigh of one of the hind legs. The reflex activity of the frog was determined by the latent period of the reflex arising on submersion of the other hind leg in a 0.5% solution of sulfuric acid. Cutting of the spinal cord was done at the level of the fourth vertebra 30 min after injecting the substances. The results of these experiments are shown in Table 7.

There are data indicating that weakening of reciprocal inhibition of the spinal centers can occur under the effect of large doses of eserine (A. N. Kabanov, E. G. Kaplun, L. M. Metelnikova, 1947; E. G. Kaplun, 1950) and also of dibazol (S. M. Vishnyakov, 1955).

These facts indicate that proserine, eserine, and dibazol weaken the inhibitory process under diverse conditions of its occurrence in various divisions of the central nervous system. This action was demonstrated both when attempting to evoke inhibition during the effect of the preparations and in cases where the substances were injected against a background of a distinctly developed inhibitory process.

TABLE 7

Action of Proserine, Eserine, and Dibazol on Spinal Shock in Frogs

Substance	Dose	Number of frogs (converted to 20) in which phenomena of severe shock (latent period of reflex greater than 45 sec) developed for 5 1/2 min after sectioning the spinal cord
Physiological solution . . .		14.5
Dibazol	10.0	4.0
	0.1	6.0
Proserine	0.1	5.7
	0.05	4.0
Eserine.	0.1	7.0
	0.05	12.0

Comment: Physiological solution was injected in an amount of
0.1 ml per 10 g.

The indicated action of eserine, proserine, and dibazol on the

inhibitory process should be taken into account when evaluating the

mechanism of therapeutic action of the preparations shown in experi-

mental therapeutic investigations and known from the results of their

clinical use.

A definite relationship exists between the action of these prepara-

tions on the inhibitory process and their therapeutic effect. This is

confirmed by comparing the degree of therapeutic effect of proserine,

eserine, and dibazol with the intensity of the action of the prepara-

tions in the same doses on different types of inhibition. This shows

that there is a distinct parallelism between these two indexes (Figs.

11 and 12).

The revelation of this relation enabled M. A. Rozin (1952) to ex-

press the hypothesis that the main therapeutic action of proserine,

eserine, and dibazol is the ability of these compounds to weaken in-

hibition which persisted owing to damage to the nervous tissue.

Consequently, on the basis of the effect of any substances, for

example on Sechenov's inhibition, we can judge the effectiveness of

new drugs in the therapy of diseases of the nervous system. For example,

S. M. Vishnyakov and A. Ye. Uglov, while investigating a group of new

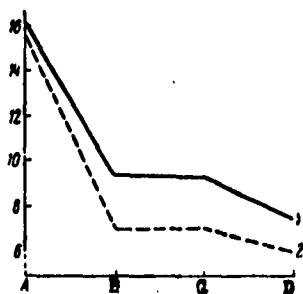derivatives of benzimidazole, found compounds preventing the development

Fig. 11. Comparison
of the therapeutic activ-
ity of proserine, eserine,
and dibazol upon dis-
ruption of reflex activ-
ity in frogs caused by
passing an electrical
current through one of
the hind extremities and
by the action of these
preparations on Sechenov's
inhibition. 1) Therapeutic
activity of various sub-
stances in hypothetical
units (left vertical axis);
2) number of frogs (con-
verted to 20) in which
Sechenov's inhibition
developed 30 min after
injecting the substances
(right vertical axis).
The substances used are
on the horizontal axis:
A) Physiological solution
(control); B) eserine (0.1
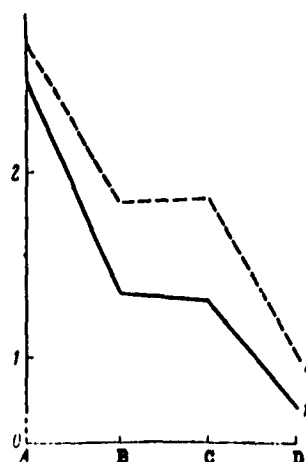mg/kg); C) proserine (0.1
mg/kg); D) dibazol (0.1
mg/kg).

Fig. 12. Comparison
of the therapeutic activ-
ity of proserine, eserine,
and dibazol in experimental
brain damage of white mice
and the effect of these
substances on suppression
of summation of impulses
caused by application of
a strong painful stimulus
to the mice. 1) Change
in the therapeutic activ-
ity of the substances; 2)
ratio of the average num-
ber of subliminal impulses
needed to evoke the flexor
reflex of the mouse hind
leg after painful stimulus
to the average number of
impulses before it. The
coefficients are presented
on the vertical axis. The
substances used are on the
horizontal axis: A) Physio-
logical solution; B) proserine
(0.05 mg/kg); C) dibazol
(10 mg/kg); D) eserine
(0.05 mg/kg).

of Sechenov's inhibition. A subsequent test of these substances

(5-amino-benzimidazole and 2-phenyl-benzimidazole) on mice with experi-

mentally caused traumatic lesion of the sciatic nerve showed the thera-

peutic activity of these compounds (A. Ye. Uglov, 1953; S. M. Vishnyakov,

1955). Analogous data were obtained by V. V. Kustov who discovered,

while testing pentoxyl on mice with experimental damage of the sciatic nerve, a dibazol-like action of the preparation. Subsequent testing of the action of pentoxyl on Sechenov's and other types of inhibition showed that the preparation prevents their occurrence. Similar results were obtained on testing other substances by R. R. Safrazbekyan (1955), Yu. D. Zil'ber (1955), and N. N. Kolosova (1955).

These facts permit the conclusion that the mechanism of the therapeutic action of dibazol, proserine, and eserine in the treatment of various kinds of lesions of the nervous system is associated with the ability of these substances to weaken the inhibitory process.

It is necessary to note in conclusion that, apparently, different types of inhibition are not similarly suppressed by the effect of proserine, eserine, and dibazol. If these substances were to remove any inhibition, including that needed to accomplish coordinated activity of an organism, they would be of purely toxological interest. It was established in earlier experiments that the administration of these substances prevents the development of Sechenov's inhibition or spinal shock in frogs, weakens inhibition arising in mice or rabbits in response to a strong painful stimulus without disturbing the reflex activity and without changing the motoricity and behavior of the experimental animals. The same phenomenon was observed by M. K. Mikushkin and M. A. Rozin when investigating the effect of dibazol on the conditioned reflex activity of dogs. It was noted that the administration of the preparation does not affect differential inhibition, but makes the development of protective inhibition.

In experimental therapeutic investigations the administration of proserine, eserine, and dibazol did not disrupt the normal coordination activity of animals, although the therapeutic action of the preparations was evident. Only the administration of large doses of eserine or

dibazol made it possible to weaken reciprocal inhibition of the spinal centers, and the use of large doses of dibazol or multiple injections of smaller doses made it possible to weaken differential inhibition in dogs impossible.

The phenomenon under discussion, characteristic not only for the action of proserine, eserine, and dibazol but noted also in a number of new derivatives of benzimidazole which demonstrated a similar therapeutic action (M. A. Rozin, S. M. Vishnyakov, A. Ye. Uglov, etc., 1955), needs further study because it can be of interest both from the point of view of elaborating the mechanism of the therapeutic action of proserine, eserine, and dibazol, and for an understanding of the nature of the very inhibitory process.

CHAPTER IV

MECHANISM OF ACTION (PRIMARY PHARMACOLOGIC REACTION) OF PROSERINE, ESERINE, AND DIBAZOL

In a discussion of the mechanism of action of eserine and proserine it is first necessary to point out their anticholinesterase activity. Proserine is especially endowed with the latter. This, in particular, was shown by the study of Repke (1937) in which the ability of a number of substances to interact with cholinesterase was studied. This property, depending on the affinity of proserine and eserine for the enzyme can be expressed in hypothetical units. If we take the affinity of acetylcholine for cholinesterase as 100 hypothetical units, the affinity of eserine will be expressed by the number 30,000 and of proserine by 80,000. Consequently, proserine and eserine hundreds of time more actively interact with cholinesterase.*

After injecting anticholinesterases into an animal, a drop is noted in the activity of the enzyme in different tissues and organs.

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* Like acetylcholine, eserine and proserine are destroyed by cholinesterase, however this process occurs extremely slowly: the destruction time of eserine is measured in hours, and of proserine in days (Krayer, Goldstein, and Plachte, 1944).

For example, Cortell, Feldman, and Gellhorn (1941) observed a 50% drop in the activity of cholinesterase of rabbit brain after the single administration of eserine in doses of 0.25-1.5 mg/kg. A particularly sharp inhibition of the activity of cholinesterase was developed after the injection of toxic doses of anticholinesterases. Thus, on injection of convulsive doses of eserine there occurred an appreciable accumulation of acetylcholine in the CNS of animals, which was, for example, shown in the experiments of Yu. D. Zil'der and M. I. Rice (1948) on frogs. Torda (1953) while determining the amount of acetylcholine in mouse brain found that convulsions after the administration of eserine occur in these animals at the moment when the content of acetylcholine in the brain is by a factor of $1^1/_2$ greater than its amount in the brain of control animals. Similar results were obtained when determining the acetylcholine level in brains of animals poisoned with proserine. According to the data of M. Ya. Mikhel'son (1958) a distinct increase in the acetylcholine level in the central nervous system was also found in experiments on frogs in which proserine in large doses caused reversible paralysis of the CNS. Herken and Neubert (1953) observed analogous results in experiments on rats administered proserine, eserine, and phosphacol.

It is known that atropine, having a cholinolytic action, weakens the effect of acetylcholine on the central nervous system. Proserine- and eserine-induced action is a result of the inhibition of cholinesterase and, consequently, of the accumulation of acetylcholine thus occurring. Therefore, the action of proserine and eserine should be completely or partially (atropine blocks only the M-cholinoreaction systems) neutralized by atropine. Experiments have confirmed the correctness of this assumption. Bulbring and Burn (1941) on investigating the action of eserine and proserine on reflex activity of dogs

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(with injection of the substances into the artery nourishing the spinal cord) established that atropine prevents and stops the action of eserine and proserine and also of acetylcholine which was tested in these experiments. The removal of the eserine effect on the reflex activity of cats by means of atropine was observed by McKail, Obrador, and Wilson (1941) Calma and Wright (1944), and Travener (1954). Analogous data were obtained by Miller, Stavraky, and Woonton (1940) who observed atropine-removal of the effect of eserine upon its direct application on the motor zones of the cerebral cortex of cats. M. Ya. Mikhel'son, Ye. K. Rozhkova, and N. V. Savateyev (1954) also confirmed the antagonism between atropine and proserine in a study of their effect on higher nervous activity in man and laboratory animals. Bradley and Elkes (1953) observed antagonism between the action of atropine and eserine on the electrical activity of the cerebral cortex.
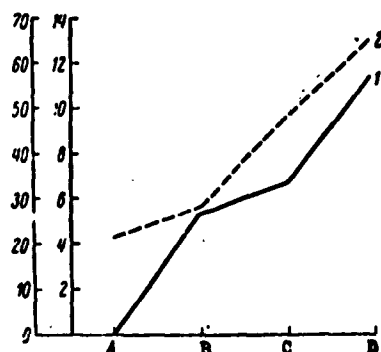

Fig. 13. Comparative assay of the effect of different doses of proserine on cholinesterase activity and Sechenov's inhibition. 1) Per cent of inhibition of cholinesterase determined by the Borisov-Rozengart method (left vertical axis), 2) number of frogs (converted to 20) in which Sechenov's inhibition did not develop 30 min after administration of the substance (right vertical axis). On the horizontal axis are the substances used: A) physiological solution, B) proserine in a dose of 0.025 mg/kg, C) proserine in a dose of 0.05 mg/kg, proserine in a dose of 0.1 mg/kg.

Based on the cited data we can assert that various changes in the activity of the nervous system must be associated with the anticholinesterase activity of proserine and eserine. The data of M. A. Rozin (1954) can be cited as confirmation that the therapeutic action of

these substances in different types of lesions of the nervous system is associated with anticholinesterase activity. He revealed the dependence between the ability of proserine and eserine to attenuate Sechenov's inhibition and the anticholinesterase activity of these substances in therapeutic concentrations. It turned out that proserine and eserine in these concentrations appreciably inhibit the activity of cholinesterase* (Fig. 13). It was reported earlier that there is a definite relationship between the action of the substances on Sechenov's inhibition and their therapeutic activity in experimental lesions of the nervous system.

The anticholinesterase activity of the substances serves as one of the criteria when selecting medicinal agents for treatment of diseases of the nervous system. Testifying in behalf of this are the data on the new, highly active anticholinesterase substances which demonstrated an evident therapeutic action in the treatment of diseases of the nervous system, for example, galanthamine (M. D. Mashkovskiy and R. P. Kruglikova-L'vova, 1951) and one of the most drastic substances of this type of action, the preparation OMPA—octamethyl pyrophosphoramide (Page, Haag, and Freund, 1953).

At the same time it is presently known that not all types of action of eserine and especially of proserine can be explained by the anticholinesterase activity of the substances. Both preparations can render a direct effect on the skeletal muscles regardless of their effect on cholinesterase. It was shown, for example, that complete suppression of cholinesterase of muscle, which can be achieved by the use of diisopropyl fluorophosphate, does not prevent contraction of the

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* The activity of cholinesterase was determined together with R. I. Krivosheina by Borisov and Rozengart's method.

gastrocnemius of cats on injection of proserine into the artery nourishing the muscle (Riker and Wescol, 1946). An analogous effect was observed in various modifications of this experiment. R. S. Rybolovlev (1948) established that proserine can increase the sensitivity of the rectus abdominus muscle of frogs to substances which are not destroyed by cholinesterase (caffeine, potassium chloride, carbachol).

It is known that proserine causes contraction of muscles in dilutions not inhibiting the activity of cholinesterase.

What has been stated permits us to assume that the direct action of proserine on the skeletal muscles, which is not associated with the anticholinesterase activity of the substance, plays a definite role in the mechanism of therapeutic action of proserine. Riker and Wescol, for example, assume that the direct action of proserine on muscle is decisive in its therapeutic effect in myasthenia.

Wilson and Stoner (1944), determining the activity of blood cholinesterase of myasthenic patients before and after injection of 1.5 mg of proserine, established that the activity of cholinesterase of blood serum after injection of the substance dropped, however "no direct relation was found between the drop in activity of cholinesterase and the clinical effect." The authors hypothesized that the therapeutic effect of proserine in myasthenia is due not only to its anticholinesterase action, but also to some kind of other factors (the authors assume that the preparation in this disease can tie-up some kind of toxic substances circulating in the blood).

The investigations of R. A. Weys and V. M. Karasik (1947) permit us to assume that certain effects of proserine on the central nervous system are not associated with the anticholinesterase activity of this substance.

The action of dibazol on cholinesterase activity was determined
by several methods. Yu. D. Zil'ber (1948), using M. Ya. Mikhel'son's
method (cholinesterase source--10% defibrinated human blood), found
that dibazol in a dilution of 1 : 50,000 has a strong inhibiting effect
on the activity of this enzyme. S. M. Vishnyakov and also R. I.
Krivosheina and M. A. Rozin, by the Borisov-Rozengart method (cholin-
esterase source--10% horse serum), established that the preparation in
concentrations reached in the blood when administered in therapeutic
doses (1 : 1,000,000 - 1 : 10,000,000) inhibits cholinesterase activity
by only 2-6%.

It was found in experiments on cats that the stimulating effect
of dibazol on the flexor reflex of the hind leg is not removed as took
place in experiments with anticholinesterase by preliminary injection
of atropine (M. S. Rozin, 1949) .

K. V. Tsomaya (1952), who determined the cholinesterase activity
of the spinal cord and the blood serum of guinea pigs poisoned with
tricresyl phosphate, established that the development of paresis and
paralysis in poisoned animals is accompanied by a decrease in cholin-
esterase activity. The injection of dibazol led to the restoration of
the disordered functions and to an increase of cholinesterase activity
to normal values.

The anticholinesterase mechanism does not underlie the action of
dibazol; this is also evident from the fact that not in one of the
doses used in the experiment did dibazol cause changes from the side
of the internal organs, which could be considered as a consequence of
acetylcholine stabilization. Yu. D. Zil'ber (1948) noted dibazol's
property, in dilutions of $1 \cdot 10^{-8} - 1 \cdot 10^{-10}$, to cause contraction
of isolated rabbit intestine (removable by atropine) which is hardly

the consequence of anticholinesterase activity because in these doses the preparation did not promote the sensitivity of isolated intestine to acetylcholine.

On the other hand, a cholinolytic action was frequently demonstrated when testing dibazol on various objects. It was found that dibazol lowers sensitivity to acetylcholine of isolated striated muscle of frog (M. A. Rozin, 1949) and isolated glomus caroticum of cats (O. D. Kozlov, 1952). Analogous results were obtained in experiments determining the effect of dibazol on the reaction of different objects in response to stimulation of the cholinergic nerves innervating them. For example, it was shown that the injection of a dibazol solution into the isolated blood circulation system of the hind extremities of frog suppresses contraction of the gastrocnemius muscle in response to stimulation of the nerves of the sacral plexus (M. A. Rozin, 1949). O. D. Kozlov, by passing a fluid containing dibazol through the vessels of the superior cervical sympathetic ganglion of a cat and observing the response contractions of the nictating membrane upon stimulation of the preganglionic trunk, noted suppression of these contractions. Only in individual experiments, when preliminary curarization of the ganglia or suppression in them of glycolytic processes by the action of sodium flouride, did the injection of dibazol increase the excitability of the ganglion.

The cited data are sufficiently convincing to preclude the possibility of understanding the mechanism of action of dibazol as being anticholinesterase. At the same time, certain facts (the direct exciting action of the preparation on isolated gut removable by atropine; the antagonism of the preparation with curare noted in the experiments on the sumpathetic ganglion, the cholinolytic action demonstrated in a number of objects) give us grounds to assume that dibazol can somehow

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act on acetylcholine transmission cf the nerve impulse, but in a different way than that of proserine or eserine.

In 1948, Rickes and team and Smith, working independently of each other isolated vitamin B_{12} in crystalline form. It was found that vitamin B_{12} is a substance of complex structure which includes a benzimidazole component: 5, 6-dimethylbenzimidazole--a compound related to dibazol. The structural formula of the vitamin in the form in which it was determined as the result of the study of Hodgkin and team (1955) is given below.
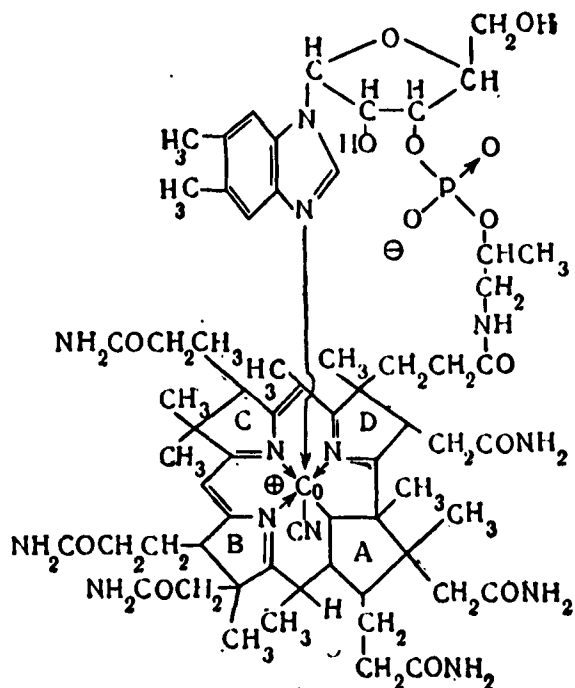
Vitamin B_{12}

According to a number of investigations, vitamin B_{12} is Castle's extrinsic hematopoietic factor, the absence of which is one of the causes for the occurrence of pernicious anemia. Since we are not concerned with the history of the problem and the data on hematopoietic and certain other properties of vitamin B_{12} (A. V. Trufanov, 1950, 1951;

A. O. Voynar, 1950; Smith, 1951; Jukes and Stokstad, 1951, Wright, 1951; G. A. Alekseyev, 1954; V. N. Bukin, L. Ya. Areshkin, and L. S. Kutseva, 1955, etc.), we will point out only several of its characteristics having a relationship to the action of dibazol.

The use of the vitamin in pernicious anemia, simultaneously with the hematopoietic effect, leads to an elimination of neuropathies accompanying anemia (excluding cases where we are dealing with deep-seated, irreversible degenerative changes of nervous tissue). Walton et al. (1954) using electroencephalgraphy studied the changes in the central nervous system of patients with different anemias. It was established that distinct changes of the electroencephalogram are detected in pernicious anemia regardless of the degree of evidence of the clinical disorders or degenerative changes in the nervous tissue. In non-pernicious anemias the electroencephalogram remained unchanged. The administration of vitamin B_{12} to pernicious anemia patients, together with the restoration of hematopoietic functions, almost in al eases led to elimination of neurological disorders and normalization of the EEG.

Recently numerous works have appeared which reported on the successful use of vitamin B_{12} in a number of diseases of the nervous system not connected with hematopoietic disorders. For example, a therapeutic effect of vitamin B_{12} was observed in multiple sclerosis, amyotrophic lateral sclerosis, poliomyelitis, polyneuritides of diabetic origin, disorders of the nervous system arising as a result of prolonged administration of folic acid, in certain muscular distrophies, etc. (Al'bert, 1953; Vega, 1953; Ventra and Anielo, 1953; Berkenheim, 1953; T. L. Krolyunitskaya, K. M. Mararova, A. A. Mittel'shtedt, Ye. A. Khrushchova, 1956, etc.). Deserving attention is the report of Sahashi, Iwamoto, and Hayshi (1953) who established that signs of insufficient vitamin B_{12}

appear in animals after heavy physical work. These phenomena could be prevented by preliminary administration of vitamins B_{12} and B_1.

Data are presently available which characterize the biochemical functions of vitamin B_{12}. It was established that vitamin B_{12} participates in the synthesis of labile methyl groups resulting in the formation of such important compounds as methionine, creatine, and choline. Vitamin B_{12} participates in the synthesis of nucleic acids, being a co-enzyme participating in the formation of nucleosides and, possibly, purine and pyrimidine bases. The data on the capacity of vitamin B_{12} to reduce the disulphide group of compounds to sulfhydryl are of great promise. Information has been published which gives us cause to assume that vitamin B_{12} affects protein metabolism, reducing the concentration of amino acids in the blood and promoting their inclusion into the protein molecule. Even the cited incomplete list of basic information on the biochemical function of vitamin B_{12} shows its important role in metabolism (Ikin, 1950; Jukes and Stokstad, 1951; Christman, 1952; L. A. Cherkes, 1953; V. N. Bukin, L. A. Areshkina, and L. S. Kutseva, 1955, etc.) and, possibly, in acetylcholine metabolism (Nachmanson and Machado. 1943).

When comparing the action of vitamin B_{12} and dibazol, it is necessary first of all to dwell on the results which make it possible to determine the significance of the benzimidazole component of vitamin B_{12} in the therapeutic effects caused by it. Apparently it does not play a decisive role in the hematopoietic action of vitamin B_{12}.

The facts show that on oral administration the therapeutic activity of vitamin B_{12} is almost halved although the benzimidazole ring is not destroyed. It is known that the benzimidazole ring of the vitamin can be replaced by the benzene, purine, and other rings for the hematopoietic effect without detriment.

At the same time it is known that folic acid participating in nucleic metabolism is effective in pernicious anemia, but when not containing the benzimidazol ring it does not eliminate nervous disorders accompanying this disease.

The information presented on the possible role of the benzimidazol component of vitamin B_{12} in its therapeutic action in lesions of the nervous system and the similarity in structure of the benzimidazol component of vitamin B_{12} and dibazol permit the assumption that this similarity is not by chance and the mechanism of the primary pharmacologic reaction induced by dibazol is possibly associated with interference in the metabolism of vitamin B_{12} (M. A. Rozin, 1955).

N. N. Kolosov established that 5,6-dimethylbenzimidazole in a dose of 10 mg/kg and vitamin B_{12} in a dose of 0.2 T/kg, like dibazol, weakens Sechenov's inhibition and spinal shock in frogs and sharply attenuates suppression of the summation of impulses caused in white mice by a strong painful stimulus. Like dibazol, these substances weakened narcosis in white mice caused by ethanol and the suppression of nervous activity occurring as a result of a strong catelectrotonic effect on the brain of white mice. According to S. M. Vishnyakov's data, 5,6-dimethylbenzimidazole removes inhibition of the central nervous system induced in rabbits by a strong painful experience.

M. A. Rozin tested 5,6-dimethylbenzimidazole and vitamin B_{12} in the same doses in experimental damage of the brain and sciatic nerve in white mice. Like dibazol, both substances in brain damage almost completely prevent suppression of the summation of impulses which usually occurs after injury. These substances also have an action similar to dibazol in sciatic nerve damage.

This information not only indicates the similarity in action of dibazol and vitamin B_{12}, but, confirming the hypothesis expressed above,

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also gives us reason to assume the existence of a new, heretofore unknown action of vitamin B_{12}--a disinhibiting effect.

After citing the data on the action of proserine, eserine, and dibazol on the inhibitory effect and after examining the facts on the primary pharmacologic reaction of these compounds, it is expeditious to compare opinions on the mechanism of their therapeutic action.

From the beginning of studying these preparations it was clear that the action of proserine, eserine, and dibazol is directed not toward nervous formations which died as a result of pathogenic effects, but toward zones of nervous tissues in which a condition of suppression, retained for a more or less long time, occurred. Clinicians and experimenters long ago indicated the existence of such zones of functionally excluded nervous formations capable of long existence under different pathological states of the nervous system. We can, for example, cite the expressions of Goltz (1876) on the "phenomena of inhibition" which arise in the cerebral cortex as a result of its damage, bear a temporary character, and are caused by a disorder of the activity of nervous apparatuses not damaged anatomically. I. P. Pavlov (1927) observed the phenomenon of prolonged diffuse inhibition in the cerebral hemispheres in dogs after surgical manipulation on the cortex. Later, analogous data were collected concerning other divisions of the nervous system (M. P. Berezina, 1947; E. A. Astrytyan, 1949; Yu. M. Uflyand, 1952, etc.).

Clinicians also know of phenomena of prolonged functional suppression of nerve centers. For instance, V. M. Bekhterev (1911) pointed out the existence of "indirect" symptoms of suppression bearing a temporary character and arising as a result of indirect effects of traumatic action on neighboring areas of the brain. K. N. Monakov (1914) attracted the attention of clinicians to the inhibition in acute

damage of the nervous system, occurring both in the vicinity and at a distance from the pathological focus, and called this phenomenon diaschisis.

Physiological investigations of recent years carried out in neurological clinics have obtained facts confirming the correctness of these assumptions of the clinicians and showing that the state of prolonged functional disorder of the activity of the nervous system bears the character of inhibition (M. P. Berezina, 1947; D. A. Lapitskiy, 1948; Yu. M. Uflyand, 1952; S. Ye. Rudashevskiy and I. Ye. Prigonnikov, 1953; etc.).

We could expect that a study of the mechanism of the therapeutic action of proserine, eserine, and dibazol will make it possible to determine not only how these substances act, but also what is the physiological essence of the disorders in the activity of the nervous system. The solution of this problem followed two different paths. In the first case the authors, when explaining the mechanism of the therapeutic action of proserine and eserine, proceeded from the concept of the anticholinesterase activity of these substances, i.e., they analyzed the problem of the chemical mechanism of the primary physiologic reaction. In the second case the authors, when studying the mechanism of the therapeutic action of dibazol, proceeded from their data on the effect of the preparation on the inhibitory process, i.e., they studied the problem of the relationship of the primary pharmacologic reaction to basic nervous processes. Since the facts used for solving the problem of the mechanism of the therapeutic action of these agents were cited in detail in preceding sections, we will give below only the arguments of the authors concerning the mechanism of the therapeutic action of the substances.

On examining the problem of the mechanism of action of proserine, N. I. Grashchenkov (1944, 1946, 1948) proceeded from data on the anticholinesterase activity of the preparation. He hypothesized that the therapeutic action of the substance is associated with this property of proserine. In support of this opinion the author cited his observations of the high vulnerability of synaptic apparatuses of the nervous system to different kinds of damaging actions. Hence from these concepts the author put forward the hypothesis that the synaptic apparatus of the nerve cells is the first to suffer in the presence of various kinds of injuries to the central nervous system. Insufficient liberation of acetylcholine for conducting the nerve impulse takes place at the synapses. This condition the author called "functional asynapsia." Proserine, inhibiting cholinesterase, eliminates this deficit in acetylcholine and restores the work of the synapse. Thus, according to the opinion of N. I. Grashchenkov, the mechanism of the therapeutic action of proserine is its anticholinesterase effect and underlying the temporary functional exclusions of nervous tissue is "functional asynapsia"--the impairment of the acetylcholine cycle in synapses of the central nervous system.

G. N. Sorokhtin (1946, 1948, 1950), who studied the mechanism of the therapeutic action of eserine, also proceeded from the concepts of the decisive role of anticholinesterase activity of this substance in its therapeutic effect. However, in addition to this, the author, to solve the problem stated, used his own considerable experimental material, primarily concerned with the effect of eserine on spinal shock of dogs. As was already reported earlier, by the administration of eserine G. N. Sorokhtin was able to prevent the development of spinal shock. When interpreting the results of these experiments the author started from the notion that under normal conditions the constantly incoming

supraspinal impulses maintains the motor cells of the spinal cord in a
state of a certain working tone. Cutting of the spinal cord, leading
to spinal shock, stops the entrance of these impulses, as a result of
which the motor cells lose their working tone This condition G. N.
Sorokhtin called "atony of the nerve cell." The atonized cell is in a
state of passive rest, which "cannot be replaced by the concept of
"true inhibition" from the point of view of modern neurophysiology"
(G. N. Sorokhtin, 1950).

Atony of the nerve cell from the point of view of chemical trans-
mission of a nerve impulse occurs as a result of the cessation of the
entrance of those portions of acetylcholine which were liberated at
the appropriate synapses in the presence of supraspinal impulses. The
administration of eserine induces an accumulation of acetylcholine in
the synaptic apparatuses left preserved, thus making up the deficit of
the actions tonizing the nerve cell and ending its atony. According to
the opinion of G. N. Sorokhtin, the mechanism of the therapeutic action
of eserine is wholly caused by the anticholinesterase activity of the
preparation. In contrast to N. I. Grashchenkov, who considered the
synaptic apparatus of nerve cells the point of application of proserine,
G. N. Sorokhtin suggests that eserine owing to its lipoid solubility
acts intracellularly.

The first observations devoted to a study of the mechanism of the
therapeutic action of dibazol showed that the anticholinesterase activ-
ity of this preparation is weakly expressed and cannot have a substantial
value in the mechanism of its therapeutic action. Therefore, further
investigations were carried out to study the action first of dibazol
and then of proserine and eserine on the basic nervous processes. It
turned out that all three preparations attenuate the inhibitory process
evokable under different experimental conditions, and a distinct

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relation has been determined between the degree of therapeutic activity of these substances and their capacity to weaken inhibition.

These data made it possible to conclude that the mechanism of the therapeutic effect of dibazol, proserine, and eserine lies in their ability to weaken the inhibitory process. The nature of the temporary functional suppression of the nerve formations can be regarded as a condition of unique persistant inhibition (M. A. Rozin, 1952; N. V. Lazarev and M. A. Rozin, 1954). Such a point of view does not suggest a single biochemical mechanism of the primary pharmacolic reaction for all substances. There are no grounds to doubt that the therapeutic action of proserine and eserine is associated with their anticholinesterase activity. It is completely possible that dibazol to some extent can affect the course of the acetylcholine cycle and the synthesis of acetylcholine. However, the latter assumption requires further experimental confirmation.

CHAPTER V

THE EFFECT OF PROSERINE, DIBAZOL, AND CERTAIN OTHER SUBSTANCES
ON THE EFFICIENCY OF HEALTHY PERSONS

We presently know of a number of drugs which increase the efficiency of healthy persons lost as a result of fatigue. Such substances are called stimulants. These include proserine and dibazol.

The stimulating action of proserine was first detected by I. I. Brekhman (1945, 1946) by ergographic investigations. The observations were performed on persons 20-25 years of age during the second half of the day: a cuff connected by a string over a pulley with a load on the end was fastened to the index or middle finger of the test subject (the weight of the load for men was 7 kg and for women, 3.7 kg). At a signal the patient, by flexing the finger, started to raise the load, repeating these movements to the rhythm of a metronome (60 beats a minute). The task was performed until the patient because of fatigue either got out of rhythm with the metronome or could no longer lift the load. This task was repeated four times with two minute intervals. On completing the task the test subject received a powder of a composition unknown to him and an hour later again repeated four times the task of lifting the load. The value of the worked performed up to

ingestion of the powder, measured by simple devices, was taken as 100%; the worked performed after ingestion of the powder was compared with it and also expressed in per cent.

In control observations the test subjects were given glucose powders (0.5 g). A distinct decrease in performance occurred an hour after ingestion of the powder; after ingestion of proserine powder in a dose of 0.001 g (with the addition of 0.5 g glucose) a drop in performance was not only not observed but conversely, it was higher than before ingestion of proserine. In addition to proserine, I. I. Brekhman tested phenamine, caffeine, and also substances studied for the first time to check the stimulating action. It turned out that proserine is inferior only to phenamine (amphetamine) and the combination of phenamine and proserine with respect to the strength of the stimulating action.

Investigations using an ergograph showed the ability of proserine to enhance performance only on execution of coarse muscular work. Subsequent investigations studied the effect of proserine on the performance of work requiring precise dyanmic coordination of movements, wherein the element of heavy muscular work was reduced to a minimum (I. I. Brekhman and M. A. Rozin, 1946).

In these experiments the test subjects on a signal lowered a thin glass rod into a hollow glass cylinder. On its tip was a contact which when touched to fine wires stretched along the inner walls of the cylinder caused closure of a circuit which was recorded by special devices. An increase in the number of closures was regarded as an index of a disorder in precise coordination. The experiment lasted 2 hr. The test subjects took powders of a composition unknown to them and immediately returned to performing the task; then they repeated it 15 times at equal intervals. The average data obtained during the first half an

hour was taken as 100%; the average data obtained in the subsequent half-hour intervals were compared with the first value and expressed in per cent. In addition to proserine, the effect of the drugs used in the preceding investigations with the ergograph were studied.

It was shown that the stimulating effect of these substances was not the same: the strongest effect was obtained from using a combination of phenamine and proserine, phenamine and caffeine showed almost the same effect, then methyl-caffeine, and proserine was least effective.

Thus, the stimulating action of proserine was most evident with respect to work associated with considerable physical stress.

While carrying out these investigations the following fact was noted. Twenty or thirty minutes after taking a combination of phenamine and proserine, phenamine, caffeine, or methyl-caffeine, the test subjects started to feel distinct emotional excitement, an active interest in the work was demonstrated, and the tasks were performed with greater lift and facility. What was going on around them was perceived keenly, evoking many bright and colorful associations, speech became rapid and picturesque. During the period of the action of these stimulants the investigated subjects did not feel the need for sleep and, having lain down on a bed, did not fall asleep for a long time.

After ingestion of proserine these phenomena did not occur. This property of proserine should be considered as a definite virtue of the preparation since an antihypnotic effect of a stimulant is undesirable in a number of cases. The emotional uplift occurring under the action of other preparations is needed in certain cases and is beneficial in stimulating mental work.

Thus, proserine is shown as a stimulant only in those cases where it is needed to restore efficiency weakened as a result of physical

fatigue.

An ergographic investigation was carried out when testing diba-
zol to reveal its stimulating action, and its effect on the maximal
rhythm of motor forces are determined (M. A. Rozin, 1949, 1951).

The procedure of the ergographic investigation was the same as
in testing proserine.

In addition to dibazol, used in a dose of 0.005 g, a combination
of phenamine and proserine was tested for comparison. It was shown
that an hour after ingestion of dibazol it was possible to prevent
completely a sharp drop in performance, which was noted in the cor-
responding control observations.

Similar results were obtained in experiments with a combination
of phenamine and proserine, wherein both stimulants were about ident-
ical with respect to the force of the stimulating action.

TABLE 8

Effect of Dibazol and a Combination of Phenamine and Proserine
on Muscular Work (based on Data of the Ergographic Investigation)
and on the Maximal Rate of Motor Forces

Name and dose of substance	Change of ergograph an hour after ingestion of powder (value of work up to ingestion is taken as 100%)	
	Work on ergograph (in %)	Maximal Rate of movements (in %)
Glucose 0,5	78	94,9
Dibazol 0,005		
Glucose 0,5	100,6	102,9
Phenamine 0,02		
Proserine 0,001	101,3	106,9
Glucose 0,5		

A study of the action of dibazol on the maximal rate of movements
was carried out at the same hours as the ergographic investigation.
After performing work on the ergograph, the test subjects were supposed
to beat on the head of a telegraph key as fast as possible, then they
were given a powder of a composition unknown to them, and after an

hour the investigation was repeated as before. The combination of the test of the maximal rate of movements and the work on the ergograph was used because it is possible to "lose" maximal rhythm, which is usually rather stable even with some fatigue, only by preliminary massive physical labor. Even under such severe conditions of the experiment the number of beats on the key dropped an average of 5.1% in the control experiments an hour after ingestion of the powder with glucose. After taking dibazol and a combination of phenamine and proserine, the frequency of the beats increased somewhat. The results of these observations are shown in Table 8.

No signs of emotional excitement were noted after taking dibazol. Moreover, soon after ingestion of dibazol one of those investigated fell asleep and could not be awakened to perform the next task on the ergograph.

Like proserine, dibazol is shown as a stimulant in cases where it is necessary to increase physical fitness.

CHAPTER VII

TREATMENT OF DISEASES WITH PROBABLE DISORDERS
OF THE MYONEURAL JUNCTIONS

Proserine has been used in the Soviet Union since 1940 for the treatment of myasthenia (L. A. Lotsman and L. B. Perel'man, 1940; N. I. Grashchkov, 1946; M. A. Yavchunovskaya, 1951; etc.).

Like other anticholinesterases, proserine renders a temporary therapeutic effect in this disease. For several hours (from 3 to 6) the muscle force is restored to some degree, and aphonia, swallowing disorders, and labored breathing are removed; myoneural excitability is changed. The brevity of the therapeutic effect compels repeated administration of preparation, and progression of the disease necessitates gradual increase of the dose.

However, the therapeutic effect is not always directly proportional to the increase in the amount of administered substance. For example, it was proved for prostigmine—the foreign analogue of proserine, that sometimes the increase of its dose causes a curareform action, i.e., an enhancement of myasthenic demonstrations, and in such cases it is necessary to reduce the amount of prostigmine to produce a therapeutic effect (Kennedy and Wolf, 1938).

During the exacerbation period it is necessary to avoid frequent and parenteral administration of proserine in large doses. Slow intravenous administration of proserine is permissible under conditions threatening life. Bini Lucio (1937) successfully used intravenous administration of proserine to save a patient with paralysis of respiratory muscles.

With average severity of the disease or on improvement of the patient's condition, it is advantageous to combine intramuscular administration of the drug with its oral administration.

We must point out that certain authors emphasize the great effectiveness of oral administration of prostigmine in comparison with parenteral administration (Bear, 1939; Radovich, Missirlin, and Schachter, 1939).

During the remission period, the proserine dose and the frequency of administration of the drug can be reduced appreciably. In these cases just oral administration of the drug is sometimes possible.

The proserine dose, like the method of administration, is selected individually for each patient. Proserine is perscribed per os in powders from 15 to 180 mg per day and is administered subcutaneously as 1-4 mg (M. A. Yavchunovskaya, 1951). Atropine, from 0.3 to 0.65 mg. is used to reduce the side-effect of proserine.

M. A. Yavchunovskaya called attention not only to the dose, but also to the scheme of using proserine. When compiling a scheme it is necessary to take into account the normal regime of the patient. As a rule the injection of proserine is timed to the ingestion of food.

Sometimes a better therapeutic effect is attained by the simultaneous administration of proserine, strychnine, and thyamine.

There are indications in the literature that the therapeutic action of prostigmine can be enhanced by the administration of potassium

chloride (Laurent and Walker, 1936; Watts, Mitchell, and Schwabe, 1937; Nowotny and Redlich, 1938; Schlesinger, 1940). Ephedrine, according to the data of Wilson and Stoner (1944), prolongs the effect of prostigmine.

In special studies devoted to the mechanism of action of anticholinesterase preparations it was proved that under the influence of prostigmine, splitting of acetylcholine is inhibited (Pichler, 1937). This apparently depends on a decrease in the activity of cholinesterase. For instance, 30 min after the injection of 1.5 mg of prostigmine the activity of cholinesterase was reduced 34%. The addition of ephedrine caused, moreover, a more prolonged decrease in the activity of cholinesterase (Wilson and Stoner, 1944). Along with the decrease in the activity of cholinesterase, the potassium-calcium ratio changed substantially, which created optimal conditions for the action of acetylcholine.

According to the data of L. B. Perel'man (1946), an increase in the content of potassium salts in the cerebrospinal fluid is observed at the height of action of proserine, while the concentration of calcium salts remains at the former level. This shift reaches its maximum by the time the myasthenic phenomena are eleminated.

Claar and Colarusso (1937) indicate that simultaneously with an improvement in the condition of the patient after the injection of prostigmine, the sugar and calcium concentration in the blood reached the norm and creatinuria was eliminated.

However, it is necessary to emphasize that not in all cases is anticholinesterase therapy in this disease effective.

Attention was given to the "protigmine-resistant" cases of myasthenia by Fraser (1937), Nowotny and Redlich (1938), Tarlau (1939),

and Meredith (1941). Myasthenia requires long treatment. Anticholin-
esterase therapy, being symptomatic, replacement treatment, in no case
precludes the use of other treatment of this severe disease, for ex-
ample, irradiation of the thymus with large doses of X-rays (O. A.
Pokrovskaya, 1954; A. G. Panov, V. I. Zhuchenko, and V. S. Lobzan,
1954).

The administration of substances disturbing the functions of the
neuromuscular junctions, such as the widely used quinine, is countra-
indicated in myasthenia. Kennedy and Wolf (1937) observed a sharp
deterioration of the condition of myasthenic patients upon ingestion
of quinine.

This is illustrated by the observation which we cite from the
study of I. I. Rusetskiy (1953).

> Patient K., age 19, suffering from myasthenia,
> ill with malaria, in connection with which she
> was administered quinine. During the period of
> ingesting quinine the condition of the patient
> deteriorated—attacks of asphyxia were demon-
> strated. The administration of proserine pro-
> duced a smaller effect than before quinine ther-
> apy. When administration of quinine was stopped,
> the health of the patient improved and she was re-
> leased to go home where she was administered 2 mg
> of proserine 1-2 times a day.

> After several months the attack of malaria re-
> curred and the patient was again administered
> quinine. Here condition rapidly deteriorated, it
> was necessary to resort to proserine administration
> each 1 1/2 - 2 hr, but in spite of this the patient
> died upon increasing weakness of the respiratory
> muscles.

In addition to quinine, the administration of substances having a
curariform action are countraindicated in myasthenia.

Myotonia

Anticholinesterase preparations are not effective in myotonia. On the contrary, there are indications of a deterioration in the condition of the patients with myotonia when prostigmine is administered. This deterioration is expressed by an increase in myospasms. Good results from the use of quinine in myotonia have been described. Quinine reduces myospasms, thus facilitating active movements (Kennedy and Wolf, 1937; Laruel Massion-Verniory, and Maldaver, 1937). Ascorbic acid acts the same way.

Myotonia Atrophica

Ye. F. Kul'kova-Davidenkova and B. S. Vilenskiy (1951) published interesting data on the results of proserine treatment of myotonia atrophica—a unique disease combining the symptoms of myopathy and myotonia. After each administration of proserine the authors observed an increase in muscle force in the patients. However, contrary to expectation by analogy with myotonia, myospasms were not enhanced in these patients but, conversely, weakened. The simultaneous administration of carbachol with proserine caused an increase of muscle force and of myotonic developments. This difference in the action of proserine, on one hand, and of proserine and carbachol, on the other, is not fully understood. It cannot be explained, indicates S. N. Davidenkov (1952), by starting from the schematic concept of the action of anticholinesterase preparations.

It seemed that both proserine and carbachol in combination with proserine, by acting choline-positively, should have yielded the same effect. However, proserine in myotonia atrophica has an effect only on the myopathic component of the disease, with aggravating the myotonic syndrome.

The indicated property of proserine to increase force, without increasing myospasms in myotonia atrophica makes this preparation of practical value in this disease.

S. N. Davidenkov in "Clinical Lectures on Nervous Diseases" (1952) cites data of Troto on the successful treatment of myotonia atrophica with quinine and ascorbic acid. An appreciable decrease of myotonic symptoms was observed by the author in two cases.

CHAPTER VIII

TREATMENT OF PROGRESSIVE MUSCULAR DYSTROPHY

The effectiveness of proserine in progressive muscular distrophies has been studied in detail since 1945 in the clinic of S. N. Davidenkov, and Ye. F. Kul'kova (1949) and Ye. F. Kulkova-Davidenkova and B. S. Vilenskiy (1951). These authors observed a total of 80 patients; of these patients, 50 had myopathy (Erb's form), 8 had scapuloperoneal amyotrophia, 21 had neuralgic amyotrophia, and 1 patient had opthalmoplegia progressiva. All patients were characterized by a considerable duration of the disease, massive muscular atrophies, considerable retraction of the muscles and tendons, and coarse disorders of walking. Nevertheless, in all patients except four an increase in muscle force was observed after treatment, and in some patients movements that were previously absent were developed.

The most active were the first injections of proserine: subsequent injections only strengthened the effect. In most of the patients the obtained result was persistant and could be traced over a period of a year and more. In eight cases only a short-lived increase in muscle force was observed after each injection of proserine, similar to that noted during treatment of myasthenia with prostigmine. A positive

therapeutic effect was achieved in 5 of 7 patients during proserine treatment of far-progressed forms of myopathies (P. M. Chernomordik, B. Z. Vishnevnik, A. G. Volkova, R. I. Moskvina, Yu. V. Kugaro and N. M. Babal'skaya, 1951).

S. N. Davidenkov (1952) considers it advantageous to carry out a combined treatment of patients with progressive muscular dystrophies. In myopathies he recommends the administration of proserine, vitamin E (α-tocopherol), sympathominetin, the use of repeated blood transfusions, calcium iontophoresis, roentgenotherapy, wherein it is necessary to avoid overfatigue of the muscles. S. N. Davidenkov indicates that in neuralgic amyotrophia "proserine is indicated not in a lesser, but even in a greater degree than in myopathy." At the same time it is expeditious to use in this disease thiamine, vitamin E, massage, gymnastics, and electrogymnastics. (TRANS. NOTE: rhythmic electrical stimulation of muscles).

N. N. Pyatnitskiy and A. G. Glaurov (1953) observed a therapeutic effect in myopathies from the administration of proserine by means of iontophoresis, while no improvement was seen in two patients with a parenteral injection of the preparation.

N. A. Kryshova (1948) hypothesized that in myopathy proserine acts not only as an anticholinesterase substance, but to some extent influences vitamin metabolism.

We successfully used eserine in the treatment of Erb's type of myopathy (TRANS. NOTE: pseudohypertrophic muscular dystrophy) and progressive neuropathic (peroneal) muscular atrophy. After each injection of eserine an increased was observed in the volume and force of movements. The 2nd and 3rd injections were most effective. An apparant effect can be ascertained up to the 7-8th injection. Subsequent injections of the drugs in large doses were without results.

After the course of eserine therapy, the patients freely began to climb the stairs and could walk longer distances than before treatment. The improvement in the condition of the patients lasted several months, then it was necessary to repeat the eserine treatment. The best therapeutic effect was obtained in neuralgic amyotrophia. However, in two patients with progressive muscular dystrophy no therapeutic effect was observed. I. D. Sapir, R. D. Irkho, and T. M. Ferber (1948) later reported a positive therapeutic effect in the treatment of myopathies with eserine.

Ye. A. Al'tusher (1948) observed a positive effect in three patients with Erb's type of myopathy on administration of eserine and phenamine.

Dibazol was first used for treatment of progressive muscular dystrophies by N. A. Kryshova (1950). On administration of dibazol for 25-30 days, she observed an increase of muscle force and normalization of the functions of the sympathetic nervous system in 25 patients. G. I. Mirzoyan, A. S. Nersesyan, and A. A. Antoyan (1953) noted only a temporary therapeutic effect from the use of dibazol in three cases of myopathies dating back 3-5 years. An increase in the muscle force was ascertained only during the period of dibazol ingestion, even over a prolonged course of treatment (60 days).

We did not obtain any definite data indicating the effectiveness of dibazol in the treatment of myopathies.

There are indication of the therapeutic action of dibazol in amyotonia congenita (N. A. Kryshova, 1950).

Recently, attempts have been made to treat progressive muscular dystrophies with pachycarpine, which is used in doses of 0.05-0.1, 1-2 times a day for 30-40 days. According to the data of N. A. Kryshova (1952), after treating 42 patients their sense of well-being improved,

strength and amount of movements increased, and walking, standing, running, and other complex motor acts improved. However, M. B. Eydinova, G. A. Rupcheva, and E. A. Edel'shteyn (1952), on the basis of treating 10 patients, did not form a definite opinion on the effectiveness of pachycarpine in this disease.

CHAPTER XII

DISEASES NOT AFFECTED BY ANTICHOLINESTERASE PREPARATIONS AND
DIBAZOL. PROSPECTS FOR TREATING THESE DISEASES

The use of proserine, eserine, and dibazol in patients with post-encephalitic parkinsonism, based on our observations, is not effective. Rigidity, tremor, vegetative disorders did not lessen after treatment with these preparations. L. Ya. Nemlikher, V. M. Kanter, and Ye. S. Perepletchik (1947) also did not observe an improvement from the administration of eserine in this disease.

No therapeutic effect was observed after the use of anticholinesterase preparations in the hyperkinetic type of encephalitis, chorea, and hepatolenticular degeneration. Not in a single one of our patients with such diseases wt s there any noticeable improvement from treatment with proserine, eserine, or dibazol. The ineffectiveness of anticholinesterase preparations in striatal hyperkinesia was also reported by Kennedy and Wolf (1938), K. G. Kaplan (1947), Ye. F. Kul'kova-Davidenkova and B. S. Vilenskiy (1951).

Nevertheless one can still find in the neurological literature individual indications of a diminuation of hyperkinesis under the effect of anticholinesterase agents (Kabat, 1946). The improvement in

these cases does not depend on the specific action of eserine or pro-serine, but most probably is caused by an entire complex of therapeutic measures.

For restorative treatment in striatal-pallidal lesions, it is evident that drugs with another mechanism of action must be used. For this purpose a number of new preparations of cholinolytic action have recently been proposed.

Of these we must first of all indicate substances with curariform action. An attempt to use curare in various spastic states was made long ago. An intramuscular or intravenous injection of the preparation in an amount of 0.025 not less than 3 times a week improved the move-ments in spastic paresis and muscular dystonia (Michael and Burman, 1939). An especially valuable property of curare at a certain dose is the selective action on hyperintervated muscles without affecting the normal ones.

However, curare and its poorly purified preparations often cause toxic phenomena in regard to the central nervous system, and the cardio-vascular system. According to the data of Michael and Burman (1939), at a dose of only 0.032-0.035, phenomena of poisoning were observed, which compelled them to resort to the use of a curare antagonist— prostigmine. Such toxicity limited the use of curare in the clinic.

At the present time we have available nontoxic, Soviet curarelike preparations of vegetable origin: K, D-Z, and the synthetics pyrolaxon, diplacine, etc. The preparation K was used by N. A. Kryshova, M. A. Zhilinskiy, N. M. Kovalenkov, and Ye. A. Bychenkova (1954) for treat-ment of disorders of muscle tone of an extrapyramidal character. In 26 patients with post-encephalitic parkinsonism, the authors observed a decrease in rigidity and tremors and an improvement in movements and walking after treatment with preparation K. The therapeutic effect in

a number of cases lasted several months. Preparation K was administered internally in an amount of 0.025 with glucose in powders, then the dose of the drug and the number of ingestions were gradually increased to 0.05 t.i.d.

The average duration of the course of treatment is 10 days. In some cases treatment was repeated after a 7-10 day break.

In addition to preparation K, the USSR Minister of Health has authorized a new agent having curariform action, D-Z, for wide clinical testing.

Among other cholinolytic substances we must first of all mention tropine diphenylacetate hydrochloride, tropacin. This substance, according to the data of M. D. Mashkovskiy (1953), has the property to block muscarine-sensitive and nicotine-sensitive cholinoreaction systems.

The use of tropacin in the neuropathic clinic showed its therapeutic properties in post-encephalitic parkinsonism (M. B. Eydinova and Ye. N. Pravdina, 1953; D. A. Markova and K. Z. Dolgikh, 1953; S. A. Rossin and Yu. V. Abozin, 1955; Ye. A. Bychenkova, 1955). The preparation was administered in a dose of 0.0125-0.025 1-3 times a day depending on its tolerance by the patients. The course of treatment is from 10 days to 3 and even 7 months. Torpacin is recommended to be given at night in disorders of accommodation.

N. A. Kharauzov (1954) suggested using pentaphene together with scopolamine in parkinsonism. Pentaphene,.like tropacin, is a cholinolytic, but it acts more weakly than the latter on nicotine-sensitive cholinoreaction systems. The combined use of pentaphene and scopolamine in parkinsonism, according to the data of P. M. Chernomordik and B. Z. Vishevnik (1954), was more effective than treatment with just scopolamine. M. Ya. Mikhel'son (1953), on the basis of experimental
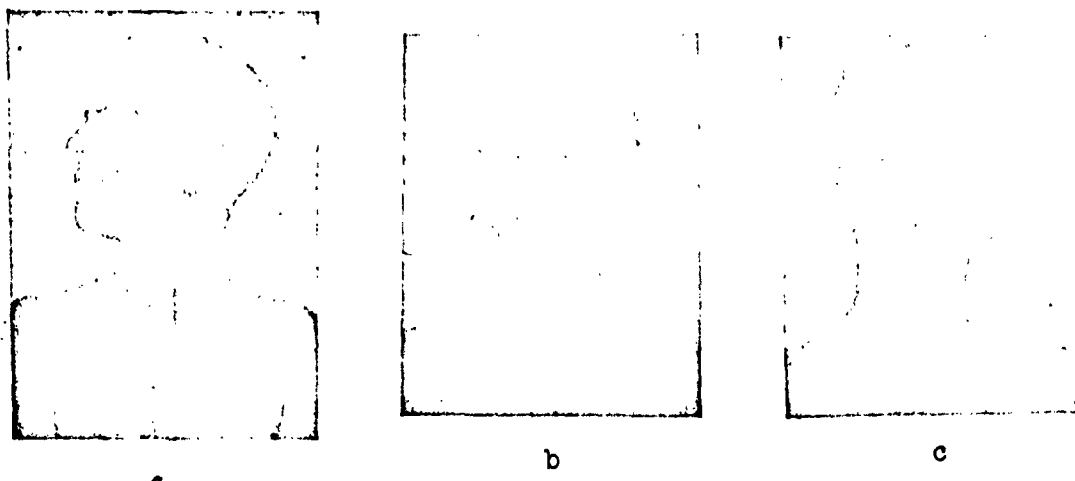
b   c

a

Fig. 34. Diminuation of hyperkinesis induced by treatment
with a mixture of benzimidazole, gangleron, and atropine in
a patient with an atypical form of myoclonia. a) Forcible
turn of head. The photograph was made before the administra-
tion of benzimidazole, gangleron, and atropine; b) same pa-
tient 20 min after administration of a mixture of these
drugs; c) the same patient 2 weeks after completing the
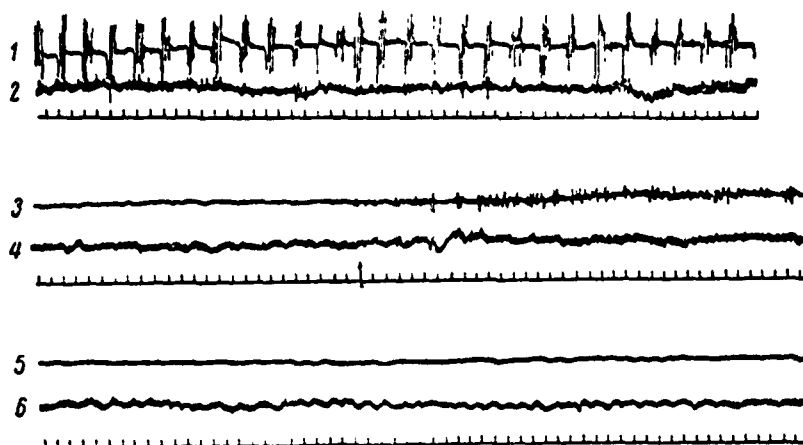course of treatment.

Fig. 35. Changes in electromyography and electro-
encephalography in a patient with an atypical form of
myoclonia. 1) electromyograph of the left sternoc-
leidomastoideus before administration of mixture of
benzimidazole, gangleron, and atropine; 2) simul-
taneously produced electroencephalogram, right in-
ferior central lead; 3) electromyogram of the left
sternocleidomastoideus 30 min after administration
of a mixture of these drugs (to the right of the
arrow is the recording of the moment of provoking
hyperkinesis by turning the head); 4) simultaneously
produced EEG, right inferior central lead; 5) elec-
tromyogram of the same muscle after the course of
treatment; 6) simultaneously produced EEG, right in-
inferior central lead.

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investigations, recommends the use of combined therapy with substances of narcotic and cholinolytic action in hypermyotonia, spastic states, and hyperkinesis. When selecting these substances he considered it necessary to use preparations blocking the muscarinic and nicotinic reaction systems. For this purpose he suggested the simultaneous administration of benzimidazole, gangleron, and atropine. Benzimidazole was used earlier for relaxing muscle tonicity in Little's disease (Goodman and Hart, 1944). M. Ya. Mikhel'son emphasized the narcotic action of benzimidazole. The second ingredient of this mixture, gangleron, is a new Soviet cholinolytic capable of blocking the nicotinic effect of acetylcholine.

Our experiment of using benzimidazole, gangleron, and atropine, showed their effectiveness in certain hyperkinetic syndromes (N. N. Ansov, 1953). Of 18 patients treated with the indicated preparations, an improvement was noted in 13 (Figs. 34 and 35).

S. P. Vorob'yev (1954) used these substances also with positive results in parkinsonism.

The stated facts compel us to presume that in the future treatment of diseases associated with lesions of the extrapyramidal system, we should follow the line of using preparations of curariform action and cholinolytics, possibly, in combination with certain types of drugs of a narcotic action.

CONCLUSIONS

Now that we have given an account of the factual material relative to the use of preparations of a restorative action in various diseases of the nervous system, we must briefly sum up the main principles of using these preparations.

Preparations of an anticholinesterase action and dibazol are used in paresis, paralysis, hyperthesia, anesthesia, disorders of the co-ordination of movements, disorders in sphincter functions, etc.

Proserine, eserine, and dibazol, while acting on temporarily in-active nervous elements and while fostering restoration of their func-tion, at the same time do not eliminate the cause of the disease. There-fore, the indicated substances should be administered together with an etiological treatment.

Pharmacologic substances are not the only means of restorative therapy, as a consequence they should be used along with other thera-peutic measures promoting restoration of the functions—therapeutic gymnastics, electrogymnastics, and other means of physical therapy.

Proserine, eserine, and dibazol are not identical in respect to their mechanism of action, therefore, it is advantageous to alternate dibazol treatment with treatment by various anticholinesterase

preparations. Dibazol is especially valuable in the syndrome of flaccid paralysis. The simultaneous use of proserine or eserine with strychnine, thiamine, and caffeine deserves attention. Proserine should far from always be injected intramuscularly: in a number of cases it is advantageously administered orally or as a combination of intramuscular injection with peroral administration.

It is necessary to determine the optimal dose in each specific case when administering anticholinesterase preparations and dibazol. The best therapeutic effect does not always follow an increase in the amount of the administered substance, sometimes it is better to reduce the dose to obtain a positive result.

The effectiveness of anticholinesterase preparations and dibazol depends to a certain extent on the stage of the disease. These preparations are most active in the recovery stage of a disease. An early administration of these substances in neural infections, disorders of cerebral circulation, and traumas shortens the recovery period.

The indicated preparations are less effective in stable, residual phenomena, but in these cases persistant treatment will produce satisfactory results in a number of patients.

The use of proserine and especially eserine in chronic diseases (disseminated sclerosis, syringomyelia, etc.) promotes remissions.

Anticholinesterase substances and dibazol are not effective in hyperkinesia, extrapyramidal rigidity, and parkinsonism. In these cases it is necessary to use substances with a counter-type action. Preparations of a curariform action, cholinolytics, and a combination of cholinolytics and substances of a narcotic action are presently used in lesions of the extrapyramidal system.

In conclusion we must emphasize that the contemporary use of a restorative action together with therapeutic means widens the

therapeutic possibilities in various diseases of the nervous system.

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