# HIGHLIGHTS OF SOVIET PHARMACOLOGY[1]

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The progress of Soviet pharmacology has been closely associated with the development of a national pharmaceutical industry which may be said to have sprung up only after the Revolution, since such industry was practically nonexistant in tsarist times and since drugs, especially synthetic ones, were, as a rule, imported from abroad. The general industrialization of the Soviet Union brought about the creation of large chemical plants which, by the beginning of World War II, were able to supply the country with pharmaceutical products of Soviet make. To our pharmacologists fell the task of furthering the introduction of effective new drugs into industry and medical practice.

In order to meet the requirements of a newly created pharmacological industry there arose a number of scientific institutions. The first to be founded was the VNIKhFI (All-Union Scientific Research Chemo-Pharmaceutical Institute, Moscow) with Professor M. D. Mashkovski heading its department of pharmacology. A similar Ukrainian institute was created in Kharkov. The VILAR (All-Union Medicinal and Aromatic Plants Institute), situated in the vicinity of Moscow, has local branches in many districts of the U.S.S.R. Special institutes attached to the Academies of the Armenian S.S.R. (Erevan) and Latvian S.S.R. (Riga) are engaged in drug synthesis. After World War II the oldest medical research institute in the country, the Institute of Experimental Medicine, created a department of pharmacology, which is directed by the present writer. A few years ago the Academy of Medical Sciences in Moscow founded the Institute of Pharmacology and Chemotherapy, headed by Professor V. V. Zakusoff.

In addition, pharmacological research is carried on throughout the Union by the chairs of pharmacology of various medical and chemopharmaceutical faculties, or institutes. In tsarist Russia there were only 11 chairs of pharmacology; their total number has now risen to almost 80. The number of scientists working in this field has undergone a similar increase. Up to recent times Soviet pharmacologists formed a special section in the All-Union Physiological Society. The last conference of pharmacologists decided to create a separate Pharmacological Society attached to the Academy of Medical Sciences.

The most important review publishing original papers by Soviet pharmacologists is *Farmakologiya i Toksikologiya*, an English translation of

[1] The survey of the literature pertaining to this review was concluded in June, 1960.

which appears in the U.S.A. Moreover, there is a pharmacological section in *Byulleten' Eksperimental'noy Biologii i Meditsiny* issued by the Academy of Medical Sciences.

As in all other branches of science, pharmacological investigation in the U.S.S.R. is carried out on planned lines. The planning of pharmacological work, i.e., the selection of the problems considered most urgent, is accomplished by a special Problem Commission formed of the leading pharmacologists of the country and attached to the Institute of Pharmacology and Chemotherapy of the Academy of Medical Sciences. Such a plan embraces the most pressing problems of public health, such as search for drugs effective in the therapy of tumors, pharmacology of the cardiovascular system, investigation of neurotropic drugs, chemotherapy of infectious diseases, etc. The plan agreed upon by the commission does not, however, preclude private initiative on the part of individual laboratories—all scientific achievements are gratefully acknowledged and encouraged.

Space limitations prevent coverage of the whole field of Soviet pharmacology in a single short review. Accordingly, the present paper will be limited to problems more closely related to the work of this writer (namely, researches in the pharmacology of the nervous and cardiovascular systems) and, as a rule, will mention recent publications only.

The special interest shown by Soviet pharmacologists in the pharmacology of the nervous and, particularly, the central nervous system is, to a great extent, attributable to the influence of I. P. Pavlov's ideas. Energy has been focussed on the search for an investigation of agents blocking the transmission of nervous impulses in different portions of the reflex arc, since central and peripheral rest is of prime importance in effecting the cure of various pathological conditions.

Among the work in the pharmacology of the central nervous system, mention should be made of the investigations in the central cholinergic synapses, which were reviewed at the last International Physiological Congress in Buenos Aires [Anichkov (6)]. These investigations resulted in the isolation from the vast body of cholinolytic agents of a special group of so-called central cholinolytics, i.e., substances exerting a predominant blocking action upon the central cholinergic synapses. Besides well-known agents belonging to this category, such as adiphenine (Soviet equivalents: spasmolytin, diphacil), caramiphen (Soviet equiv.: pentaphene), benactyzine (Soviet equiv.: diazil), the following central cholinolytic agents were recommended in the U.S.S.R. for clinical use: tropacin (tropin ester of diphenylacetic acid hydrochloride); aprophen (β-diethylaminoethyl ester of diphenylpropionic acid hydrochloride); tiphene (β-diethylaminoethyl ester of thiodiphenylacetic acid hydrochloride); gangleron, synthetized by Mnjoyan (23) (α,β-dimethyl-γ-diethylaminopropyl ester of *p*-iso-butoxybenzoic acid hydrochloride); methyldiphacil (β-diethylamino-iso-propyl ester of diphenylacetic acid hydrochloride); methyldiazil (β-diethylamino-iso-propyl ester of diphenylglycollic acid hydrochloride). The central action of the sub-

stances pertaining to this group was proved by observations on patients, experiments upon the conditioned reflexes of animals, and electroencephalographically; their cholinolytic character was shown by their antagonizing the central action of anticholinesterases and cholinomimetics [Mikhelson *et al.* (20); Denissenko (11)]. It was furthermore observed that in accordance with the peculiarities of their peripheral action, some central cholinolytics, e.g., adiphenine and methyldiphacil, show preponderant antagonism to the central action of nicotine, whereas benactyzine and methyldiazil antagonize mainly the central effect of arecoline. The latter group exerts a selective blocking action upon the synapses of the efferent system of the reticular formation. The cholinoreceptors of the central synapses, as well as the peripheral ones, thus belong to two distinct classes, namely, nicotine-sensitive systems (or N-cholinoreactive, as they should be called), and muscarine-sensitive ones (M-cholinoreactive, according to our terminology). Central cholinolytics enhance the effect of hypnotics and narcotics, a fact used to great advantage in clinical practice [Anichkov & Denissenko (5)]. Their action upon reflex-induced trophic disorders is very important. Benactyzine, and, to a lesser degree, caramiphen, prevent, in animals, the formation of reflex-induced gastric ulcers that are caused by intense irritation of the duodenum. This effect does not depend upon the peripheral atropinomimetic action of the drug, since quaternization of central cholinolytics enhances their peripheral atropinomimetic properties and diminishes their action upon reflex-induced ulcers [Zavodskaya (33, 34)]. The regulating effect on trophic processes obviously depends upon the central action of the cholinolytic. One may suppose that this central action is part of their curative effect not only in the case of gastric, but in other internal diseases as well. Some central cholinolytics, such as adiphenine, tiphene, etc., stimulate hormonal activity in the adrenal cortex [Anitschkov & Poskalenko (8)].

Soviet pharmacologists eagerly search for new sedatives and investigate their action. By using various methods, chiefly that of conditioned reflexes, it was discovered that certain aglycones of cardiac glycosides, such as strophanthidin and erysimidin, possessed these properties in a degree fully justifying their application in clinical practice [Asratian (9)]. It was furthermore shown that several anticonvulsants, such as diphenylhydantoin and trimethadione, act as vestibular tranquilizers and may be used in the treatment of Ménière's disease [Malyghina (18); Milstein (21); Yaroslavski (31)]. Certain amines of 2-phenyl-1,3-indandione were found to possess a tranquilizing and anticonvulsant effect, and the structure-activity relationship was investigated [Belenki and co-workers (10)]. Synthetic alkyl derivatives of diamide and imidazoldicarboxylic acid were shown to possess a depressing effect upon the conditioned reflexes antagonistic to caffeine and a stimulating one upon the subcortical region [Anichkov & Borodkin (7)]. The action of analgesics and several other drugs upon the efferent system of the reticular formation was investigated by Valdman (28).

The study of another branch of nervous system pharmacology actively pursued in Soviet Russia is that of the ganglia and neuromuscular synapses. Thanks to the work of Mashkovski and co-workers (19), use is made in this country of a number of natural alkaloids such as pachycarpine (an optic isomer of sparteine), obtained from *Sophora pachycarpus,* and sphaerophysine, extracted from *Spaerophysalsula.* Both alkaloids are bis-tertiary bases and possess a "mild" ganglion-blocking action, do not lose their properties on oral administration, and are used in the same way as oxytocic drugs.

In the search for new ganglion-blocking agents the Latvian and Ukrainian pharmacologists, headed respectively by Professor Belenki [Schuster (25)] and Professor Tcherkes [Dombrovskaia and co-workers (12)], carried out researches in the field of structure-action relationships of gangliolytics. Tcherkes' group has shown the important role played by anions in the gangliolytic action of salts of bis-quaternary bases. It was ascertained that hexamethonium benzene sulfonate was a more powerful gangliolytic and was less toxic than the usual iodide. In the U.S.S.R., hexamethonium dibenzene sulfonate, known as benzohexonium, is widely used as a gangliolytic. Kharkevitch (17) showed that the best criterion for estimating gangliolytic depressive action was the reduction of functional lability of ganglionic neurons. All gangliolytics further Vvedenski's inhibition following irritation of preganglionic fibers by high-frequency impulses. This decrease in functional lability appears much earlier than the change in amplitude of postganglionic potentials. Obviously, the reaction of ganglionic cells to gangliolytics is not restricted to a decrease of sensitivity to mediators. Research carried out by the same author has shown that gangliolytics not only retard impulse transmission in ganglionic synapses, but actually exert a definite influence upon the subsequent processes, preventing post-tetanic, impulsive after-discharges.

Mitrofanov (22) showed that ephedrin, in contrast with gangliolytics, heightened the lability of ganglionic neurons and shortened the period of hexamethonium- and tetraethylammonium-induced blockade. Vysotskaia (30) studied the influence of gangliolytics upon ganglion metabolism. It was found that hexamethonium, a ganglion-blocking agent acting as a competitive antagonist to acetylcholine, did not lower the level of adenosinetriphosphate and of creatine-phosphate in the cervical ganglion tissues, whereas a depolarizing agent such as nicotine, by blocking the ganglia, caused a fall of adenosinetriphosphate and a rise in inorganic phosphate. For this reason, nicotine-induced blockade is impaired by adenosinetriphosphate, although the same substance exerts no action upon hexamethonium blockade. While studying gangliolytics, Soviet pharmacologists investigated their action not only upon the function of autonomically innervated organs, but also their action upon the tissue metabolism of these organs [Anichkov (3) and Zavodskaya (33)]. It was found that gangliolytics depress protein resynthesis in the gastric and intestinal mucosa, as estimated by the in-

corporation rate of labelled methionine. On the other hand, they bring this resynthetizing process nearly to normal level after depression by reflexes induced by intense irritation. Normalization of trophic processes is considered by Soviet pharmacologists to be the main factor in the preventive and curative effect of gangliolytics in cases of reflex gastric wall distrophy underlying peptic ulcer.

Because plants containing curarine or any previously known curariform alkaloids do not grow in the U.S.S.R., a search for curariform drugs has been a very urgent problem in this country. A systematic study of the alkaloids extracted by the late academician, A. P. Orekhov, led to the discovery in certain species of *Delphinium* of alkaloids with curare-like action (delcimine, elatine, condemarine, mellitine) [Mashkovski (19)]. These are tertiary amines; they are orally active and have been adopted mainly in neurological clinic work for depressing muscular tone. The drug evolved by VNIKhFI under the name of diplacin is synthesized using a natural alkaloid as primary material. It is a dichloride 1,3-di-(β-platineciniumethoxy)-benzene [Mashkovski (19)]. Another Soviet synthetic curariform drug is paramione (diiodide-mezo-3,4-diphenyl-hexane-n,n'-bis-trimethylammonium) brought forth by the Institute of Experimental Medicine [Torf and co-wokers (27)]. Conclusions as to the dependance of curare-like activity of bis-ammonium compounds upon the rigidity of their molecules were reported in 1958 at the Symposium on Curariform Drugs in Venice [Anitchkov & Khromov-Borissov (4)]. The influence of cholinolytics, narcotics, anticholinesterases, and of poisons impairing conjugate phosphorylization, upon the pathological stimulation elicited in neuromuscular synapses by the action of guanidine and other poisons was the subject of an investigation by Karasik (14). The same author (13) availed himself of the so-called "Holden's paradox," apparent in the reaction of hemoglobin with $O_2$ and $CO_2$ for the interpretation of the competitive antagonism existing between acetylcholine and synaptic poisons.

The pharmacology of the cardiovascular system is another province of traditional scientific activity in the Soviet Union. This was the sphere of study of N. P. Kravkov, one of the founders of Russian pharmacology who proposed the isolated rabbit-ear method and studied on a large scale the pharmacology of vessels by perfusing isolated animal and human organs. During recent years, extensive work on cardiac glycosides has been performed by the Kharkov Chemo-Pharmaceutical Institute [Angarskaja and co-workers (1)]. A systematic investigation of various plants has led to the extraction of hitherto unknown cardiac glycosides, such as syretoxin from *Syrena angustifolia* and homphotine from *Homphocarpes fruticosces*. According to their pharmacological properties, these glycosides may be classed with the strophanthine group, although the data obtained by the Kharkov pharmacologists show that homphotine differs from strophanthine in that it is able to dilate coronary vessels. Experimental myocarditis was investigated by Vedeneieva (29), who obtained lesions of the myocardium by

massive doses of epinephrine and norepinephrine, as well as by intense irritation of the ganglion stellatum. Sympatholytics prevent this myocarditis. Extensive work has been devoted to searching for vasodilators, especially coronary vasodilators. Kaverina (15) undertook a systematic study of the influence of drugs upon the lumen of coronary vessels. Most promising among the newly proposed preparations is chloracizine (10,β-diethylaminopropionyl-2-chloro-phenothiazine) a drug evolved by the Pharmacological Institute. Chloracizine increases coronary blood flow, preventing the pituitrin-induced spasm of the vessels. This process is not accompanied by a fall in blood pressure and does not increase the cardiac oxygen consumption. In experimental infarction of the myocardium, chloracizine stimulates the formation of collaterals [Zakusoff (32)]. Kharkov phytochemists and pharmacologists [Angarskaja & Chadjai (2)] have been engaged in the search for vasodilators of plant origin. Preparations obtained from the seeds of the common carrot (diucarine), parsnip (pastivacine), and fennel (anethine) were proposed as such vasodilators. Diucarine and anethine, as compared with other preparations of the same type, have proved to possess low toxicity associated with relatively high spasmolytic activity.

The individual substances extracted from these plants have shown that some furocoumarins and flavones possess coronary vasodilator properties. Experimental therapy of vascular diseases is represented by works on the pharmacotherapy of experimental cholesterol atherosclerosis according to the well-known method of the eminent pathologist, N. N. Anichkov. Among the numerous Soviet works in this field must be noted the investigations of the last few years devoted to the influence upon cholesterolemia and cholesterol aortal atheromatosis of the gangliolytic hexamethonium [Novikova (24)], the spasmolytic dibazol [Kharauzov & Novikova (16)], and the saponines of *Dioscorea* and *Polemonium coeruleum* [Sokolova (26)]. These substances bring about a certain amelioration in the course of cholesterolemia and cholesterol atheromatosis.

The present writer has not been able to mention in such a brief article all the work done by Soviet pharmacologists even in the restricted field reviewed. All he could do was to show, by a few examples, how Soviet Pharmacologists, on a basis of exact data, have endeavored to serve in a practical way the cause of public health.

## LITERATURE CITED


1. Angarskaja, M. A., Besruk, P. M., Hendenstein, E. I., Sokolowa, W. E., and Chadjai, J. I., *Arch. exptl. Pathol. Pharmakol. Naunyn-Schmiedeberg's,* **236,** 236–37 (1959)
2. Angarskaja, M. A., and Chadjai, J. I., *Congr. All-Union Soc. of Physiol., Biochem., Pharmacol., 9th Congr.,* **3,** 217–20 (U.S.S.R. Acad. Sci., Moscow-Minsk, 1959)*
3. Anitchkov, S. V., *Congr. intern. physiol. 20e Congr.,* 29–30 (Brussels, 1956)
4. Anitchkov, S. V., and Khromov-Borissov, N. V., *Atti Congr. Soc. ital. anestesiol. 11th Congr., Simposio intern. curaro, curarosimili, curarizzanti,* 187–97 (Venice, 1958)
5. Anichkov, S. V., and Denissenko, P. P., *Medicina Experimentalis,* **1,** 256–59 (1959)
6. Anichkov, S. V. *Congr. intern. cienc. fisiol., 21st Congr.,* 1–5 (Buenos Aires, 1959)
7. Anichkov, S. V., and Borodkin, Y. S., *Vestnik Akad. Med. Nauk S.S.S.R.,* **1,** 14–19 (1959)*
8. Anitschkov, S. V., and Poskalenko, A. N., *Arch. exptl. Pathol. Pharmakol. Nauyn-Schmiedeberg's,* **236,** 89–91 (1959)
9. Asratian, S. N., *Zhur. Vysshei Nervnoi Deyatel'nosti im. I. P. Pavlova,* **9,** 887–91 (1959)
10. Belenki, M. L., Ghermane, S. K., and Ratenberg, N. S., *Congr. All-Union Soc. of Physiol., Biochem., Pharmocal., 9th Congr.,* **2,** 40–41 (U.S.S.R. Acad. Sci., Moscow-Minsk, 1959)*
11. Denissenko, P. P., *Vestnik Akad. Med. Nauk S.S.S.R.,* **2,** 20–28 (1960)*
12. Dombrovskaia, A. M., Krementoulo, V. A., Simon, I. B., and Tcherkes, A. I., *Congr. All-Union Soc. of Physiol., Biochem., Pharmacol., 9th Congr.,* **2,** 105–6 (U.S.S.R. Acad. Sci., Moscow-Minsk, 1959)*
13. Karasik, V. M., *Progr. in Biochem.,* **3,** 315–41 (U.S.S.R. Acad. Sci., Moscow, 1958)
14. Karasik, V. M., *1958 Year-Book of the Institute of Experimental Medicine,* 197–205 (Medgiz, Leningrad, U.S.S.R., 538 pp., 1959)*
15. Kaverina, N. V. *Congr. All-Union Soc. of Physiol., Biochem., Pharmacol., 9th Congr.,* **3,** 220–24 (U.S.S.R. Acad. Sci., Moscow-Minsk, 1959)*
16. Kharauzov, N. A., and Novikova, N. A., *Symposium on Atherosclerosis,* 24–25 (Leningrad, U.S.S.R., 1959)*
17. Kharkevitch, D. A., *Congr. All-Union Soc. of Physiol., Biochem., Pharmacol., 9th Congr.* **3,** 214–16 (U.S.S.R. Acad. Sci. Moscow-Minsk, 1959)*
18. Malyghina, E. I., In *Selective Action of Drugs upon the CNS,* 32–45 (Medgiz, Leningrad, U.S.S.R. 198 pp., 1958)*
19. Mashkovski, M. D., *Drugs—A Guide for Practitioners,* 132–34; 149–55 (Medgiz, Moscow, U.S.S.R. 811 pp., 1957)*
20. Mikhelson, M. Y., *et al., Physiological Role of Acetylcholine and Search for New Drugs,* 25–33 (1st LMI, Leningrad, U.S.S.R., 462 pp., 1957)*
21. Milstein, T. N., In *Selective Action of Drugs upon the CNS,* 166–83 (Medgiz, Leningrad, U.S.S.R., 198 pp., 1958)*
22. Mitrofanov, A. I., In *Gangliolytics and Blocking Agents of Neuro-Muscular Synapses,* 130–40 (IEM, Leningrad, U.S.S.R., 164 pp., 1958)*
23. Mnjoyan, A. L., *Gangleron and the Experience of Its Clinical Application* (Arm. S.S.R. Acad. Sci., Erevan, 391 pp., 1959)
24. Novikova, N. A., *1958 Year-Book of the Institute of Experimental Medicine,* 410–15 (Medgiz, Leningrad, U.S.S.R., 538 pp., 1959)*
25. Schuster, J., In *Gangliolytics and Blocking Agents of Neuro-Muscular Synapses,* 50–63 (IEM, Leningrad, U.S.S.R., 164 pp., 1958)*
26. Sokolova, L. N., *Farmakol. i Toksikol.,* **22,** 1, 42–48 (1959)
27. Torf, S. F., Khromov-Borissov, N. V., Butaiev, B. M., and Grebenkina, M. A., *Farmakol. i Toksikol.,* **15,** 6, 12–17 (1952)
28. Valdman, A. V., In *New Data on the Pharmacology of the Reticular Formation of the Cerebrum,* 64–74 (1st LMI, Leningrad, U.S.S.R., 272 pp., 1958)*
29. Vedeneieva, Z. I., *Congr. All-Union Soc. of Physiol., Biochem., Pharmacol., 9th Congr.,* **2,** 65 (U.S.S.R.

Acad. Sci., Moscow-Minsk, 1959)*
30. Vysotskaia, N. B., *Farmakol. i Toksikol.*, **20**, 2, 12–15 (1957)
31. Yaroslavski, A. P., In *Selective Action of Drugs upon the CNS*, 184–90 (Medgiz, Leningrad, U.S.S.R., 198 pp., 1958)*
32. Zakusoff, V. V., *Hungarian Conf. on Invest. Drugs and Therapy, 1st Conf.* 73–74 (Budapest, 1960)
33. Zavodskaya, I. S., *Arch. intern. pharmacodynamie*, **97**, 174–84 (1958)
34. Zavodskaya, I. S., *Medicina Experimentalis*, **4** (1960, in press)

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