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I. V. ZAVADSKII AND THE BEGINNINGS OF BEHAVIORAL PHARMACOLOGY: AN HISTORICAL NOTE AND TRANSLATION

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I. V. Zavadskii, who worked in Pavlov's laboratory between 1907 and 1909, performed a study that has many of the characteristics of modern behavioral pharmacology. He studied the effects of alcohol, morphine, cocaine and caffeine on the conditioned salivary reflex. A translation of his paper and some brief comments on his life are presented.

Key words: Zavadskii, behavioral pharmacology, classical conditioning, morphine, alcohol, caffeine, cocaine, conditioned inhibition, salivary conditioning, dogs

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. . . I salute this new method and its introduction in the study of pharmacologic problems. It is precisely because of the lack of a strictly objective method that pharmacologic knowledge in the domain of the central nervous system is still so sketchy.

—N. P. Kravkov (1908)

These words were spoken by a leading Russian pharmacologist during the discussion of a paper delivered to the medical society in St. Petersburg more than 70 years ago (Zavadskii, 1908a). The author of the report was Igor Vladimirovich Zavadskii, who spent the years 1907 through 1909 with Pavlov. He first completed his doctoral dissertation on delayed reflexes (Zavadskii, 1908b). Pavlov then asked him to investigate the behavioral effects of some drugs, using dogs that had been trained for other studies. Although both he and Pavlov regarded the results as only "preliminary," Zavadskii himself did no more with drugs. Pharmacological studies were continued by another student, P. M. Nikiforovskii (1910); a short description in English of this work has been given by Anichkov (1965).

Zavadskii published only one more paper from Pavlov's laboratory, a pioneering investigation of olfaction (Zavadskii, 1909), and then left the field of behavior completely; no other publications by him appear in Kleshchova's comprehensive bibliography of the conditioned reflex literature (Kleshchova, 1955). He became a professor in the Department of Medical Diagnostics at Kazan University in 1913, participated in World War I as a physician, and ended his career as Chief of the Tropical Diseases Clinic in the city of Rostov-on-Don. He died in 1944. A short account of his life and his experiences with Pavlov appears in a recent collection of reminiscences of Pavlov (Zavadskii, 1967).

Is this the first paper in *behavioral* pharmacology?

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REFERENCES

Anichkov, S. V. Pavlov's method of conditioned reflexes in pharmacology. In M. Ya. Mikhel'son and V. G. Longo (Eds.), *Pharmacology of Conditioning, Learning and Retention*. New York: Macmillan, 1965, pp. 17-24.

Kleshchova, N. K. *Bibliography on Conditioned Reflexes, Vol. 1, 1901-1936*. Ed. by E. G. Ayrapetjants. Moscow-Leningrad: Publishing House of the Academy of Sciences, USSR, 1955.

Nikiforovskii, P. M. Pharmacological methods in application to conditioned reflexes. Thesis, St. Petersburg, 1910, 200 pp.

Zavadskii, I. V. An application of the method of conditioned reflexes to pharmacology. Toward the problem of the effects of certain drugs (alcohol, morphine, cocaine, and caffeine) on the function of

the higher regions of the central nervous system. Proceedings of the Russian Medical Society in St. Petersburg, 1908, **75**, 269-287. (a)

Zavadskii, I. V. Inhibition and dis-inhibition of conditioned reflexes. Thesis, St. Petersburg, 1908. 195 pp. (b)

Zavadskii, I. V. Gyrus pyriformis in its relation to the sense of smell in the dog. Proceedings of the Russian Medical Society in St. Petersburg, 1909, **76**, 523-528.

Zavadskii, I. V. I. P. Pavlov in the laboratory. In E. M. Kreps (Ed.), *I. P. Pavlov: Reminiscences by his contemporaries.* Leningrad: Academy of Sciences of the USSR, 1967, pp. 97-100.

AN APPLICATION OF THE METHOD OF CONDITIONED REFLEXES TO PHARMACOLOGY. TOWARD THE PROBLEM OF THE EFFECTS OF CERTAIN DRUGS (ALCOHOL, MORPHINE, COCAINE, AND CAFFEINE) ON THE FUNCTION OF THE HIGHER REGIONS OF THE CENTRAL NERVOUS SYSTEM

By I. V. Zavadskii

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This work, whose results I shall presently have the honor to communicate, is the first attempt to use the methods of conditioned salivary reflexes toward the pharmacology of the higher regions of the central nervous system.

The experiments were carried on exclusively on dogs, of which four were at our disposal.

Conditioned reflexes were established as follows: in the first dog, named Strekoza (Grasshopper), scratching served as conditioned stimulus, while the unconditioned stimulus was the pouring into the mouth of ¼% hydrochloric acid; in the second dog (Gordon), the sound of a whistle was associated with the feeding of meat powder; in the third (Negr), scratching was associated with the feeding of meat powder; in the fourth (Russlan), scratching was associated with the ¼% hydrochloric acid poured into the mouth.

In the first two dogs, the length of the conditioned stimulus was 4 minutes, while the unconditioned stimulus was brought in only on the fourth minute—in the first 3 minutes the conditioned stimulus was thus applied alone. In the other two dogs, the scratching lasted 2 minutes, while the unconditioned stimulus was applied 1 minute after the beginning of scratching.

The third dog (Negr) differed from the others in that it had a so-called conditioned inhibitor. A noiseless rotator made of feathers, a vertuska, served as the conditioned inhibitor. The [unreinforced] combination of the spinning stimulus with the scratching was bringing about a complete inhibition of salivation, while the scratching alone produced about 1 cc of saliva per minute.

In order to make it easier to visualize the characteristics of salivation of these dogs, I give examples:

Strekoza

Date, month, time of beginning of scratching [i.e., the stimulus]	Type of Stimulus	*Magnitude of Conditioned Reflex in drops per ½ minute* — *Parotid Gland*						Remarks
		1st ½ min.	*2nd ½ min.*	*3rd ½ min.*	*4th ½ min.*	*5th ½ min.*	*6th ½ min.*	
4 January								
10:33	Scratching	0	0	0	0	4	4	At 4th minute, HCl poured in
:45	"	1	0	0	1	4	4	"
11:05	"	0	0	0	1	3	9	"
:25	"	0	0	0	1	5	5	"
Gordon								
		Submaxillary Gland						
11 January								
3:39	whistle	0	0	1	3	5	5	At 4th minute, feeding meat powder
:53	"	0	0	0	1	5	5	"
4:12	"	0	0	0	5	4	4	"
:37	"	0	0	0	0	3	5	"

A typical characteristic of the reflexes in these two dogs is the delay of salivation. The conditioned salivation does not begin immediately with the application of the stimulus, but after 1½-2 minutes. This delay of secretion depends on the method of associating the conditioned stimulus with the unconditioned one. In our cases, as stated above, the unconditioned agent is superimposed to the conditioned one 3 minutes after the beginning of the latter. The conditioned salivation represents an advantageous adaptation of the organism, i.e., the secretory reaction occurs only when there is an actual need, in the examples above, at the moment preceding the application of the unconditioned stimulus. Now it can be asked, to what physiologic category of phenomena should belong the delay of the reflex? To this question the laboratory of Professor I. P. Pavlov answers as follows: under the influence of the particular conditions of these tests, the specific action of the initial part of the conditioned stimulus is inhibitory through the process of internal inhibition. All cases of inhibition are called internal when no stimulus other than the conditioned one is present. (Details about the delay of reflexes are presented in my report to the Russian Medical Society of St. Petersburg, 29 November 1907, and in the dissertation "Materials toward the Problem of the Inhibition and the Spread of Inhibition of Conditioned Reflexes," 1908, St. Petersburg.)

The opposite type of inhibition is called "external" inhibition. As an example of the latter we can mention our third dog, in whom the association of a rotating object with scratching brings about a complete stop in salivary secretion. For instance:

NEGR	Magnitude of the conditioned reflex in cc/minute. Submaxillary gland
9 January	
3:23 scratching alone	1.2 cc
:35 scratching and rotating object	0 cc
:40 scratching alone	1.0 cc
4:00 same	0.9 cc
:12 scratching and rotating object	0 cc
:22 scratching alone	0.7 cc

The fourth dog, Russlan, had a reflex comparable to that of the dog Negr, only the unconditioned stimulus was not meat powder but the acid solution, and there was no conditioned inhibitor.

Besides the "artificial" conditioned reflexes, all the dogs presented the so-called natural conditioned reflexes, i.e., reflexes on the sight of meat powder or of the test tube with the acid.

Having acquainted ourselves with the characteristics of the reflexes of all the four dogs, we shall now proceed with the description of the pharmacologic experiments.

We have so far tested four substances out of the abundant domain of pharmacology: alcohol, morphine, caffeine, and cocaine.

Alcohol was instilled into the stomach through a feeding tube; the other substances, subcutaneously.

We have eight experiments with alcohol: five with relatively large doses, and three with small ones. A large dose we consider one from 1.5 to 2.0 cc 96% solution per kg weight; a small one, from .25 to .5 cc for the same weight. For these experiments we used three dogs: Strekoza and Gordon (three experiments each) and Negr (two experiments). Let us first examine the effect of large doses.

In all the five experiments, the results obtained were, with small individual variations, completely analogous.

As soon as 5 minutes after the introduction of alcohol, a complete disappearance was observed, not only of the artificial conditioned reflexes but also of the natural ones. No salivation was obtained from scratching, nor the whistle, nor even from showing the meat powder or the acid. After ½, or 1 hour, the natural conditioned reflexes were reestablished; that is, showing the stimulating substances again acquired the ability to produce salivation. After 2, 3, or 4 hours, depending on the dog, the specific activity of the artificial conditioned stimulus was also restored.

Besides the direct action of the alcohol, we had also the occasion to observe an aftereffect, manifested particularly clearly with delayed reflexes. Out of four experiments (two on Strekoza and two on Gordon) three showed, the day after the instillation of alcohol, a very noticeable intensification of salivation. The number of drops of saliva increased two- to three-fold above the norm. It is quite possible that this phenomenon would have also occurred in the fourth experiment, if this last

Table 1

Scratching for 4 min: 3 min alone, in the 4th combined with the pouring in of the acid solution. When the natural conditioned reflex was tested (showing of the test tube with the acid solution), then the solution was poured 3½ min after the beginning of scratching.

STREKOZA Weight: 1 pood 20 lbs (Russ.) [1 pood = 40 Russ. lbs = 36 lbs avoidupois]

Date, month, time of beginning of scratching	*Magnitude of the conditioned reflex in drops. Recording every ½ min* — *Parotid gland* — *1st ½ min*	*2nd ½ min*	*3rd ½ min*	*4th ½ min*	*5th ½ min*	*6th ½ min*	*Showing of the test tube with the acid*	*Remarks*
15 January							Drops per ½ min	At 11:45 36 cc 96% alcohol in 200 cc water are introduced through a tube into the stomach [1.139 g, i.e., 1.139 g/kg]. Salivation stopped at 11:52. At 11:46 30", the dog began shaking its ears vigorously. The shaking is very frequent: 15 to 20 times per minute.
11:30	1	0	0	2	3	7	—	
11:56	0	0	0	0	0	0	0	Shaking of ears weaker and less frequent.
12:16	0	0	0	0	0	0	2	Shaking of ears ceased.
12:28	0	0	0	0	0	0	—	Dog is standing still.
1:11	0	0	0	0	0	0	10	
1:40	0	0	0	0	0	0	—	
2:21	0	0	0	0	0	0	—	
16 January								
10:17	0	0	2	7	11	12		
10:30	0	0	0	3	10	10		
10:50	0	0	3	12	10	10	Aftereffect	
11:15	0	1	1	2	9	9		
11:30	0	0	0	7	10	13		

one had not been complicated by the illness of the dog (Gordon): the day following the instillation of alcohol, the animal developed a strong diarrhea, which, as it is well known, markedly lowers the magnitude of conditioned salivary reflexes, particularly ones established in association with food substances.

Apart from the increase in salivation, the sequential timing of salivation should also be noted: 1) salivation begins markedly earlier —at the end of the first minute or at the beginning of the second, while normally the first drops of saliva appear almost always at the end of the second or at the beginning of the third minute. 2) Very often the graph of salivation changed markedly and the maximum rise occurred in the second and not the third minute. The impression given by the graph is such as if we were facing a state of asthenia, i.e., increased irritability and rapid fatigue. For examples of the effect of alcohol, see Tables 1 and 2.

Small doses of alcohol produced exactly the same effect as the larger ones, except that with the decreased amount of the drug, the disappearance of the artificial conditioned reflexes lasted a shorter time, while the natural reflexes did not disappear but only diminished. Aftereffects after small dosages have not been observed. We bring as an example Table 3.

Thus, to summarize, alcohol in dosages of .25 to 2.0 cc per kilogram inhibits the activity of the higher sections of the nervous system. A preliminary stage of stimulation of salivation activity has never been observed. The aftereffects after large doses manifest themselves in the disturbance of the functional balance: 1) in the predominance of stimulation over inhibition, and 2) in a state of asthenia.

Table 2

Whistle for 4 min: 3 min alone, during 4th combined with the feeding of meat powder. When the natural conditioned reflex is tested (showing of meat powder), then the powder is given 3½ min after the beginning of the blowing of whistle.

GORDON Weight: 1 pood 8 lbs (Russ.) = 44 lbs avoirdupois

Date, month, time of beginning of whistling	*Magnitude of the conditioned reflex in drops per ½ min* — *Submaxillary gland* — *1st ½ min*	*2nd ½ min*	*3rd ½ min*	*4th ½ min*	*5th ½ min*	*6th ½ min*	*Showing of the meat powder*	*Remarks*
							Drops per ½ min	
29 December 1:53	0	0	1	3	5	5	—	At 2:05 35 cc 96% alcohol in 200 cc water [1.34g/kg] are introduced into the stomach through a tube. Starting at 2:07, continuous and vigorous ear shaking.
2:30	0	0	0	0	0	0	0	Ear shaking continues during the blowing of the whistle. When the meat powder is shown to the dog, the dog looks, but does not move toward it—the ear shaking is less frequent. The meat powder is eaten only during ½ min —then again the ear shaking begins.
2:53	0	0	0	0	0	0	—	Ear shaking weaker and less frequent. Meat powder is eaten during a full min.
3:15	0	0	0	0	0	0	—	During the blowing of the whistle a positive reaction as directed movement of the animal. Shaking of ears stopped. At 3:25 the dog lowers itself on the strap of frame, and hangs without supporting itself on its feet.
3:45	0	0	0	0	0	0	4 drops	During the blowing of the whistle, the dog gets up a few times, but immediately falls back. At showing of meat powder, gets up and moves toward it.
4:25	0	0	0	0	0	0	—	During whistle the dog stands up.
4:50	0	0	0	0	0	3	—	
8:00	1	0	0	2	3	5	—	At 5:00 the dog is taken off the frame, and replaced there at 7:50.
8:15	0	0	0	4	2	3	—	
30 December 2:10	0	0	8	6	5	5		Aftereffect
2:25	0	2	3	8	4	4		
2:45	0	2	8	7	4	4		
3:05	0	0	0	4	4	4		

Table 3

Scratching for 4 minutes: 3 preceding the pouring of the acid, 4th minute during the pouring. If the natural conditioned reflex is to be tested, i.e., the showing of the test tube, then the acid solution is poured not at the beginning of the 4th minute, but ½ minute later, i.e., 3½ minutes from the beginning of scratching.

STREKOZA

Date, month, time of initiation of scratching	*Magnitude of the conditioned reflex in drops per ½ min* — *Parotid gland*						*Showing of the test tube with the acid*	*Remarks*
	1st ½ min	*2nd ½ min*	*3rd ½ min*	*4th ½ min*	*5th ½ min*	*6th ½ min*		
5 January							Drops per ½ min	
10:26	0	0	0	0	3	6	25	
10:40	0	0	0	1	9	12	—	At 10:53, ten cc 96% alcohol in 200 cc water [0.3 g/kg] are introduced through a stomach feeding tube. After the tube is removed the dog licks itself; salivation ceases at 10:58. At 10:55 it begins to shake its ears, 2-3 shakes per min.
11:03	0	0	0	0	0	0	6	Shaking of ears continues, but at long intervals.
11:18	0	1	2	1	0	2		
11:35	0	0	0	1	0	4		At 11:40 the shaking ceases. The dog stands quietly.
11:53	0	0	0	2	11	10		
12:20	0	0	0	0	6	12		

Morphine was used three times, in doses of .01 g of morphium muriaticum, instilled under the skin. All three experiments, with three different dogs (Strekoza, Gordon, and Russlan), gave exactly comparable results. Ten to fifteen minutes after injection, the natural and artificial reflexes disappeared for a very long time. The natural reflexes reestablished themselves after ½ to 1 hour, the artificial ones after 7 to 8 hours. Aftereffects were not observed in two of the experiments and in one were of an indeterminate character: six applications of the conditioned stimulus gave four times a weakened salivation, and twice an increased one, of the asthenic type. I report that experiment in Table 4.

Caffeine has been tested four times (with two experiments each on the dogs Gordon and Strekoza), in doses of .1 g, subcutaneously.

All four injections brought forth an increase in the size of the reflexes. A clear effect was apparent after 10 to 15 minutes following the injection and lasted about an hour. The covert phase of salivation was significantly shortened, but the appearance of the secretory curve did not differ from the norm, i.e., there was a clear increase in secretion at the end of the 3 minutes of action of the conditioned stimulus. Aftereffects from caffeine have never been observed. Thus: Table 5.

We have tested cocaine in the form of hydrochloric salt in doses of about one-fourth of a grain: we have eight experiments with cocaine (two on Strekoza and three each on Gordon and Negr).

The effect of cocaine on conditioned salivation was grossly similar to that of caffeine but significantly less constant. Each dog reacted to cocaine in his own peculiar way. In Strekoza, cocaine brought out effects completely analogous to those of caffeine, and we are not, therefore, reporting them. In Gor-

Table 4

GORDON

Date, month, time of initiation of whistle	Magnitude of the conditioned reflex in drops per ½ min: Submaxillary gland 1st ½ min	2nd ½ min	3rd ½ min	4th ½ min	5th ½ min	6th ½ min	Meat powder shaken for 30 sec	Remarks
4 January							Drops per ½ min	
2:55	0	0	0	1	3	6		At 3:07 a solution of morphine hydrochloride is injected subcutaneously (0.01 g) [0.5 mg/kg]. Beginning at 3:10, licking and salivation. At 3:17 the dog vomits. At 3:23 the licking and salivation cease.
3:26	0	0	0	0	0	0	0	The dog stands quietly. The dog pulls toward the meat powder. Eats lazily, but does not refuse it. There is no positive movement at the sound of whistle.
3:46	0	0	0	0	0	0	3	The dog hangs on the straps but does not sleep. No positive reaction at whistle.
4:20	0	0	0	0	0	0	—	same
4:50	0	0	0	0	0	0	—	same
5:26	0	0	0	0	0	0	2	Movement toward meat powder extremely weak. The dog is freed from the frame, and replaced at 7:40.
7:46	0	0	0	0	0	0	—	The dog stands in a fairly alert fashion, but there is no positive movement toward meat powder at whistle.
8:10	0	0	0	0	0	0		
5 January								
1:18	0	0	0	0	3	3		
1:43	0	0	0	0	2	2		
1:58	0	0	3	4	3	2	Aftereffect	
2:17	0	0	10	10	5	2		
2:40	0	0	0	0	0	3		
2:55	0	0	0	0	0	1		

don, immediately after injection, an inhibition of secretion for from 20 to 50 minutes was observed. Its duration was a function of the dose (in this dog, we have used dosages from .008 g to .016 g). After the inhibition, there always followed a rise lasting about 1 to 1½ hours. An example follows (Table 6).

The third dog, Negr, is interesting in that in it one could observe the effect of cocaine on the manifestations of external inhibition.

After the injection of cocaine, the conditioned inhibitor lost significantly in strength

as to its effects: the association of the rotator stimulation to the scratching was no longer producing complete inhibition of salivation.

NEGR	Submaxillary gland cc per minute
20 January	
2:18 scratching alone	0.5 cc
:30 scratching and rotating object	0 cc
:37 scratching alone	0.7 cc
2:46 0.016 g cocaini muriatice subcutaneously	
:55 scratching alone	2.2 cc
3:05 scratching and rotating object	0.5 cc
:11 scratching alone	1.3 cc

All the above indicate that conditioned salivation can be used as an excellent indicator of pharmacologic effects of various drugs on the higher sections of the nervous system.

In conclusion, I wish to mention the effects of the pharmacologic substances used above on unconditioned reflexes and to touch on the motor reactions of the dogs. In certain of my experiments, a complete reversal could be observed between the sharp reaction of the salivary glands and minimal, hardly noticeable changes in the movements of the animal.

The unconditioned reflex was measured in two dogs only, Negr and Russlan. Within the

Table 5

STREKOZA

Date, month, time of initiation of scratching	*Magnitude of the conditioned reflex in drops per ½ min* — *Parotid gland*						*Remarks*
	1st ½ min	*2nd ½ min*	*3rd ½ min*	*4th ½ min*	*5th ½ min*	*6th ½ min*	
20 January							
10:43	0	0	0	0	3	5	At 10:50 subcutaneous injection of 0.1 g caffeini puri [4.1 mg/kg]. During the period of the experiment it was not possible to observe any change in the dog's position, or movement.
10:55	0	0	0	1	4	13	
11:12	0	1	3	5	10	13	
11:35	0	1	3	2	4	10	
12:00	0	0	0	0	2	7	

Table 6

GORDON

Date, month, time of initiation of whistling	*Magnitude of the conditioned reflex in drops per ½ min* — *Submaxillary gland*						*Remarks*
	1st ½ min	*2nd ½ min*	*3rd ½ min*	*4th ½ min*	*5th ½ min*	*6th ½ min*	
25 January							
1:55	0	0	0	0	1	3	At 2:19, 0.016 g cocaini muriatic [0.8 mg/Kg] cocaine hydrochloride injected subcutaneously.
2:10	0	0	0	0	0	4	
2:30	0	0	0	0	0	2	No positive motor reaction The dog lowered himself with his hind legs on the straps, drooping his head.
2:50	0	0	0	0	1	2	At the beginning of the 3rd min of the whistle, the dog lifts himself and looks in the direction from where the meat powder is given.
3:10	0	0	0	1	2	2	The dog is on its feet all the time the whistle is on. Positive motor reaction.
3:33	0	2	2	2	6	5	same
3:47	0	0	1	3	4	3	same
4:05	0	1	1	2	3	4	same

limits of the doses used, I could not observe any particular changes in it.

With regard to the behavior, or, perhaps better, the motor reactions of the dogs, I can say that in many cases I could find no variations from the norm. In particular I observed the following: under the effect of large doses of alcohol, an increase in motor activity occurred as a rule in all dogs, manifesting itself in the shaking of head and ears. These shakings began 2 to 3 minutes after the introduction of alcohol and lasted, depending on the dose and the individuality of the dog, from ¼ to 2 hours. Following the stimulation there usually followed, 1½ to 2 hours later, a weakening of muscular strength, the dog hung on the straps, and, taken off the frame, quickly assumed a prone position.

The injection of morphine, in two experiments out of the total of three, produced vomiting, while there were no other effects on motor stimulation. In all three cases, there was a muscular weakening and a tendency in the dogs to assume the prone position.

The effect of caffeine, so sharply and clearly acting on the conditioned activity of the salivary glands, did not manifest itself with any visible effects on the motile system.

Cocaine produced a different effect on each of the dogs.

In Strekoza, no divergence from the norm ever showed itself. Immediately after the injection, Gordon drooped his head down and hung on the straps; later there occurred a light stimulation expressed as continuous movements on the frame and frequent glances toward the place where the meat powder was kept.

Negr presented a similar stimulation, only in a sharper form, which occurred shortly after the injection of cocaine, but without a preliminary motor inhibition.

[*The paper was followed by an abstract in German that serves well as a summary.*]

The reporter has initiated the application of the method of conditioned salivary reflexes to the investigation of the effect of alcohol, morphine, cocaine, and caffeine on the functions of the higher parts of the central nervous system. Four dogs served as experimental subjects. The first had a conditioned reflex built toward scratching, established with the help of a solution of hydrochloric acid poured into the animal's mouth; in the second dog, a conditioned reflex was established to the sound of a whistle, which was produced simultaneously with his being fed meat powder; in both animals, there occurred a "retardation" of about 3 minutes. In the other dogs, the conditioned reflexes established were the usual ones: scratching reinforced with the simultaneous feeding of powdered meat in one case and scratching combined with the pouring of HCl solution into the mouth in the other. Besides that, the next to the last animal had a conditioned inhibition from the visual area present.

The reporter comes to the following conclusions:

In doses of .25 g to 2.0 g per kg weight, alcohol inhibits the activity of the higher parts of the central nervous system: this manifests itself in the disappearance not only of the artificial but also of the natural conditioned reflexes. A preliminary state of excitation was never observed. Effects of large doses of alcohol manifest themselves in the predominance of the excitation activities, and a state of asthenia. Under the effect of morphine (.01 g of morphium muriaticum, subcutaneously), both the artificial and the natural conditioned reflexes disappear for a shorter or longer period. The introduction of caffeini puri (.1 g under the skin) brought in all the experiments a strengthening of artificial conditioned reflexes. An aftereffect of caffeine could not be observed. The effect of cocaine was similar to that of caffeine, only was not so constant. Finally, the writer observed that in certain cases (e.g., with caffeine), a complete reversal between the strong reaction of the salivary glands, and the barely perceptible change in the movements of the animal could be noticed; that is, the conditioned salivary reflexes are a very sensitive indicator of those changes which are elicited through the action of this or that drug on the central nervous system.

[*There then followed a transcription of the discussion of the work.*]

I. P. Pavlov. Before beginning the discussion of the report, I have to say that these experiments have to be considered as only pre-

liminary. We had on our hands some magnificent dogs from the experimental point of view, giving clear, one could say stereotypic reflexes. The thought came to use them in testing certain pharmacologic substances. Since transferring these animals into other hands would have determined a set of new conditions, I asked the distinguished reporter to make these observations. His experiments constitute an initial exploration; therefore, it is clear that there can be no question of any definitive conclusions. After these explanations, I beg you to express yourselves in regards to the report just read.

I. Ia. Perelzweig. I would like to ask why you use the term "internal inhibition."

I. V. Zavadskii. In opposition to external inhibition, where extraneous external [stimuli] come into play.

N. P. Kravkov. I am interested to learn that the conditioned reflexes do not seem to weaken; neither caffeine nor alcohol seem to affect them?

I. V. Savadskii. In the doses used by us, they are not affected.

N. P. Kravkov. In regards to your work, I salute this new method and its introduction in the study of pharmacologic problems. It is precisely because of the lack of a strictly objective method that pharmacological knowledge in the domain of the central nervous system is still so sketchy. We know about stimulation and about paralysis, but any closer characterization of these phenomena is lacking. In our view alcohol, morphine, and caffeine all stimulate the central nervous system, but we have no objective criteria of this. The method introduced now does offer an objective approach; therefore, we salute it. Of course, we do look on your results as preliminary. I also think that, in making the analysis, we must distinguish between conditioned reflex changes and the other actions a drug has after complete absorption.

I. V. Zavadskii. We had, of course, foreseen this problem, and were using the weak solutions with these considerations in mind.

R. A. Grekker. What were the control experiments preceding and following your observation?

I. V. Zavadskii. The control consisted in establishing immediately before the experiment that the conditioned reflex was still present. With this objective, first we produced the stimulus and then the drug was introduced. Further controls, following the experiment, were not carried out because the drug was circulating in the organism and we had no means to know when it was eliminated. In essence, all the previous observations constituted a control in regards to the experiment, but a comparison of figures could only be made with those obtained the same day. Two different days cannot be compared, but in the limits of one day the figures obtained were very close.

I. P. Pavlov. I have to point out first the extreme sensitivity of this method, and from this stems its importance for pharmacologic studies. Using minute doses of various drugs, we obtained no observable deviations in the motor activity of the animal. The animals appeared completely normal, and nevertheless the method of conditioned reflexes showed a sharp change: for instance, the disappearance of the conditioned reflex. This study makes possible a deeper characterization of the effect of a drug on the central nervous system, as it solves the problem of how to interpret, in each given case, the nature of the stimulation; if it is stimulation in its proper sense, or whether it is a defect in function, a weakening of the action of inhibitory centers. The question was resolved simply. We tried to give the smallest doses of alcohol, and never obtained a stimulating effect. This has to be understood in the sense that, from the beginning, the effect of alcohol is a paralyzing one and not a stimulating one.