Recent Work of Pawlow and His Pupils

CONDITIONED REFLEXES; SYMPATHETIC NERVOUS SYSTEM (ORBELI); EPILEPSY AND CEREBROSPINAL FLUID (SPERANSKY)

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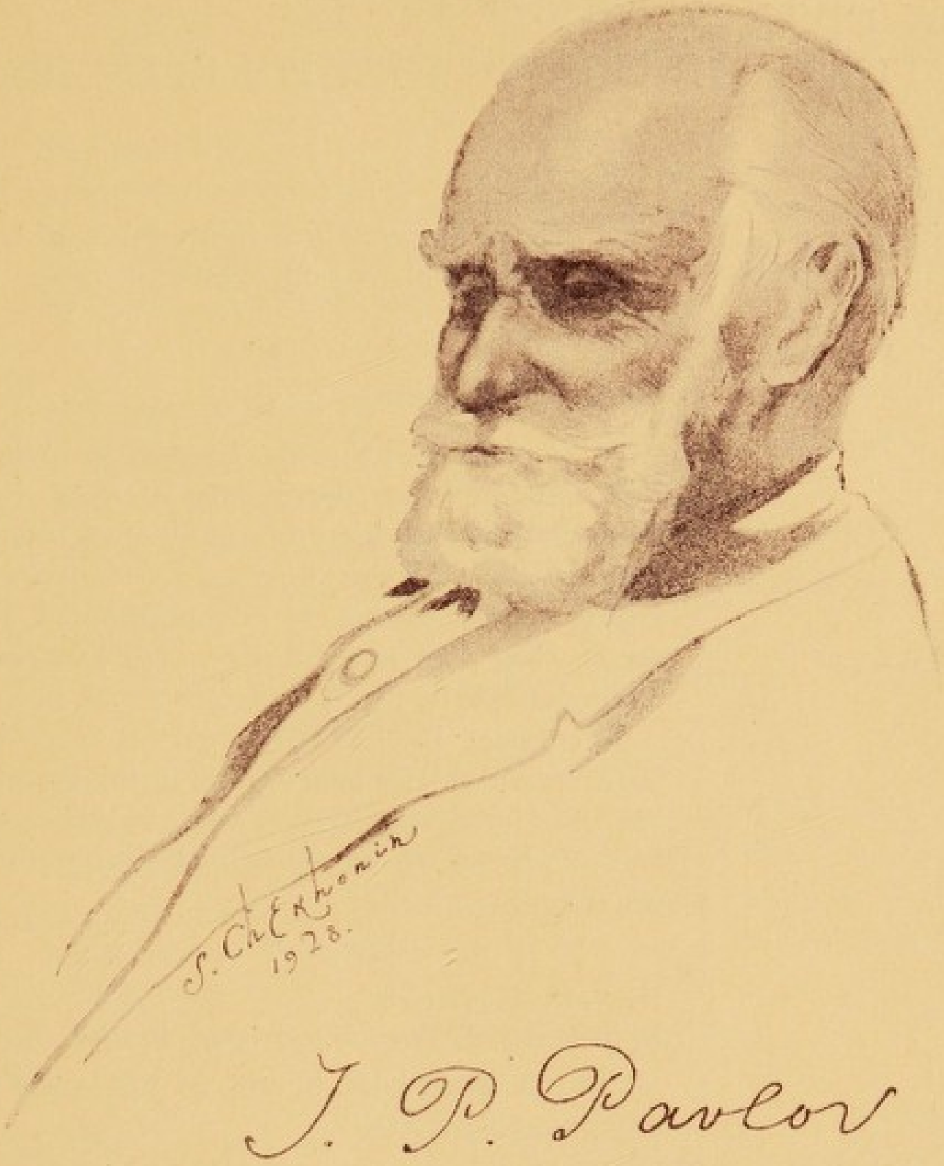

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CONTENTS OF
"LECTURES ON CONDITIONED REFLEXES"

[OVER]

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W. HORSLEY GANTT, M.D.
LENINGRAD, RUSSIA

The following is a sketch of the work of Professor Pawlow on conditioned reflexes, of Orbeli on the sympathetic nervous system, and of the new work of Speransky on pathology of the brain.

As Pawlow's two books [1] are soon to appear in English, what I have to say about his work is in no way intended as a comprehensive review. On the other hand, I desire to call attention to Pawlow's achievements in this field—so long obscure; perhaps the personal experience of one who is not a specialist in this question, but who has learned the Pawlow method first hand may help to clarify this intricate subject. Let it be said at the outset that, although it is easy to grasp the principles on which the work of conditioned reflexes has been built and to understand a simple experiment, the comprehension of the whole subject is extremely difficult. I am in agreement with the opinion in the Pawlow laboratories after two years of work there—that besides Pawlow, there are few, if any, even his own pupils, who are capable of giving a complete exposition of the work in all its ramifications. The longer one is acquainted with Pawlow and his work, the greater becomes one's conviction that it is he who has been entirely responsible for its success.

CONDITIONED REFLEXES

Pawlow, who considers all acts as reflex, distinguishes between two kinds: the simple physiologic reflex, inborn and unalterable, and the more complicated reactions, usually called psychic, which are acquired and formed only under certain conditions. The former are his unconditioned, the latter his conditioned reflexes.

Seeing the psychic flow of saliva, Pawlow was not satisfied to explain this in the vague and meaningless terminology of psychology but sought a method of measuring this psychic activity. For this purpose he felt that the salivary glands were admirably adapted to his new work; [2] they

1. These books deal with work on the brain by the method of conditioned reflexes. They are now in the course of publication in the English language. The first, "Conditioned Reflexes," will be published by the International Publishing Company, New York; and the other, "Activity of the Cerebral Hemispheres," translated by Dr. G. V. Anrep, will be published by the Oxford University Press.

2. Anrep, G. V.: Proc. Roy. Soc. London, *B*, **94**:405, 1923.

are closely connected with the unconditioned food reflex, and the food reflex can be connected by coincidence with a large number of diverse stimuli, such as the ringing of a bell, the sight of a lamp, irritation of the skin or application of cold. After a number of associations, these conditioned stimuli come to produce a flow of saliva even without the presence of the original unconditioned stimulus (food). Thus the flow of saliva resulting from the sound of a bell alone, because it formerly accompanied feeding, is a conditioned reflex in contradistinction to the inborn (unconditioned) reflex.

METHOD

It was Pawlow's next idea to measure these processes set up by the various stimuli—taste of food (unconditioned), or bell, light, odor, touch (conditioned) stimulus, with which the unconditioned reflex had been connected by association. To do this he devised a method of making a salivary fistula so that the fall of each drop of saliva could be recorded, and he chose the dog for this work, "the faithful companion of man for ages," as he says. With the aid of Hannecke, he has worked out a delicate apparatus for carrying on these experiments. Doubtless their success is the result, largely, of the mechanical perfection of the apparatus. His new laboratory is devised so as to eliminate every external stimulus from the dog except that given by the experimenter. The building is surrounded by a moat several feet deep, filled with sawdust to prevent vibrations from the street. Furthermore, the arrangement of the working chamber isolates the operator and dog from the outside world and from one another. The eight working rooms are widely separated, occupying only the corners of the building, and the upper rooms are separated from the lower by an intervening story. The walls of the eight chambers are 2 feet thick, and admission is through double iron doors, padded with rubber, like those of a large bank vault. The operator sits in an outer room. Within this outer room is the dog's cell, which also has double walls and concrete doors, 8 inches thick, rubber padded and with large iron bars. The dog's cell consists of two concrete shells, the walls of each being 8 inches thick. The inner concrete shell is separated from the outer by a 6 inch air jacket and is in contact nowhere with the outer shell, being suspended from the roof of the other shell by a huge iron hook. When the doors are closed, the dog on its stand is completely isolated from the vibrations, sights and sounds of the outside world. The experimenter sits at a table on the outside of the dog's cell, facing an electric switchboard, by which he may, by pressing a button, give the dog any desired conditioning stimulus—a skin irritation, a light, a metronome, a whistle or an application of cold. He may also feed the dog (unconditioned stimulus). The response of the dog is measured through the flow of saliva from its parotid fistula, to which is attached a reservoir communicating with a manometer on the outside of the cell in front of the operator, capable of registering one-tenth drop. The manometer may be connected further with a recording drum on which is written the number of drops in tenths.[3] The operator may observe the dog through a periscope.

Such complete isolation is useful in those experiments in which the dog has to discriminate between delicate sounds, etc., but for many experiments one can use an ordinary room for the dog with the operator seated outside at the electric board and manometer.

Although Pawlow uses the food reflex as the unconditioned reflex in most experiments, a movement reflex may be used, such as the withdrawing of a paw when electrically shocked. Of course, the conditioned stimulus may be the same in both cases. If the conditioned stimulus is the metronome of 120 beats, when this metronome starts the dog will either secrete saliva or howl and jerk up its foot, depending on whether this stimulus has been connected with the food or the motor reflex.

In order to form the conditioned reflex, the conditioned stimulus must be associated with the unconditioned stimulus a certain number of times (twenty or more, depending on the dog and other conditions). Pawlow has found that the conditioned stimulus must always precede the unconditioned. For example, if the metronome follows the food by five seconds instead of preceding it, the metronome does not develop the power of producing a flow of saliva. This is probably because the brain process, excited by eating, is strong enough to keep out stimuli from the receptor organs.

The metronome, or other stimulus that has always been associated with food, becomes a positive stimulus, although when first used it was an indifferent one. Another metronome, e. g., 150 beats, when first used in a dog with a conditioned reflex on a metronome of 120 beats, also produces a flow of saliva, because of the common qualities of the stimulus. However, if this metronome 150 is repeatedly used without food, the dog comes to differentiate between the two. Metronome 150 becomes a negative conditioned stimulus; it calls forth in the dog having a positive conditioned reflex on metronome 120 an active inhibition. The closer the rates of the two metronomes, the greater the inhibition necessary to prevent flow of saliva on the negative metronome.

Instead of using metronomes, two points on the skin may be irritated, one for the positive and the other for the negative conditioned stimulus; or two lights differing in intensity, color,[4] position, etc., or heat and cold, odors (camphor and tincture of valerian), or different chords on a

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3. Details of this apparatus are described by Anrep, G. V.: J. Physiol. **53**:367 (May) 1920.

4. The differentiation of color has not been obtained in all cases, and Pawlow thinks there may be color blindness among dogs.

pipe organ may be used. With the negative stimulus, there may be a slight response because inhibition is not complete.

Some of the theories worked out by Pawlow need new terms, such as: "analyzer, inhibition, irradiation, delayed reflex, trace reflex, chain reflex, induction in the brain."

Analyzer is the term given by Pawlow to include not only the receiving sense organ, but its brain connections, whereby it can discriminate between unimportant and important stimuli. Thus there is the eye analyzer, the skin analyzer, the ear analyzer, etc.

Inhibition may be internal or external;[5] it may be local or spread over the whole brain, resulting in sleep. This occurs in dogs when the same stimulus is repeated too often without alternating it with other stimuli, so that a given analyzer becomes fatigued, or when the stimulus is too intense or disagreeable (often in skin irritations). If a positive conditioned stimulus, i. e., one which always has been followed by feeding, is given and feeding withheld for more than thirty seconds, the conditioned reflex is delayed; inhibition occurs during this interval and prevents a flow of saliva, but if some indifferent stimulus is given during this interval, the inhibition is inhibited, the brake is lifted, and saliva begins to flow. If the feeding does not follow for some minutes after the end of the conditioned stimulus (e. g., four minutes), the conditioned reflex—the flow of saliva—is delayed for three minutes; it becomes a trace reflex, as the flow of saliva now comes on the trace or memory of the conditioned stimulus. Conditioned reflexes have also been formed on time intervals.

Induction is used in relation to conditioned reflexes in somewhat the same sense as Sherrington's spinal induction. This subject has been elucidated by Foorsikov in Pawlow's laboratory. The following example will illustrate: A dog that has a positive conditioned reflex on metronome 120 gives five drops of saliva in ten seconds on this conditioned stimulus. If a few minutes before trying this conditioned stimulus one uses a negative conditioned stimulus and a few seconds later tries metronome 120, the positive conditioned reflex is greater, e. g., seven drops, because it follows the negative stimulus. Vice versa, a negative conditioned stimulus has a stronger inhibiting effect when it has been just preceded by a positive conditioned stimulus.

Reflexes of higher orders have been worked out as follows (Foorsikov): In a dog a positive conditioned reflex is formed on a light, food being used as the unconditioned stimulus. Several times a day the light is turned on, and at the same time a whistle is blown, and this combination is not supported by feeding. Soon the whistle acquires the character of the positive conditioned stimulus because of

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5. These facts are dealt with briefly here because they are recorded in the paper by Walshe.

its association with the positive light; i. e., the whistle sounded alone produces a flow of saliva, although the whistle has never been followed by feeding. The whistle is called the reflex of the second order.

By the use of a defense reflex, the work has been carried a step further. An electric current (unconditioned stimulus) is passed through the foot of the dog; it howls and draws up its foot (unconditioned reflex). The current is then preceded by a skin irritator (conditioned stimulus) and, after some repetitions, the conditioned stimulus alone produces the howling and movement of the foot (conditioned reflex). Now the skin irritation is combined several times daily with the sound of bubbling air through water, but without the electric current. Soon the bubbling sound alone acquires the character of a positive conditioned stimulus, i. e., it evokes the howling and the movement of the dog's foot, though it has never been combined itself with the electric current. This is a reflex of the second order. Now the bubbling is repeated simultaneously with a whistle for several days. Soon the whistle acquires the property of the conditioned stimulus; it causes the dog to howl and draw up its foot. It is a conditioned reflex of the third order. Higher orders have not been formed.

Inhibitory conditioned reflexes of higher orders have been formed in a similar manner; i. e., by associating an indifferent stimulus with a negative conditioned stimulus. The indifferent stimulus takes on the quality of the negative conditioned stimulus. This leads to the deduction that inhibition and stimulation are different sides of the same process. Of great interest is the work indicating that the brain functions as a mosaic of inhibition and excitation points.[6] Seriatsky formed a series of positive conditioned reflexes with tones of a pipe organ, alternating with a series of negative conditioned reflexes, i. e., a positive conditioned reflex on the note C 512 (followed by food), a negative conditioned reflex on the note three tones lower and three tones higher (not followed by food), and another positive conditioned reflex three tones higher than this, until the whole keyboard of five octaves was used up. This is a rhythmic mosaic, as the excitation and inhibition points are equidistant. In a second dog a positive and a negative conditioned reflex were formed at unequal distances on the keyboard, i. e., a positive on 363 vibrations and a negative one note lower, another positive two notes lower, another negative one and one-half notes lower, etc. This is an arrythmic mosaic. It was much more difficult to form and was often followed by neurasthenic symptoms in the dog.

A year after forming six excitation and six inhibition points at regular intervals, the effect of those tones lying beyond the limits, i. e., higher and lower than the original twelve notes, was tried. It was

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6. This work was performed by one of Pawlow's younger pupils, V. V. Seriatsky, who died in April, 1926.

found that these notes were preformed positive or negative points, following the same regular rhythm as the original notes; that is, they produced a flow of saliva (though they had never been accompanied by food) or they produced inhibition, depending on their position on the scale.

What is the nature of the tones lying between the positive and the negative notes? It was found that their nature depended on their position—those on either side of the positive were also positive, and those adjacent to the negative were also negative. According to Seriatsky, "Thus excitation and inhibition zones were formed in the cortex, and the territory of each of these spread to the extent of six semi-tones." After six months the inhibition zones had encroached on the excitation zones, so that each occupied twelve semitones instead of six. At the end of a year, the inhibition fields had become indifferent.

An interesting effect was noted by frequent successive repetitions of positive conditioned stimuli, not interrupted by other stimuli: the dog became irritable and excited. On the other hand, if only negative conditioned stimuli were used, the dog became sleepy, and after several repetitions, folded its paws and fell asleep.

Seriatsky said:

> The cortex of the large hemispheres as regards its functional powers must present an example of an exceptionally delicate and variegated mosaic, enormous in its dimensions and complexity. This mosaic consists of various excitation, inhibition and indifferent points which are closely interlayed with one another, and possess the quality of slowly concentrating during life. The ultimate aim of the brain is to break up the previously irradiated processes into a series of excitation and inhibition partitions. We do not consider this mosaic as constant, motionless and fixed. On the contrary, we believe that it undergoes a constant change depending on the surroundings, etc.

NEURASTHENIA

The production and treatment of neurasthenia in dogs has recently been studied in Pawlow's laboratory by Seriatsky, Federoff and Petrova. The symptoms were produced by repeating too often, without intervals for rest, a conditioned stimulus, or by presenting a problem of too difficult differentiation. For example, if the dog is given metronome 100 as a positive conditioned stimulus (followed by food) and metronome 110 as a negative conditioned stimulus (not followed by food), the intervening beats, e. g., metronome 104, being close to metronome 100, will require much inhibition from the dog to prevent a flow of saliva. As Dr. Volborth explained to me, when metronome 100 is followed by metronome 104 (while inhibition has not had time to disappear), there is a collision between the positive and negative processes, which results in an abnormal state, giving symptoms similar to neurasthenia. These dogs whine, refuse to eat, show a disinclination for their daily work, etc. Such dogs recovered with rest and rectal injection of potassium bromide given just before the experiments. Whether the symptoms will tend toward sleep and depression or excitation depends on the type of dog. Normally, these processes of excitation and inhibition are in equilibrium. Induction prevents spreading of a single process, because around an area of excitation is a zone of inhibition which walls in the excitation process and prevents its spreading.

EFFECTS OF REMOVAL OF THE BRAIN

The removal of the frontal half of the cortex appeared more injurious than the removal of the posterior half. Animals with the whole cortex removed fare better, probably because the spinal reflexes are free to act. In partial extirpation of different regions of the brain, there may be partial compensation by the remaining parts. When the cortex of a cerebral hemisphere is removed, it is impossible to form the defensive conditioned reflex. In such an animal a strong electric current applied to the foot caused only a chaotic defensive reflex, beginning on the sound side and extending to the other. A conditioned reflex did not form after 250 combinations of the conditioned stimulus with the electric current.

CONDITIONED REFLEXES IN OTHER ANIMALS

Conditioned reflexes have been formed not only in dogs but in such diverse animals as fish, mice, puppies and children by Pawlow's method. A tank of water enclosed in a cabinet is used for work with fish. Inside this cabinet are red and green electric lights, a metronome, etc. The unconditioned reflex is the motor response to an electric current sent through the clamp holding the fish. The conditioned stimulus may be light, metronome, etc. A red light may be used for a positive conditioned stimulus (given before the electric current) and a green light for a negative conditioned stimulus (not followed by a current). After a large number of trials, the fish jumps (conditioned reflex) when it sees the red light (conditioned stimulus), but not the green. The motor response of the fish is recorded on a drum outside the cabinet.

The apparatus for forming conditioned reflexes in mice is ingenious and was perfected by Hannicke. When a given bell sounds, the mice run to a certain place to get food, and in going there they have to cross a platform attached to springs. When they step on this platform, the movement is registered on a revolving drum. A revision of the former work on the inheritance of conditioned reflexes is being carried out with this entirely new apparatus. A clock arrangement makes twenty electric contacts during the night. These ring a bell, and a few moments later open a valve which allows grain to drop into a certain room of each cage. When the bell rings, one sees the general migration of the mice into the "dining room." The mice are never fed without the bell.

Males and females are kept in separate cages so that the number of oncoming generations can be carefully regulated. When an experiment is to be made, the mice are removed to a special cage in which the results can be registered automatically.

WORK OF KRASNOGORSKI ON CHILDREN

The work of Krasnogorski in the Children's Clinic of the Medical Institute (Filatov Hospital) deserves mention here. Krasnogorski is one of Pawlow's older pupils and Pawlow confers with him frequently. He published his first work on conditioned reflexes in children in 1907.[7] He has twelve physicians working under him on the subject, and three well equipped rooms for the study of conditioned reflexes in children. He has received money from the Soviet government for three additional rooms.[8]

Children develop conditioned reflexes much more quickly than the dog—from ten to twenty-five trials compared to the dog's thirty to 100; they retain them much longer and more strongly than the dog without intervening practice; they can be destroyed more quickly in the child, e. g., when a positive conditioned stimulus is repeated several times without being supported by food.

Krasnogorski uses children aged from 1 to 5 years. He has found it impossible to develop conditioned reflexes in infants less than 2 weeks old. In children under 1 year, the mechanical irritation of the skin is not specific. The skin analyzer begins to function at about 3 months. At the age of 7 months, the child differentiates between red and white light and at 8 months between odors of camphor and cologne. The movement analyzer appears at 6 months of age.

Krasnogorski has shown the clinical importance of conditioned reflexes; abnormalities indicate a disturbance in the balance between inhibition and stimulation. His work gives a rational basis for classification and treatment of neuroses. He suggests its use also as the basis for child education. In 1925, he told me that he had found by his method of conditioned reflexes that an idiot child in his clinic had a brain on the level of a fish; i. e., it was as slow as the fish in forming conditioned reflexes. In myxedema, epilepsy and neuroses, internal inhibition develops in the child. Imbeciles developed conditioned reflexes with difficulty, but some neurotic children develop them more quickly and lose them more quickly than a normal child. Leonov, in Krasnogorski's laboratory, found in rachitic children that the movement, taste and smell analyzers are disturbed; orientation and adaptation

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7. Krasnogorski, N. I.: Russk. Vrach, no. 36,907, 1907.

8. Kroll, M.: Jahresb. d. ges. Neurol., 1922; Krasnogorski, N. I.: Rev. de méd. **40**:294 (May) 1923; Der Schlaf und die Hemmung, Monatschr. f. Kinderh. **25**:372 (March) 1923.

are weak; motor reflexes are slowly formed, but when once formed disappear slowly.[9]

COMMENT

The actual work on conditioned reflexes is not nearly so simple as it would seem from the description. The dogs, as a rule, are easy to work with, and remain quiet during the experiment; they seem to enjoy the work (except when it is extremely difficult), and run and jump on their stands with as much zest as they might show during a rabbit hunt.

As an illustration of some of the pitfalls, I shall describe what happened in one of my dogs. A dog that had never been worked with before was assigned to me. Before I could begin working out a problem, it was first necessary to form some conditioned reflexes in the dog. For this purpose, I was to work one hour daily with the dog for five or six days in the week. The dog was quiet, stood well in its harness, and did not object to having the glass reservoir fastened (with a modified sealing wax) over the opening of its salivary fistula. The first conditioned stimulus I used was a metronome of 120 beats. After from five to thirty seconds, I followed the metronome with food. The interval between the conditioned stimuli (metronome) was from five to fifteen minutes. The dog was clever, and after thirty trials began to secrete saliva on hearing the metronome. Then I used a whistle and later a skin irritator as conditioned stimuli. The latter, I noticed, was the weakest. It took much longer before it developed the power of producing a secretion of saliva and seemed to divert the dog's attention, although it was not in the least painful. In order to strengthen this effect, as I thought, I employed it more frequently than the others. In a week, however, this led to disastrous results. Being used too often, the skin irritator became a negative conditioned stimulus instead of positive as I desired, setting up inhibition instead of stimulation, because the skin analyzer became fatigued. The skin analyzer, as I did not know then, is more easily fatigued than the ear or eye analyzer. After the skin irritator was used, the dog, instead of secreting saliva, became apathetic and drowsy and frequently would not eat until I entered the room and gave it food from my hand, thus arousing it from its state of inhibition. After several months' work this animal had to be rejected entirely. As Dr. Volborth expressed it to me, "The difficulty of the problem is not in the mechanical work, but in maintaining a proper equilibrium between inhibition and excitation in the brain. For this, very careful judgment, experience, and extreme vigilance are necessary in every experiment."

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9. For further description of conditioned reflexes in neurotic children, see Krasnogorski, N. I.: Conditioned Reflexes and Children's Neuroses, Am. J. Dis. Child. **30**:753 (Dec.) 1925.

WORK OF ORBELI ON THE SYMPATHETIC NERVOUS SYSTEM

Much work has been done recently in the laboratory of Orbeli on the function of the sympathetic nervous system. This has been mentioned in Stanley Cobb's review on the tonus of skeletal muscle,[10] and also in the *British Medical Journal.* Since Cobb's review, more work has appeared, an account of which I give here. I am grateful to Professor Orbeli for giving me permission to include his unpublished work, and for having read over the description that I submit here.

The influence of the sympathetic nervous system on spinal reflexes in the frog has also been studied. The spinal cord was cut in the occiptal foramen, and the brain was destroyed. The aorta was tied at the junction of the arches. The sympathetic trunk on one side was taken on a ligature and cut through at the level of the fifth to sixth ganglia so that the peripheral end could be stimulated. The rami communicantes to all the upper nerves were cut, leaving the sympathetic on the ligature in connection only with the plexus lumbalis through the rami communicantes of the eighth, ninth and tenth spinal nerves. On the other side, all the rami communicantes were sectioned.

The experiment was performed an hour later. The reflex irritability of the spinal cord was tried every five minutes, according to the method of Turk (i. e., both hind feet were dipped in a 1 per cent solution of sulphuric acid and then rinsed with water). The reaction time—the time between dipping the feet in the acid and their withdrawal—was reckoned with a metronome. After the reflex had been tried several times in this manner, the sympathetic trunk on the ligature was stimulated (four minutes after the last trial), either through an interrupted induction current lasting one minute or by chemical stimulation (0.1 per cent nicotine), with the following results: (1) bilateral lengthening of the reaction time; (2) bilateral acceleration of the reaction time; (3) acceleration of the reaction time only on the stimulated side; (4) lengthening of the reaction time on the stimulated side; (5) lengthening of the reaction time on the side opposite the stimulated side. These results were corroborated in a completely bled preparation of a spinal frog, in which all the viscera together with the heart were removed, and also in a decapitated toad after removal of all the viscera and after opening the spinal canal so that the spinal cord, denuded of part of its covering, lay free in the spinal canal.

On the strength of these facts, Orbeli avers that the efferent sympathetic fibers have a direct influence on the central part of the spinal reflex arc. The possibility of the influence on the peripheral receptors is not excluded.[11]

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10. Cobb, Stanley: Physiol. Rev. **5**:534 (Oct.) 1925; Brit. M. J., Sept. 20, 1924, p. 533; A Medical Review of Soviet Russia. VI, Brit. M. J., in press, 1927.

11. Translation from Russian J. Physiol., 1926, vol. 8.

INFLUENCE OF THE SYMPATHETIC NERVOUS SYSTEM ON THE ACTIVITY OF MUSCLE FATIGUED UNDER AN ANAEROBIC CONDITION

The following experiments were made by Ginetzinsky in an atmosphere of hydrogen: The motor roots of the eighth and ninth nerves were stimulated by single maximal break shocks (from thirty to forty times a minute). At the moment of the development of fatigue, the sympathetic cord was stimulated with an interrupted current, and the contraction of the gastrocnemius muscle was increased as in an atmosphere of air. Thus it follows that the effect provoked in the skeletal muscle by stimulation of the sympathetic nervous system cannot be explained exclusively by sympathetic augmentation of oxidation of the products of metabolism.[12]

EFFECT OF THE SYMPATHETIC NERVOUS SYSTEM ON THE PERIPHERAL APPARATUS OF THE MOTOR NERVE

The gastrocnemius muscle of the frog was fatigued by single induction shocks sent alternately through the motor roots of the eighth and ninth nerve, and then through the muscle itself. If the sympathetic system was stimulated, the contraction provoked by the indirect stimulation was sharply increased, and the curve of fatigue from the direct stimulation remained unchanged.

In another series of experiments, the sartorius muscle of the frog was immersed in Ringer's solution, which was replaced at a certain moment by a 0.25 per cent solution of chloral hydrate. The excitability for maximal induced currents was tried every minute, the current being applied to the motor roots of the nerve or to the muscle itself. Usually, in the replacement of pure Ringer's solution for Ringer's chloral hydrate, the height of the contraction provoked by direct and indirect irritation was equally decreased, and after fifteen minutes showed a complete loss of excitability for the indirect stimulation, and only slight contraction with direct stimulation. If, under these conditions, the sympathetic trunk was stimulated, the indirect excitability in certain cases fell quickly to zero; in others, on the other hand, it rose just as quickly; the direct excitability remained without change.

Orbeli concludes, therefore, that the sympathetic effect in the skeletal muscle takes place in the peripheral apparatus of the motor nerve.[13]

THE PSEUDOMOTOR (TONOMOTOR) LINGUAL EFFECT OF THE SYMPATHETIC AND HYPOGLOSSAL NERVES

The hypoglossus was cut in several dogs in the osseous canal, just above its junction with the sympathetic fibers originating from the

12. Unpublished work.
13. Unpublished work.

superior cervical ganglion. Several days after this operation, the pseudomotor effect of the lingual nerve on the musculature of the tongue was exactly as clearly marked as after the usual peripheral section. If now, immediately before the lingual stimulation, the cervical sympathetic nerve is stimulated, there is a marked increase of the pseudomotor effect with lowering of the threshold of irritation, strengthening of the tonic contraction, shortening of the latent period and lengthening of the residual contraction. On the contrary, an outspoken lessening of the lingual effect, many times even to the point of complete inhibition, is produced by the stimulation of the hypoglossal trunk just below the section (i. e., the stimulation of the real bulbar hypoglossal fibers).

Orbeli summarizes his work as follows: The sympathetic nervous system exerts a profound influence over the physicochemical changes occurring in skeletal muscle, accompanied by a modification of the functional ability of that muscle. These changes influence, it seems, the conditions of the motor end-plate, calling forth transformations in the efficiency of the corresponding muscles. This forms a sort of regulatory mechanism for the expenditure of muscle strength, and governs the condition of impulses by the motor nerves. From this point of view, the sympathetic innervation of skeletal muscle is an adaptive innervation through which the functional ability of the muscle is determined.

SPERANSKY'S WORK ON EPILEPSY AND ON THE CEREBROSPINAL FLUID

Dr. A. D. Speransky, formerly a surgeon, who for the past three years has been working with Pawlow, finished work in 1925 that showed the following: (1) Slight freezing of the dog's cerebral cortex causes epileptic convulsions after from two to five hours, followed by death in from twelve to fifty hours. (2) The result is the same regardless of the portion frozen, with the exception of the motor region. (3.) If the frozen part is removed immediately after freezing, no symptoms result. (4) If, on the other hand, the frozen part is not removed until after the onset of symptoms, death is not always prevented. (5) Transplantation of a part of the frozen brain to the subdural space of a healthy dog causes symptoms of epilepsy and death. (6) Subcortical symptoms are the first to appear after freezing and the last to disappear.

Speransky thinks that an autoneurotoxin is formed, which passes into the blood, producing hyperkinetic symptoms. An intense motor excitement, although not epilepsy, is produced by injection of from 150 to 300 cc. of defibrinated blood from the ill animal into the blood of a healthy dog. Immunization against the symptoms of freezing has been tried with some success; i. e., freezing the brain gradually in increasing "doses." Attempts to immunize by subcutaneous injection of an emulsion of the frozen brain of a dying animal were without results, but if this frozen brain emulsion was injected subdurally in a healthy dog, it later could withstand larger "doses" of freezing.

Following up this idea (that an autotoxin is formed by freezing the brain) and related facts (such as the production of a lesion in the opposite testicle when one of the testicles is frozen), Speransky proposes to study the effect of freezing malignant tumors.[14]

INFLUENCE OF THE CEREBROSPINAL FLUID ON PHYSIOLOGIC AND PATHOLOGIC PROCESSES IN THE BRAIN

Speransky, working on the properties of the autoneurotoxins formed by freezing parts of the living brain in dogs, observed that in the transfer of parts of the brain of the ill dogs to the meninges of healthy dogs there was absorption of the transplanted parts without reaction in the surrounding tissues. The disappearance of the transplants is not accompanied with adhesions between the dura and pia mater. Not a trace of any kind remains on these membranes—not any thickening or pathologic change that might show that there was a reaction of the vessels.

Supposing that the dissolution took place through the agency of the cerebrospinal fluid, the author performed the following experiments in vitro: Pieces of the brain of the dog or mouse (from 7 to 8 mm. thick and 2 by 2 mm. broad) were placed in a fresh extract of cerebrospinal fluid of the dog in the thermostat at from 39 to 40 C. For control, such pieces were placed in physiologic sodium chloride solution or fresh blood serum of the dog. Every hour the tubes were shaken. After twelve hours the pieces of the brain in the cerebrospinal fluid fell to pieces, became finely divided, the liquid became muddy and there was a flaky sediment. After from twenty-four to thirty-six hours, all the pieces had been transformed into turbid fluid and flaky sediment. But in the blood serum and physiologic sodium chloride solution, the pieces of the brain began to dissolve only at the end of the third day, and even after five days the dissolution was not complete. Further experiments showed that egg white, blood fibrin and boiled brain are not changed in the cerebrospinal fluid. Only the fresh or frozen brain is dissolved. It was also shown that in the dissolving pieces of brain only the brain substance itself is split off. The pia and blood vessels maintain their resistance for a long time after the brain substance has disappeared entirely.

From this, Speransky deduces that in the cerebrospinal fluid only those albumins which enter the composition of the brain tissue are decomposed. The other albumins are not changed or are changed slowly.

As the bacterial toxins appear closer in their chemical nature to the albumins, and consequently should not be quickly destroyed in cerebrospinal fluid, the following experiment was proposed: A mixture of

14. Speransky, A. D.: Compt. rend. Soc. de biol. **94:**262 (Feb. 5) 1926.

tetanus toxin and brain emulsion was taken in the proportion according to Wassermann so that all the toxin should be completely neutralized. To one part of this mixture was added increasingly a few grams of cerebrospinal fluid of the dog; both parts were placed in the thermostat for from five to six hours. The subsequent introduction of these mixtures into the brains of more than thirty pigs, mice and dogs showed that the Wassermann mixture plus cerebrospinal fluid caused tetanus, whereas the introduction of a pure Wassermann mixture did not cause any disturbance in the animal. Further experiments showed that the autodigestion of dead and vital brain was the same as the autodigestion of the dead and vital stomach. It was shown that in the frozen portions of the cortex of dogs, neurotoxins developed, perhaps products of incomplete combustion. These products reach the cerebrospinal fluid in large quantities. The introduction of such toxic cerebrospinal fluid beneath the dura mater of a healthy dog gives the same symptoms as freezing the cortex.

The clinical and pathologic appearances caused by the subdural introduction of the toxic cerebrospinal fluid were the same as those seen after freezing the cortex but were more weakly expressed. Withdrawing of the cerebrospinal fluid from the sac of the dura mater immediately before the freezing of the brain causes a sharp delay in the reaction. If the withdrawal is done two or three hours after the freezing, the development of the symptoms is not prevened, and the animals die.

Speransky concludes:

> In local disease of the nervous system a destruction of the brain substance occurs in the affected parts. Parts of the products of the incomplete combustion arising from this destruction are transported into the cerebrospinal fluid, and through it poison the brain. In such a way local disease becomes general, and to this we owe the mechanism of the development of diffuse encephalitis.
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> The greatest quantity of cerebrospinal fluid comes into relation with the brain substance in the ventricles. This explains the development of subcortical symptoms. The undamaged pia mater gives protection to the brain substance better than the ependyma; thus subcortical destruction often occurs earlier than the cortical.
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> The pathologicanatomic changes in the brain and the clinical symptoms in all toxic encephalitis, as tetanus, hydrophobia, diphtheria, epidemic encephalitis and toxic encephalitis from freezing the brain cortex, have many things in common. In all of these the parts of the brain lying in the vicinity of the ventricles are affected; in all are observed changes in the cornu ammonis; in all there is an infiltration of the shallow parts of the brain substance, near the ependyma, and a thickening of the ependyma; the brain substance in nearly all of these cases has an infiltration in a circle of cells, not around the blood vessels as was formerly asserted, but around their adventitial sheaths which are filled with cerebrospinal fluid. Thus there is an organization of defense proceeding from the side of the cerebrospinal fluid.

All these facts lead Speransky to believe that the mechanism of development of all toxic encephalitis is one and the same. Although different parts of the brain differ in their sensitiveness to different injurious agents, not all the changes depend on this specific sensitiveness. The constant changes that occur in the cornu ammonis, encountered in the diseases mentioned in the foregoing and in epilepsy, occur because this part of the brain is bathed on three sides with the cerebrospinal fluid. The subcortical parts are affected because of their proximity to the ventricles.

Speransky recommends careful study of the cerebrospinal fluid, of its ferments and its hydrogen ion concentration. He says that every change in this concentration is evidence of changes in the fermentive processes. There should first be a study of such processes as flow rhythmically with a periodic improvement and relapse—epilepsy, sclerosis disseminata, cyclic psychosis, etc. In the further study of such processes as tetantus and epidemic encephalitis, it is necessary to consider carefully the part played by the cerebrospinal fluid.[15]

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15. This account of Speransky's unpublished work has been translated from an original account which he was kind enough to hand to me.

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