NEW DATA ON THE SCIENTIFIC ARGUMENTATION OF THE PHYSIOLOGY OF APPLICATION OF BEE VENOM AS A MEDICINE

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About 10 years have elapsed since the publication of our hypothesis related to the nature of the action of bee venom on the mammal organism (N.M. Artemov 1958). During this period the research in this field continued. In this paper I want to deal with our future works underlying the hypothesis as showed in our former works.

1. At present, the opinion that the organism responds to bee venom by a general reaction of defence and adaptation relying upon the stimulation of the activities of the lipophyso-surrenal system is more and more spread. This was confirmed not only experimentally (N.M. Artemov, L.N. Tarasova and A.A. Filimonova, 1961) but also clinically (M.P. Gusev, 1962, E.M. Alexer, 1964 and others). Of late I had the possibility to elucidate this problem of another viewpoint also, namely by the research carried out relating to the bee venom influence on the activity of the genital system (L.G. Konicova). It should be noted that the depression of the genital system under stress conditions attracted G. Selie's attention as far back as in 1936.

The oestrus cycle in white rat females is studied by means of the vaginal smear. Ten rats were watched for one month. In 40 animals in course of investigation, the cycle was checked for 10 days until the introduction of bee venom and then for a month after inoculation (10 injections per animal or 2 mg of bee venom preparation). The control females (10 in number) were injected physiological salt instead of bee venom.

When bee venom was inoculated, considerable modifications were noticed in the sexual cycle of females. First of all the frequency and the duration of different stages of the cycle were changed. In most of animals (80%) the frequency of the calm stage increased 1.5 times and even more and the duration of the same stage increased, too, from 1.2 day - that is the normal – up to 4 – 4.2 days.

It should be noted that in a whole series of cases the introduction of bee venom into rats resulted in the removal of all the cycles. At the same time, the rut period either missed or could be noticed very rarely (1 – 2 times a month). However, among the rat females in course of investigation, there were also individuals (20%) in which the sexual cycle did not change essentially.

All the females in the control group showed a normal cycle. The number of normal cycles per female was considerably less in those of the experimental group. (2-3 cycles instead of 6-8, that occurred usually).

Thus, the bee venom action interrupts the sexual cycle in rat females, which reflects in a prolonged dioestrum, in a more rare appearance of the estrus, a decrease in the number of females with a normal cycle and a decrease in the number of normal cycles in each female. This symptom supplements very well the symptom complex of stress which is noticed when bee venom is inoculated.

2. In analyzing the physiological reactions brought about by the introduction of bee venom into the organism, special attention was paid to the variation of permeability of the blood capillary vessels. Lately new data testifying to the increase in the permeability of blood capillary vessels for albumine as well as for its going out have been obtained in our laboratory. (V.F. Kireeva, 1966). It is interesting to notice that one part of the albumine going out of blood is released at the same time with the gastric juices (T.I. Poberejscaia, V.F. Kireeva, I.A. Baranova, 1966).

The analysis of the neurotoxic features of bee venom was in the centre of attention of our last works. These researches offer a particularly important material for the substantiation of the apitherapy both from a physiological and experimental point of view.

3. We have also continued the research on the collinolitic qualities of bee venom. Recently L.I. Sergheeva (1965, 1966) making use of a new system of utilizing the electrophysiological method has confirmed the conclusions relating to the bee venom collinolitic qualities of shutting off the ganglions. N.M. Artemov, I.V. Goreacev, O.N. Lebedev and A.S. Stepanov (1964) showed that bee venom has indisputably an influence, although not very great, on the transmission of the excitation from the motory nerve to the skeleton like muscle.

The shutting off action of the ganglions brought about by the bee venom allows us to explain the results obtained in treating hipertension, endoarthritis, trophic ulcer as well as other diseases with bee venom.

Further research on the bee venom quality opens a new path towards stepping in the activities of brain and spinal marrow. These facts have already been revealed in a paper delivered at the XIXth International Apicultural Congress. (N.M. Artemov, B.N. Orlov, 1963; B.N. Orlov, 1963).

It is very important to notice that the difficulty in transmitting the excitations through the spinal marrow under the bee venom action is relating not only to the direct action on the corresponding centers, but also to the changing of the action of the superior portions of the nervous system, which regulates the spinal marrow activities.

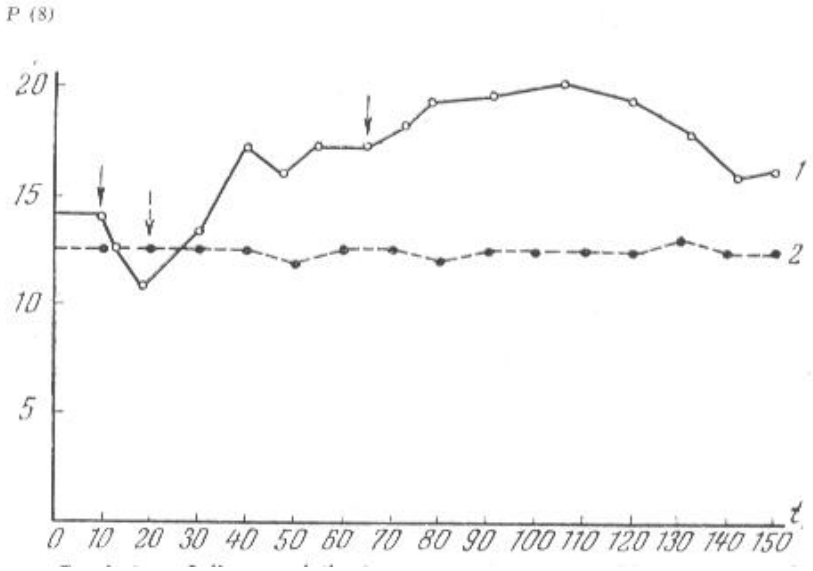
In particular bee venom can shut off the descending reticular formation encroaching upon its proper functions and also the admittance of the regulating influences of the cerebellum to the spinal marrow. (N.M. Artemov, B.N. Orlov, 1965; B.N. Orlov, 1965).

Recently, our researches relating to the bee venom action on the superior portions of the nervous system have been completed by a series of data of paramount importance for the interpretation of its neurotoxic action. We performed the analysis of the variation of the motory excitability of cortex by means of the cronaximeters method (D.B. Gelashwilly).

The experiments were tried upon dogs, which were slightly anaesthetized by means of hexenal. Animals underwent a trephination of the brain. On that occasion certain points of the cortex corresponding to the motion analyzer were subject to an electric stimulation which resulted in a bending and contraction of the hind pad on the part opposite to excitation. Excitability of the motory zone was evaluated according to the contraction of muscles, that set in motion the thighbone of the contralateral extremity.

The bee venom doses introduced intravenously varied from 0.2 mg/kg to 1 mg/kg. The variations of the rheobase were recorded every 5-15, for 2-3 hours immediately after the introduction of bee venom. The control animals were injected physiological salt. These experiments showed that bee venom exerts a particular influence on the excitation of motory zone of the cortex.

As it follows from Graph 1, the physiological salt injection did not change practically the value of the rheobase. On the contrary, the introduction of bee venom induced after 2-3 minutes a decrease in the rheobase for o short time and then a very strong and steady increase of the same. After a single bee venom injection, the rheobase increased frequently by 30-50% as compared to the original value, and subsequently – except some variations – came back to the original level. The changes noticed in different experiments (depending upon the dose) manifested for up to 1-2 hours. Thus bee venom causes a change in the motory rheobase, which takes place in two stages. At the same time the main effect finds expression in a real increase of the excitability of the cortex (the second stage of the bee venom action).



Graph 1 – Influence of the intra-arterial injection of bee venom on the rheo-base of the zone of cortex
1. – bee venom in doses of 0.25 mg/kg. (1st injection) and of 0.15 mg./kg (2nd injection).
2. – Physiological salt – 0.5 mg (control). The Ordinate stands for the rheo-base (P) in voltage;
The abscissa stands for the observation time (t) in minutes. The arrow indicates the moment of injecting bee venom and physiological salt.

The data obtained are fully in keeping with those of researches carried out previously, which aimed at studying the dynamic of the modifications of the bioelectric activities of the motory and visual regions of the cortex under the action brought about by bee venom (N.M. Artemov, B.N. Orlov, 1963; B.N. Orlov, 1964). The depressions of the potentials of cortex which we studied in our experiments can be attached to the decrease in the excitability and lability of cortex under the bee venom action.

The change of the character of the bioelectric activation of the big hemispheres of the cortex when intoxicated with bee venom has probably a complex and complicated nature. The depression of the electroencephalogram (EEG) can be supposed to be not only a result of a depresive influence of bee venom on the cortex cells, but also a result of the action of the same bee venom on the ascending reticular system. At the same time we have also to take into consideration the possibilities of the modification of the E.E.G. under the influence of the interoceptive impulse caused by the bee venom action on the different zones producing reflexes.

Our attention was seized log since by the possibilities of bee venom to excite the chemoreceptors of intestine, lungs and carotid sinus and bring about reflex variations of composition and coagulation in blood as well as reflex variations of respiration and blood pressure (N.M. Artemov, 1958, 1962). At present, a great importance is attached to chemoreceptors, to a more constant maintenance of the internal medium of organism (homeostasis) and to the regulation of biochemical process (S.V. Anichicov, M.L. Belenky, 1962 and others).

In the last two years, new data were obtained in our laboratory, which testify to the participation of reflexes, in which chemoreceptors interpose, in the complicated mechanism of the bee venom action (Data obtained by N.V. Korney).

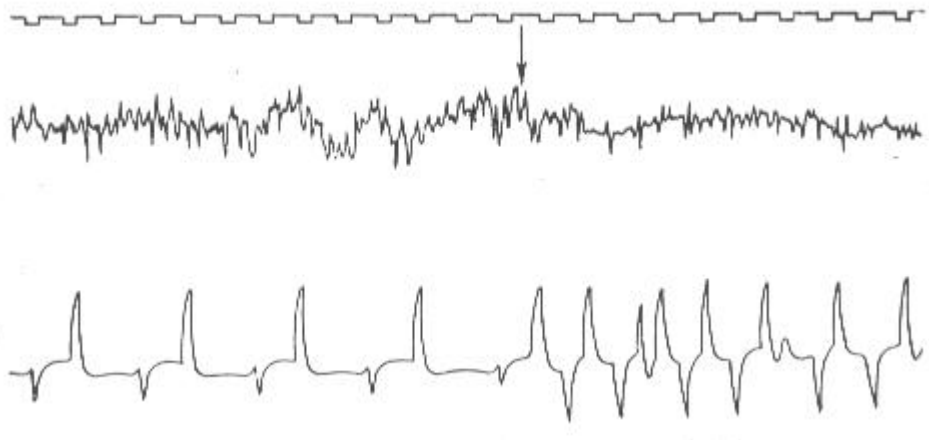
A series of experiments were devoted to the study of nature of the brain and breathing variations when a bee venom solution is injected direct in the region of the carotid sinus where particularly sensitive chemoreceptors are concentrated. Experiments were tried upon hares and cats anaesthetized with hexenal or uretan.

The record of the biopotentials was performed in the motory zones of the cortex unipolarly and some times bipolarly. With that end in view, steel electrodes were used, which were introduced into the bone, 3-4 mm distant from one another.

Besides micron electrodes were also applied, which were introduced extra dura mater. The electroencephalogram was recorded by means of an encephalograph with 4 canals (4 EEG – 1).

At the same time with the record of the encephalogram, the respiration of the animal was also recorded by means of the thermoresistance according to a method developed by us.

Bee venom solutions in doses of 0.1-to 0.5 mg/kg were introduced into the isolated carotid sinus, or directly in the carotid artery lower than the point where the chemoreceptor zone of the sinus is placed. In the electroencephalogram recorded in animals before the bee venom introduction oscillations of 6-8 Hz frequency as well as lower rhythms were noticed. The maximum dimensions of the amplitude of electric potentials did not surpass 100 microvolts (Graph 2).



Graph 2 – Changes in the electroencephalogram and the electropneumogram in a cat as a result of the intra-carotid injection of bee venom. Experiment tried on February 17, 1966 (left motory zone, unipolar branch). This graph represents (from top to bottom): time record (1 sec), electroencephalogram, electropneumogram. The arrow marks the moment of the bee venom injection.

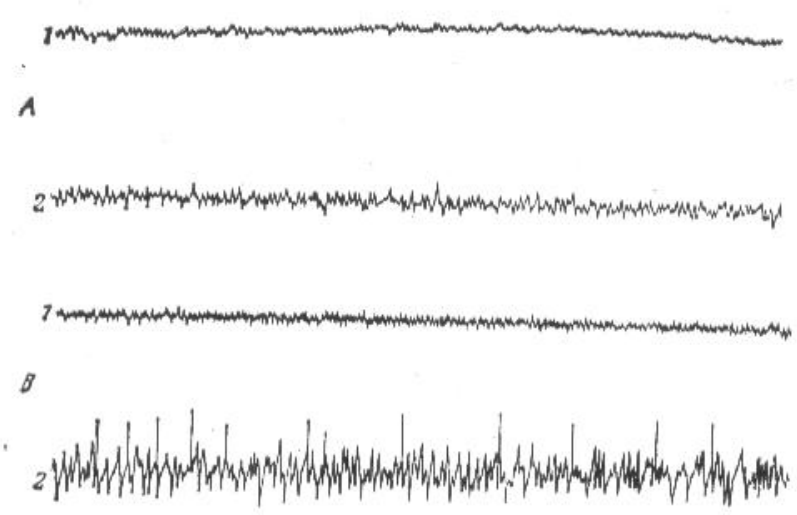
The bee venom solution was introduced only after obtaining some firm records for both the electroencephalogram and the respiration. The effect induced by the introduction of bee venom on respiration found expression in a strong acceleration of the respiratory activities; the rhythm of respiration accelerated 2-3 times whereas the amplitude of the same increased 1.5-2 times as compared to the original

value. Simultaneously a well-marked depression of the electric activity was noticed. The amplitude of electric potentials decreased up to 30-20 microvolts and even less.

30-70" later after injection respiration decreased and rhythm became irregular. This occured on the depression background of the electroencephalogram.

It is supposed that the excitations of the chemoreceptors of the zone producing reflexes of the carotid sinus are responsible for the disorders which were produced in the respiration and the ectroencephalogram and recorded immediately after bee venom was introduced.

Applying the method of S.S. Crîlov, 1956 (perfusion of the isolated carotid sinus in a cat) *in vitro* it was found that the injection of bee venom solutions at the same time with the perfusion liquid results in the appearance of a specific electric activity in the sinus nerve (Graph 3, A) due to the bee venom action on the chemoreceptors of the sinus.



Graph 3 – The bee venom influence on the character of the impulsion induced in the nerves of the sinus and in those of the intestine.
A. Modification of the electric activities of the sinus nerve under the influence of bee venom on the chemoreceptors of the isolated carotid sinus. Dose of bee venom – 0.5 mg; 1 – The original electric activity; 2 – The electric activity 8 seconds later after injecting bee venom;
B. Modification of the electric activities of the intestinal nerve as a result of the bee venom action on the interoceptors of the small intestine. Bee venom dose – 0,3 mg: 1 – Original electric activity; 2 – Electric activity 7 seconds later after injecting bee venom

It should be noted that an electric impulsion was also recorded in the intestinal nerves where this appears as a result of the bee venom action on the chemoreceptor formation of the small intestine. Experiments tried upon cats *in vivo* showed that the injections of bee venom in the artery of the anse (loop) of the small intestine brought about in the afferent nerves electric potentials of 60-70 Hz frequency (Graph, 3 B).

In conclusion we can say that our researches on the physiological mechanisms of the bee venom action are viewed with a friendly eye by the practitioner physicians.