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Review Article

## How Temperature Pharmacology Was Formed: History in Personalities

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### ABSTRACT

It is shown that temperature pharmacology is a new scientific and practical direction in which the local interaction of drugs is considered taking into account the local temperature of selected parts of the body. It is indicated that the main provisions of this direction were formulated in Russia by 1988. Catalysts for the formation of a new direction were the results of *in vitro* experiments with isolated mitochondria at different local temperatures. The chronology of the resolution of contradictions between the existing public opinion and new ideas about the role of local temperature in the mechanism of action of drugs in hypoxia and ischemia is indicated. Scientists, doctors and journalists who were the first to believe in the prospects of temperature pharmacology are listed. The first scientific articles and inventions that formed the basis of a new scientific direction are presented. The latest achievements and visible prospects for the development of temperature pharmacology in medicine, biology, pharmacology and pharmacy are indicated.

**Keywords:** history of science, pharmacology, pharmacy, medicines, local temperature.

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### INTRODUCTION

Until now, doctors choose, prescribe and inject drugs into the body of healthy and/or sick patients and animals, based on the mechanism of action, which is described in reference books and textbooks without taking into account the general and / or local body temperature of people and animals.<sup>1</sup> At the same time, treatment standards for sick people and animals require doctors to monitor their body temperature daily (from the first to the last day of treatment). This is done everywhere and for a long time by placing a thermometer in the axillary area (in the patient), in the mouth and/or in the rectum (in patients and animals), or by touching the skin of the patient's forehead and the nose of the animal, or by infrared imaging of open parts of the body using a thermal imager. The dynamics of the body temperature of patients during treatment is recorded in medical documents and is one of the important symptoms of disease diagnosis, assessment of the severity of the disease, health status, and a criterion for evaluating the effectiveness of treatment.<sup>2</sup>

Students of medical faculties of all universities of the world study the main forms of daily dynamics of body temperature in healthy and sick people and from the first year of training learn that people are warm-blooded animals and that all people's body temperature is not a constant value. Moreover,

textbooks convince students that normally people have a daily rhythm of fluctuations in their body temperature. It is shown that during the day the body temperature changes by an average of one degree, having the highest values at the end of the day and taking the lowest values in the morning. In addition, the characteristic daily rhythms of body temperature fluctuations in patients suffering from certain diseases, in particular, infectious diseases, which have become classics, are demonstrated.<sup>3</sup>

Encyclopedias and textbooks on physiology show that all people and all patients suffering from different or the same diseases have different body temperatures. Moreover, the most variable temperature of their body becomes in severe infectious diseases and critical conditions.<sup>4</sup>

The study of the dynamics of body temperature of various patients, conducted in recent years with the help of a thermal imager, revealed an even more significant difference between living people from each other in terms of the total temperature of their bodies, and especially significantly - in terms of the local temperature of various parts of their body. It was found out that on the thermal imager screen, in normal and in cases of illness, living people are always depicted in different colors. This indicates a different temperature of all parts of their body and this is good, since it indicates that people are alive. Moreover, it has been

shown that the most significant changes in local and general body temperature are detected in people who have the most significant reserves of adaptation to critical conditions. Surprisingly, it is only in the process of death that the temperature of all parts of the human body begins to equalize. However, it is unfortunately reduced down to the ambient temperature. In this case, the corpse becomes cold and looks one-color on the thermal imager screen.<sup>5</sup> Therefore, equalization and stabilization of temperature values in parts of the human body is a symptom of trouble.

Thus, during life, parts of the body of all people always have different local temperatures.

However, the generally accepted version of the description of the mechanism of action of drugs does not provide for a significant change in human temperature. The standard description of the mechanism of action of drugs is based on a virtual object, namely, a person with a body weight of about 70 kg with a constant and uniform temperature in all parts of his body.<sup>6</sup> However, today it becomes clear that the generally accepted virtual object of an "ever-living" (in fact, immortal) person must be changed. It is time to introduce an additional parameter to this special educational tool, namely, a different local and general temperature, which, in addition, constantly changes episodically and/or cyclically.

The fact is that the modern virtual human object is not a worthy analogy for either the "first patient" of a student

and/or doctor, or a simple biological model similar in temperature dynamics to a living average statistical patient. The fact is that each particular patient, as a rule, is ill, has inflamed areas of the body and can die at any moment, because a person is mortal. So he can die despite the drugs administered (at least - from old age).<sup>7</sup>

In addition to the daily rhythm of the General temperature, there is a high probability of an increase and/or decrease in local temperature in certain parts of the body, especially in those that remain open for a long time (uncovered by clothing) in the heat and cold.<sup>8</sup> This is paradoxical, but generally accepted ideas about the mechanism of action of drugs still lack indications of how and by how much the pharmacokinetics and pharmacodynamics of drugs can change when the "sick" part of the body is heated or cooled. But this information is absolutely necessary to improve the effect of drugs.

At the same time, at the beginning of the 20th century in Russia, professor of the Military Medical Academy in St. Petersburg Nikolai P. Kravkov (Photo 1) predicted that the effect of drugs depends not only on the chemical structure, dose, concentration, dosage form of the drug, the path and method of its administration in the body, but also on the temperature.<sup>9</sup>



Photo 1. Nikolay Pavlovich Kravkov-head of the Department of Pharmacology of the Military Medical Academy, academician of the Imperial Military Medical Academy, full state Councilor, knight of the order of St. Anna of the 3rd degree and St. Vladimir of the 4th and 3rd degrees.

Indeed, a hot water bottle and an ice pack have long been used for medicinal purposes. In particular, for a long time it was believed that for ischemia of the limbs and intestines, you need to use hot water bottles to warm them, and for bleeding, you need to use an ice bubble to cool the bleeding wound and stop the bleeding.

The opposite meaning of cold was shown in 1960 by Professor Vladimir Alexandrovich Negovsky (Photo. 2). He proved that the death of a person can be overcome by its general cooling.<sup>10</sup> This data gave birth to a new medical specialty - "resuscitation". After that, it was revealed that the organisms of warm-blooded animals and people have an effective adaptive system to combat general cooling. It has been shown that during general cooling, a healthy body of warm-blooded animals and humans tends to stay warm and for this purpose increases heat production due to the trembling of skeletal muscles and the oxidation of the Krebs cycle substrates in mitochondria.<sup>11</sup>



Photo. 2. Vladimir Negovsky — Doctor of Medical Sciences, Professor, Academician of AMS of USSR, the founder and Director of the world's first Scientific Research Institute of General Reanimatology in Moscow, the founder of critical care medicine, discoverer of new nosological units (postresuscitation disease).

Then in Russia in 1983, it was shown that local hypothermia (a decrease in local temperature from + 37 °C to 20 °C or up to 0 °C) inhibits oxygen consumption in mitochondria and increases the resistance of various biological objects to a lack of arterial blood and/or oxygen.<sup>12,13</sup> Therefore, it was proposed to use local cooling to preserve the viability of organs and tissues in their ischemia and hypoxia.<sup>14,15,16</sup>

The correctness of this proposal was confirmed by the clinical success of cold protection of the heart from ischemic damage, which was demonstrated at that time during

surgical operations on the hearts of people by the famous Russian heart surgeon Yevgeny Meshalkin. The same protective role of hypothermia in protecting the viability of isolated kidneys and hearts during their preservation was shown at that time by the famous transplant doctor, Professor Valery Ivanovich Shumakov.<sup>5</sup>

Years passed, but doctors and researchers were in no hurry to apply local hypothermia to fight heart attacks and necrosis in ischemia and hypoxia. The more valuable was the support of scientists who believed in the prospects of the declared strategy. Among Russian pharmacologists, they were Professor Natalia Veniaminovna Kaverina and Director of the Institute of Pharmacology (Moscow), Professor Arthur V. Waldman.<sup>5,11</sup>

Despite this, the generally accepted view of the action of heat and cold on the human body many years remained the same and boiled down to the fact that to improve the survival of ischemic myocardium is necessary to apply medication that accelerates intracellular energy metabolism, the intensity of oxidative phosphorylation of ADP in mitochondria, and the speed creatinophosphokinase response in cardiomyocytes, that is necessary to stimulate and not to depress metabolism in the myocardium. The authors of this hypothesis, led by academician E.I.Chazov, received the USSR State Prize in Science at that time.<sup>5</sup> At the same time, oxygen was not considered as a cure for infarction and tissue necrosis in their ischemia and hypoxia. Even donor blood was not considered as an oxygen donor.

In the following years, scientists of the all-Union Cardiology Research Center under the leadership of Professor E. Chazov developed and implemented a new drug designed to stimulate the metabolism and contractility of the myocardium in ischemic conditions. But the results of clinical use of this drug disappointed the authors... How could it be otherwise? After all, earlier these same scientists in experiments with frogs showed that hypothermia protects the myocardium from hypoxic damage. But the authors ignored this fact and the fact that hypothermia does not stimulate, but depresses the intensity of metabolism and contractile activity of the heart.

Scientists of the Institute of Biophysics of the USSR Academy of Sciences, professors F. F. Belyoyartsev and M.N. Kondrashov, made a significant contribution to the development of problems of fighting hypoxia.

Professor Maria Nikolaevna Kondrashova (Photo 3) detailed the theory of professor Hans Selye on the adaptation of biological objects to stress factors in relation to mitochondria.<sup>17,18</sup> The assumption of professor M.N.Kondrashova was based on the theory of adaptation of living biological objects to stress factors (in this case, to lack of oxygen). Therefore, it was reasonably assumed that the resistance of animals and humans to hypoxia can be increased by activating energy production in the mitochondria, in particular due to the active oxidation of succinic acid in the mitochondria.<sup>19</sup>

Professor M.N.Kondrashova due to high human qualities, charm and talent attracted the attention of many researchers to the study of oxidative phosphorylation processes in mitochondria, gave an impetus to the study of mitochondrial processes by many scientists in Russia. Professor Maria Kondrashova in 1977 gave me consent to scientific guidance during my postgraduate studies.



Photo. 3. Maria Nikolaevna Kondrashova - Doctor of Biological Sciences, Professor, head of the Laboratory for Energy Supply Management of Physiological Functions of the Institute of Theoretical and Experimental Biophysics of the Russian Academy of Sciences (Pushchino-on-Oka).

Maria Nikolaevna Kondrashova's partner in scientific research was also her husband - the closest person to her, Professor Simon Elyevich Shnol (one of the most legendary figures of Russian science).<sup>20,21,22</sup> (Photo 4).



Photo 4. Simon Elyevich Shnol - Doctor of Biological Sciences, Professor of the Department of Biophysics of the faculty of physics of Moscow State University, head of the Laboratory of Physical Biochemistry of the Institute of Theoretical and Experimental Biophysics of the Russian Academy of Sciences (Pushchino-on-Oka).

In 1983, it was proved that heating of organs and tissues in their ischemia accelerates, and cooling delays the onset of tissue necrosis in ischemia, and that local cooling worsens, and local heating improves blood clotting.<sup>2,23</sup> Therefore, to

protect tissues from irreversible damage in ischemia and/or hypoxia, it was suggested to reduce their local temperature. At the same time, it was shown that local hyperthermia increases the effect of hemostatic agents. Therefore, to stop bleeding, it was proposed not to cool, but to heat bleeding wounds, in particular for parenchymal bleeding.<sup>24,25</sup>

In the next few years, the difference between the local action of drugs on various tissues of the patient's body under conditions of local cooling and local heating was discovered.<sup>26</sup> The difference between the role of General and local hypothermia and hyperthermia on the local effect of drugs was established. In particular, the ability of local cooling to enhance the action of drugs-inhibitors of metabolism and tissue function and the ability of local heating to potentiate the action of drugs-activators of metabolism and the function of organs and tissues was found. It turned out that local hypothermia potentiates the action of local anesthetics, antihistamines and other drugs-inhibitors due to the suppression of all receptors, the functional activity of cell membranes and subcellular structures (including membrane receptors), as well as the intensity of aerobic metabolism. Conversely, it turned out that local hyperthermia potentiates the action of agents that have a local irritating effect, inflammatory action due to the activation of all receptors, the functional activity of cellular and subcellular membranes, chemical, biophysical and biochemical processes according to the Arrhenius law. In addition, local cooling has been shown to increase the viscosity of drug solutions, blood, plasma, and the hardness of all "soft" biological tissues.<sup>2,26</sup>

During those difficult years, the head of the Department of Pharmacology of the First Moscow Medical University, editor-in-chief of the journal "Pharmacology and Toxicology"

(in Russia), Chairman of the Russian Scientific Society of Pharmacologists, author of the textbook "Pharmacology", academician of the Russian Academy of Medical Sciences, professor Dmitry Harkevich (Photo 5) provided exceptional, truly invaluable support in the formation of temperature pharmacology.

Today, almost 30 years after the dramatic events associated with the birth of a new scientific direction, we must admit that it was academician D. A. Harkevich who stopped all the persecution of adherents of this scientific direction and preserved peace between pharmacologists.<sup>5</sup> Moreover, it was D.A.Harkevich who became the catalyst for the formation of temperature pharmacology in Russia !



Photo 5. Dmitry Aleksandrovich Kharkevich, head of Department of Pharmacology, First Moscow Medical University, Doctor of Medical Sciences, Professor, Academician of RAMS, President of Russian Scientific Society of Pharmacologists, the author of the textbook "Pharmacology".

The first scientists to recognize temperature pharmacology were Nina Onishchenko, Professor of the Institute of Conservation and Organ Transplantation of the Russian Academy of Medical Sciences (Moscow)<sup>5,11</sup> and the world-famous cardiac surgeon, MD, Professor, Academician Fedor G. Uglov (Saint Petersburg) (Photo 6).

Due to the fact that professor F.G. Uglov believed in the prospects of a new scientific direction, in 1988 the first scientific article was published in the journal "Bulletin of surgery named after I. I. Grekov", which showed the world the high efficiency of local temperature pharmacology in the treatment of acute obstruction of the limb arteries in animals and patients.<sup>5,11,26</sup>

The first popular scientific article about the protective role of local hypothermia in myocardial ischemia was published in 1987 in the journal "Science in the USSR" thanks to the wisdom and patriotism of the Deputy editor-in-chief of the

journal Yuri Bocharov.<sup>5,23</sup> The first popular scientific article on the role of local Hypo-and hyperthermia in the mechanism of local drug action was published in 1989 in the journal "Science and life".<sup>5,25</sup> This was largely due to the wisdom of Rada Nikitichna Adjubey (Nikita Khrushchev's daughter), who worked as the Deputy editor-in-chief of this magazine in those years.



Photo. 6. Fyodor Grigorievich Uglov - Doctor of Medical Sciences, Professor, Academician of RAMS, Director of Institute of Pulmonology, head of Department of Hospital Surgery of Saint-Petersburg State Medical University named after I. P. Pavlov.

The main provisions of temperature pharmacology were first published in 1988 on the pages of the book "Prescription for temperature" (Udmurtia publishing House, Izhevsk, Russia).<sup>2</sup>

After that, very soon the list of studied physical and chemical characteristics of local drug interaction was expanded to include osmotic, acid (alkaline), and gravitational activity. This made it possible to transform temperature pharmacology itself into physical and chemical pharmacology. Thanks to pioneering research in the field of physical and chemical pharmacology in Russia, a new pharmacological group of medicines related to hygiene products (hygiene products) was discovered, which was called "Pyolytic agents" or "Agents that dissolve thick pus".<sup>27,28,29</sup> Practice has shown that the clinical use of these tools can significantly increase the effectiveness of treatment of purulent diseases.<sup>5</sup>

The success of pharmacology, pharmacy and thermology in the following years confirmed the high importance of temperature pharmacology for pharmacy, medicine and medical technology. Internationally recognized achievements of domestic pharmacology were the discovery of the following new groups of drugs:<sup>30,31,32,33</sup>

- "whitening tooth enamel cleaners" (hygiene products for dentistry)
- "oxygen-alkaline bleaching ceramic cleaners" (sanitary and hygienic means for bleaching the surface of household ceramics and faience)
- "bleaches of bruises" (cosmetics for dermatology)

In addition, the success of Russian scientists in physical and chemical pharmacology became the basis of a new direction in materials science, called "physical and chemical materials science".<sup>34</sup>

## CONCLUSION

The chronology of publications and inventions devoted to the correction of the mechanism of local action of drugs in tissues by purposeful changes in local temperature during local interaction confirms the significant advantage of combining local hypothermia or hyperthermia with local use of drugs. The facts prove that temperature pharmacology (as a scientific field) originated in Russia between 1981 and 1983. The main provisions of temperature pharmacology were formed by the end of 1988. Currently, this scientific direction is successfully developing and expanding. Moreover, it became the basis of a new direction in materials science called "Physical and chemical materials science".

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