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Times Past

Scientific Activities of Academician Nikolai Sirotinin*

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In 1996 we commemorated the 100th anniversary of the birth of the prominent Ukrainian scientist Academician Nikolai Nikolayevich Sirotinin (1896–1977). Here we wish to inform the world scientific community about our teacher who was generally agreed to be one of the leaders of pathophysiology in the former Soviet Union.

Leo Tolstoy wrote that human life has three periods. During the first, a man lives for his own sake, for his own pleasures and career. During the second period there arises an inner demand to devote himself to other people (family, society), and during third period he feels a need to approach God. We were destined to know Sirotinin during the last 6 years of his life when he was closer to God than to people. This was a gentle, delicate, and extremely modest person who kept his distance through his courteous politeness. There was a contemplation and calmness in his look. However, old photographs showed that there were storms too. As his young students, we regretted that we had missed the time of his inspired daring and struggles. But we understand that we were fortunate to follow this man at the end of his path.

For his generation, life was tough, for the country had coped with two world wars, a revolution, a civil war, two famines, and Stalin's repressions. We bend our heads before the greatness of this man's intellect and spirit, and his uniqueness. He came from another cultural and moral epoch—the prerevolutionary nobility culture. Honesty, moral excellence, and dignity were his principal guides, and under no circumstances did he ever betray them; he remained unshaken.

Nikolai N. Sirotinin was born on November 26, 1896 in Saratov and his first scientific interests were in microbiology. This was natural because the time of his study and graduation from Saratov University were years of revolution and civil war when the vast, devastated country was swept with various kinds of epidemics, carrying away human lives. While he was still a student, he began working as a laboratory assistant in a chemical-bacteriological laboratory. Later he headed the department of the Saratov Institute of Microbiology and Epidemiology devoted to plague, smallpox, and vaccines. His first published works appeared in 1922. In them, he described in detail the involutionary form of *gonococci*. His findings were later confirmed by many investigators. In his experiments on rodents (gophers) he found that *Proteus vulgaris* enhanced the course of

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*This article originally appeared as an English translation of an article in Russian in the *Hypoxia Medical Journal* 1996;4(2):6–12, published in Moscow, and is reprinted here by permission. Some editorial changes have been made to improve the English and shorten the text. The article is interesting on several counts. First, Sirotinin was very influential in the former Soviet Union, but is little known outside Eastern Europe. Next the piece is written in a somewhat lyrical style. Finally, it alludes to an incident with extraordinary political overtones. Readers who would like to refer to Sirotinin's scientific papers will find several listed in *High Altitude Medicine and Physiology in the Former Soviet Union* by E. Gippenreiter and J.B. West, *Aviat. Space Environ. Med.* 1996;67:576–485. However, all the papers are in Russian.

cholera infection. He also established that in the Wassermann reaction it was a second component of the complement that was bound, rather than the first one as had been proposed before.

In 1923, Sirotinin began working in the laboratory of general pathology headed by A.A. Bogomolets. There he was engaged in studies on anaphylaxis, and these data were later included in his doctoral dissertation. Sirotinin continued this series of investigations working with Bogomolets in the Second Moscow Medical Institute. Among his most exciting discoveries of this period was the inhibition of elements of the reticulo-endothelial system, and the decrease in blood complement during anaphylactic shock. These findings were later confirmed by many Soviet and foreign investigators. At the same time, he studied glycogen synthesis in the liver as related to sugar concentration and found a suppression of urea synthesis by the liver following blockade of its reticulo-endothelial system.

At the age of 33, this young, erudite scientist became Professor of Physiology at Kazan University. Through his great energy and enthusiasm, he reorganized the department, surrounding himself with young and efficient staff who rapidly won recognition in the medical school. The department turned into a research center attracting many clinicians.

In Kazan, Sirotinin conducted a number of studies on the reticulo-endothelial system. He also developed a new classification of allergic reactions and prepared a compendium, which was the first of its type in Russian. His extensive research led him to the study of immune reactivity and its evolution. He showed that the most phylogenetically ancient form of infection was a simple reproduction of microbes in the organism accompanied by comparatively weak reactions, of the cellular and the humoral type. A phylogenetically newer form of an infectious process involved the development of the lymphocyte/macrophage system, with the production of antibodies and specialization of phagocytic processes. A more recent historical development was the addition of allergic reactions in combating the infection.

The Kazan period was marked by the beginning of a new research direction: an interest in oxygen deficiency. After the October revolution, Sirotinin was the first explorer to climb Mt. Elbrus, and the Gerget glacier of Mt. Kazbek in the Caucasus to carry out medico-biological studies. He later continued these interests in Kiev, where he came to work in 1934 at the Institute of Clinical Physiology at the invitation of Bogomolets. This Institute was actually founded by Bogomolets and later named after him. Sirotinin's productive work culminated in the writing of fundamental chapters on allergy, inflammation, and hypoxia in a multivolume *Handbook on Pathological Physiology*, published under the editorship of Bogomolets in 1935–1936. Thirty years later, on the initiative of, and under the direction of, Sirotinin, the preparation of a new four-volume edition of the *Handbook* was undertaken. Sirotinin acted as the editor-in-chief and contributed a chapter entitled "Reactivity and resistance of the organism."

The Kiev period of the scientific activities of Sirotinin and his associates was characterized by a wide scope of research into the issues of reactivity, allergy and hypoxia, all being studied from the comparative evolutionary perspective. There were annual high altitude medico-biological expeditions to the Caucasus, Pamirs, Altai and Tien-Shan, including the war years (the last one headed by Sirotinin took place in 1976). These were combined with studies in a hypobaric chamber, which was established at the A.A. Bogomolets Institute of Physiology, and then transferred to the Elbrus Medico-Biological Station located at 2100 m above sea-level and opened by Sirotinin in 1972.

While at altitude, measurements of erythrocytes and hemoglobin were performed. It was noted that these indices increased irregularly; along with a considerable rise there was also a fall. According to Sirotinin, this happened due to lysis of erythrocytes, but the products of degradation activated hemopoiesis. The enhancement of hemopoiesis and cell lysis could overlap, thus resulting in insignificant changes in the total number of erythrocytes.

Acclimatization to high altitude was also studied from the standpoint of comparative physiology. Attention was focused on the following main indices of acclimatization: changes in the red blood cells, circulation, res-

piration, and the resistance to acute of hypoxia. Studies involved toads, frogs, lizards, grass snakes, tortoises, hens, turkeys, ducks, geese, hamsters, gophers, guinea pigs, laboratory rats and mice, rabbits, goats, rams, pigs, Himalayan bears, cats, and dogs. As a rule, the expedition participants themselves were also subjects for studies. It was shown that as the organism ascended the evolutionary scale, a higher sensitivity to hypoxia appeared with more developed mechanisms of an active adaptation. Despite this, the resistance to hypoxia is less pronounced in the higher versus lower animals. A similar pattern has been seen in human ontogenesis. In contrast to adults, youths are more sensitive to effects of high altitude, but they acclimate better.

Sirotinin always took a great interest in the effects of hypoxia on the nervous system, particularly on higher nervous activity. Following initial observations on the neuropsychological state at high altitude, the expedition members proceeded to study higher nervous activity by using various methods. As a result, certain disturbances of neuropsychological function were established. The degree of these disturbances correlated with the hypoxia level in the brain. This series of studies was associated with measurements of blood oxygen inflow and outflow in the brain. It turned out that the percentage concentration of blood oxygen, at its lower normal limits at an altitude of 2000 m, led to reduced inhibition and manifested itself as euphoria. At an altitude of 4000 m, the greater degree of hypoxia was accompanied with a more marked disturbance of nervous activity in the form of impairment of the processes of excitation and inhibition.

Sirotinin's assistant, Galina Leontjeva, recalls that Sirotinin took blood samples from his own jugular vein during his ascent of Mt. Elbrus. Academician A.D. Ado has similar recollections. During an expedition to Mt. Kazbek (during the Kazan period), he accompanied Sirotinin together with other members who were undertaking their first ascent. At an altitude of about 4000 m they felt signs of high altitude sickness. It became difficult to go on with the study, and they could hardly rotate a hand centrifuge. Weakness and sleepiness prevented them from continuing the expedition. However, Sirotinin climbed to the top of a mountain by himself and was caught in a snow storm. He did not return for a long time and the rest of the expedition were worried. It took several hours for him to fulfill his plan and come back. His task consisted of collecting blood from one of his own veins.

He was persistent in attaining his goals and demanded the same quality from his pupils. He required not only book knowledge of them, but also the ability to do everything with their own hands. He himself had gone through such a training. In the 1970s, he told one of the authors of this article that when he studied at Saratov University, the medical students were permitted work with patients only after they had shown themselves able to successfully withdraw blood from their own veins in a dark room.

Sirotinin demonstrated that the "time reserve" and "altitude ceiling" could be increased in humans after preliminary acclimatization in high altitudes. He performed these studies on himself under conditions of rapid ascent in a hypobaric chamber, thus exposing himself to danger. These studies, which were begun as early as 1937–1939, emphasized the role of high altitude acclimatization in increasing resistance to a variety of environmental extremes. Afterwards, this idea found a practical use in cosmonautics. Sirotinin is one of the people who established the foundations of space biology and medicine in Russia. Between 1960 and 1967, the laboratory headed by Sirotinin at the A.A. Bogomolets Institute of Physiology was called the Laboratory of Cosmic Biology.

It was long before the war that he first initiated studies on the influence of acceleration of various durations on organisms. For studying the effects of acceleration on animals, centrifuges of various radii (0.22 and 0.65 m) were used. An interesting feature of these studies was that the short-term effects of inertial forces on the body were to induce blood redistribution and, as a consequence, circulatory hypoxia. Sirotinin showed that the resistance to acceleration and hence to circulatory hypoxia (like other kinds of hypoxia) depended on the level of phylo- and ontogenetic development of an organism. In the 1960s, Sirotinin continued these investigations and found that the resis-

tance to acceleration could be increased by preliminary adaptation to altitude, or by decreasing body reactivity by means of hypothermia. Studies were also undertaken on the distribution of Po_2 in tissues of the small animals under the effects of acceleration, on the role of the endocrine glands in the development of compensatory reactions, and on various aspects of tissue metabolism.

In Sirotinin's laboratory, the first studies in Russia were carried out on the effects of hypokinesia on the healthy human organism, and on the result of prolonged stays in a closed limited space. Interestingly, there were studies of the preparation of potable water from human urine, and the feasibility of its repeated usage. Using evaporation methods followed by filtration through ion exchange resins for purification, it was possible to produce water that remained potable for a long time.

In this account of Sirotinin it is difficult to adhere to a strict chronology. At each new stage of work he often returned to the same issues and considered them from a new angle using new methodological approaches. In 1939, Sirotinin published his monograph *Life in Altitudes and High Altitude Diseases*, in which he wrote that the main cause of altitude disease was the alkalosis induced by hyperventilation. The monograph contained a most comprehensive and thorough analysis of this problem. Even today this book continues to be interesting for pathophysiologists, mountain climbers, ecologists, historians of science, and all those who are concerned with the life in high altitudes.

Only those people who had long worked with Sirotinin and knew how reserved he was in expressing his feelings, could understand a peculiar feature of this remarkable book, namely, that it reflected not only the author's erudition, accuracy and honesty, and the scope of his views as a scientist, but also his poetic soul, his penetrating insight into nature, and his great love of mountains. He adored mountains and maintained this love throughout his life. In fact, fidelity was a feature of his character. He remained faithful in his love of one woman, though he had to wait many years for her response. He also maintained a strong loyalty to his teacher, though this devotion brought him eventually into a psychiatric hospital. It will probably be difficult to explain to most readers how this could have happened.

The event was one of the tragedies of bolshevism and of the time when Soviet science was politicized. During the period when Pavlov's teaching had a monopoly, the academic power structure organized a kind of *auto-da-fé* against Bogomolets after his death. A scientific conference was convened at which his pupils were required to criticize his teachings to promote and consolidate Pavlov's ideas. All participants spoke except two, and Sirotinin was one of them. Clouds began to gather above his head. His friends persuaded him to be admitted to a psychiatric hospital lest he be arrested. No written documents exist that provide evidence on this, and we do not look for any. This is a delicate matter; it was told or rather whispered to us by his former associates who are now dead. Even if this is not all true, there are reasons to believe it. It is common knowledge all over the world that some dissidents of the Soviet Union were sent to hospitals for the mentally deranged, but only a few people know that there were times when dissidents went there voluntarily.

We do not know what Sirotinin felt at that time. He never mentioned this episode, nor did he ever speak about any personal affairs. But this was the hardest period in his life. It was at this time that the woman whom he had loved since his youth came to remain with him forever. He was not broken. He was as dedicated as ever to his research. He frequently served as a researcher and a test subject simultaneously. Based on those observations, he later proposed exposure to high altitude as a treatment of schizophrenia.

In the years 1950–1955, 16 cases of schizophrenia were studied in a hypobaric chamber and 30 patients underwent high altitude acclimatization in the mountains near Mt. Elbrus. In both instances, positive results were obtained. By this time, Sirotinin had developed a method for gradual acclimatization to high altitude. It consisted in staying first at an altitude of 800 m, and then ascending and staying for 3–4 days at altitudes of 2000, 3450, 4200, and 4800 m. This gradual increase in the degree of hypoxia provided for an adequate body reaction and development of compensatory

mechanisms, thus leading to an increased nonspecific resistance, and a therapeutic effect. Sirotinin used to emphasize that it was not the hypoxia itself but rather the adaptation to its effects, that is, a compensatory response of the organism to the damaging action of hypoxia, that caused the therapeutic effect.

So far as the mechanism of the curative effect of high altitude for schizophrenia is concerned, a number of factors played a role, including hypoxia, physical exercise, absence of the usual hospital regimen, novelty of impressions, etc. All the above factors led to a breakdown of the existing pathological condition, and to the formation of new interests, as well as increases in the tone of nervous and somatic processes. The stay at altitude was primarily indicated for patients who were in need of resocialization. After exposure to high altitude, the health status of the patients was followed up by Sirotinin who recorded data by means of a film that he shot himself.

In the years 1957–1958, Sirotinin and his associates obtained data on the favorable effects of graded acclimatization in patients suffering from asthma. An attempt was also made to treat anemic patients at high altitude. In the 1970s, the value of the mountain climate combined with antilymphocytic gamma globulin was demonstrated for the treatment of patients with leukemia. The school of Sirotinin found a combination of exposure to high altitude and exercise produced an even greater effect. Each of these acted in the same direction, thus enhancing the action of the other. During exercise, muscle loading induced an enhancement of bodily compensatory reactions, and the exercise level could be increased during acclimatization to altitude. The team headed by Sirotinin took part in the development of optimal high altitude training programs for athletes of various types. This work was proposed by Sirotinin in connection with preparations for the Olympic Games in Mexico.

Sirotinin often stressed that the human organism is constantly exposed to hypoxic challenges over its lifetime. Examples include intrauterine fetal development, and intense muscle activity in the adult. In addition, most human diseases and the aging process itself are accompanied by hypoxia. Death is a consequence of the development of an acute oxygen deficiency—anoxia. Sirotinin studied all variants of the hypoxic state to some extent.

Sirotinin also worked on aging and resuscitation. He made a comparative study of the variables caused by the hypoxia of altitude and old age and revealed a number of similar changes. He also carried out long-term observations (for 40 years) on long-lived individuals in the Caucasus mountains. The data were recorded on film. As a result of his studies, he made recommendations for elderly people engaged in mountaineering, and for improving the fitness of elderly people by exposure to a mountain climate. He also advocated oxygen therapy. The latter consisted in drinking oxygen-foam beverages (fruit juices, beer, etc.), eating oxygen mousse or oxygen ice cream, and using oxygenated cosmetics (oxygen foams, etc.).

Beginning in 1947, Sirotinin's collaborators studied resuscitation . Working with Prof. V.D. Yankovsky and using an artificial heart and artificial lungs, they were able to resuscitate experimental dogs after clinical death caused by drowning in salt water (up to 25 min), bleeding (up to 16 min), electrical trauma (up to 25 min), and acceleration or rapid decompression (up to 17–18 min). They noted that the higher nervous activity of resuscitated animals was not changed noticeably. The Moscow school of resuscitation headed by V.A. Negovsky did not acknowledge these results until, on the initiative of Sirotinin, a joint experiment was performed, demonstrating that successful resuscitation could be achieved because of the great speed of the blood circulation in a resuscitated animals. Studies of this problem conducted over many years led to the introduction of improvements in resuscitation equipment and the creation of artificial lungs for resuscitating newborn babies who had developed asphyxia.

In addition to studying oxygen deficiency, Sirotinin became interested in the reactions of the body to oxygen excess. In experiments involving animals, his collaborators obtained data showing the influence of hyperbaric oxygenation on Po_2 dynamics in tissues, on the processes of tissue respiration, and on the concentration of free radicals in tissues.

In the 1970s, when there was an explosion of

work concerning the transplantation of organs and tissues, Sirotinin became interested in transplantation immunity of hibernating animals, in the importance of hypoxia in allograft rejection, and in the use of oxygen therapy for prolonging the life of a graft. Thus, he had a great diversity of scientific interests, but his studies on hypoxic hypoxia were the most important. During Sirotinin's life, Kiev was called the "capital of hypoxia."

Nikolai Sirotinin, Doctor of Medical Sciences, Doctor of Biological Sciences, and Member (Academician) of the USSR Academy of Medical Sciences, was the author of more than 300 scientific works. He prepared 25 doctors of science and 60 candidates of science. His last work was a monograph entitled *Evolution of Reactivity and Resistance,* which appeared after his death, which occurred in his eightieth year after a short illness. The concepts advanced by him continue to be influential, and are being further developed by his students and followers.

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