HISTORICAL OVERVIEW OF INTERMITTENT HYPOXIA RESEARCH

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INTRODUCTION

"Respect for history distinguishes
the educated from the barbarian."
Alexander S. Pushkin
(Russian poet, 1799-1837)

The science is always inverted to the future. At the same time it is connected with the past closest among all ranges of human activity. As scientists, we have inherited the knowledge from our immediate academic mentors as well as the uncountable pioneers in a particular scientific field. An historical evaluation of scientific achievements is always an extremely delicate job, as there could be the risks of biased or unintentional omission of the men and women who have made appreciable contributions to comprehending a particular scientific problem. Nevertheless, we are taking the challenges and in the present chapter we attempt to draw a rough roadmap for indicating the original sources and noteworthy milestones of intermittent hypoxia research in the modern world, with an emphasized coverage on those happened in the former Soviet Union countries.

INTERMITTENT HYPOXIA RESEARCH IN RUSSIA AND UKRAINE

While interest in intermittent hypoxia has increased only over the last decade in Western Europe and North America, there has been intense interest in this field in the former Soviet Union and CIS (Commonwealth of Independent States) for many decades. However, because many of the scientific publications were in Russian or Ukrainian, which are rarely available in other countries, these research findings remained relatively unknown.

The beneficial effect of a mountain climate was known by the people in the ancient time. There was a legend from Carpatian Mountains (Ukraine) that in an ancient village, children who suffered from asthmatic bronchitis were ranged on foot during 7 days successively on a high sacred mountain, where they were submitted to the influence of special ceremonies and drank high-altitude herbal tea. The children had recovered.

From the 10th century folk medical knowledge was concentrated in Kiev Pechersk Lavra Monastery and other cloisters. The history kept for us the names of such outstanding healers as Holy Agapit (11th century), Georgy Drogobych (1450–1494) who was a teacher of Nicolaus Copernicus (Figure 1), Yelisey Bomell (?–1580), publicly executed in Moscow by Ivan the Terrible, and others who used folk recipes of breath holding and refined them.

Figure 1. Georgy Drogobych (1450–1494),“George from Russ”, the teacher of Nicolaus Copernicus.

Awake scientific communications between Europe and Russia/Ukraine began with establishment by Peter The First the Russian Academy of Sciences in St. Petersburg in 1724. Daniel Bernoulli, Leonard Euler, and Iosia Weitbrecht all worked at this academy. Both Russian and Ukrainian scientists worked in European laboratories during the period of 1700s to early 1900s making valuable contributions to hypoxic science [Dionesov, 1983]. F. Bidder, I. Glebov, and I. Sechenov worked in I. Muller’s lab in Berlin; P. Owsjannikov, E. Cyon, I. Sechenov, N. Kovalevsky, and A. Schmidt worked in C. Ludwig’s lab in Leipzig; L. Orbeli, E. Kreps, L. Shtern, and I. Rozental worked in J. Barcroft’s lab in Cambridge. We could mention many others. In spite of these close connections, many Russian and Ukrainian discoveries did not become the “common property” of the scientific community. We will dwell on this period a little more minutely.

The first Ukrainian researcher in the field of hypoxia professor Ivan Knigin (1773-1830) gave his lectures named "*About respiration*" and "*About slow combustion consisting of organic life*" in 1813. It was Knigin who together with another Ukrainian scientist Alexey Filomafitsky (1807-1849) 30 years prior to Paul Bert suggested that the source of animal heat was not produced from the lung but rather from biochemical transformations in the body [Lange, 1984]. If to compare this fact with another one, viz that Lomonosov in Russia 17 years prior to Lavoisier has yielded scientific bases of oxidation processes nature, it becomes apparent that Russian/Ukrainian scientists were original innovators in the solution of the central problem of physiology - the essence of respiration.

In 1884 in Kharkov University professor Ivan Schelkov (1833-1909) organized on blank space small but good equipped laboratory in which, in particular, he studied gas exchange in muscles. His innovation was that he began to investigate gas exchange not in the isolated organs, as it was accepted at that time, but in the whole organism. In particular, the new contribution to a science was his researches of blood gases flowing off from working muscles and the account of a respiratory coefficient of a muscle in a state of a tetanus. This work initiated the beginning of study the role of carbohydrates in a muscular contraction.

Being reverted to events of the first half of 19^{th} century, we should note that the exchange of information between Eastern and Western scientists was not rather abundant, and many achievements of the Russian and Ukrainian scientists have passed unnoticed. Thus, nine years prior to Claude Bernard's paper, Kiev physiologist A. Valter (1817-1889) described vasoconstrictor nerves. Stimulating frog sciatic nerve, Valter has noted the change of vessels diameter in its foot web and established vasoconstrictor effect of sympathetic nerves [Vorontsov et al., 1959].

Ludwig's Russian pupil Philipp Owsjannikov reported that he and Ludwig had located a "vasomotor center" in the medulla. With his Russian pupil Cyon Ludwig discovered the vasomotor reflexes in 1866. Five years later, while still at Vienna, Ludwig and his Russian pupil Ivan Sechenov (Figure 2) invented a mercury blood pump that allowed them to separate respiratory blood gases *in vivo*. They elucidated the physiology of tissue oxygenation and respiratory gas exchange [Kostyuk & Serkov, 1990].

Figure 2. Ivan Sechenov (1829–1905),"The physiology of tissue oxygenation and respiratory gas exchange".

Sechenov proved for the first time that CO_2 is bound directly to hemoglobin and suggested that the oxygen promotes elimination of CO_2 in lung whereas the increased entering of CO_2 from tissues to plasma facilitates the removal of oxygen by hemoglobin. These data were obtained in south Ukrainian city Odessa in 1873-76 but for a long time were ignored and were not accepted by world society. Later, when in 1928 the presence of carbohaemoglobin in blood was completely proved, scientists began to connect this discovery to names of Henrikes, Christian Bohr and others. Sechenov also has made the important conclusion that an exchange of CO_2 between both blood and alveolar gas and blood and tissues is carried out as a result of diffusion [Sechenov, 1880]. Later this conclusion was confirmed by brilliant researches of the Danish physiologist August Krogh.

Recuring to Ludwig's laboratories we shall recollect rather interesting work - "*Stuffs to Study of Lung Respiration*" executed by other outstanding Russian scientist Nikolai

Kovalevsky in Vienna. He has designed the special device for oxygen analysis. The principle of its device consisted in absorption of carbon dioxide from the animal chamber by alkali and gradual entering of oxygen instead of CO_2 [Lange, 1984]. Thus, Kovalevsky was the first who has offered a principle of gas exchange determination and calculated a respiratory coefficient.

In 1880s in Kovalevsky's laboratory a series researches of circulation and respiration central regulation was undertaken. In 1885, N. Mislavsky published the paper "*About a Respiratory Center*" in which he has established the separateness of inspiratory and expiratory centers in myelencephalon. He postulated the reflex character of rhythmic activity origin of respiratory center [Zefirov, 1984].

The bright pages of close cooperation between Russian and European science were entered by Joseph Barcroft, the outstanding figure in world physiology in every respect (Figure 3). Russian physiology is obliged to Barcroft not only by awake support at the beginning of its development but also that in our country due to his investigations, his original statement of questions and development of new research procedures, the aging and mountain physiology, the respiratory function of the blood and respiratory physiology as a whole have begun to develop and have reached a world level.

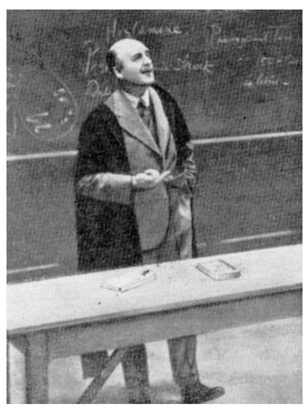

Figure 3. Sir Joseph Barcroft (1872–1947) at lecture.

In the preface to the 1936 Russian edition of the monograph "*Features in the Architecture of Physiological Function*" Barcroft has written: "*The field of physiology owes a great debt to Russian scientists. The hope that governs my thoughts as I write these lines is that Soviet biologists will find valuable crumbs between the covers of this book. I also remind myself that my small contribution does not make even a tiny dent in my debt, but I would like to think of this work as a small down payment in recognition of what we owe to those that went before.*" [Barcroft, 1936] (also see Figure 4).

The Barcroft's first acquaintance with achievement of the Russian scientists has taken place in 1897 when the young Cambridge graduate came to Langley to ask a theme for scientific work [Irzhak, 1983]. Langley has offered him to engage in blood gases flowing off from a salivary gland. Barcroft has addressed to Sechenov's model of the device published in 1859. However, the closest contacts have begun with the YII International Physiological Congress in Heidelberg in 1907. On this congress Barcroft and Lina Shtern have met.

Figure 4. At the XY International Congress of Physiology, St. Petersburg, 1935.
From left to right: A. Hill, N. Shamarina, J. Barcroft, I. Lihnitskaya, E. Chenikaeva, R. Leibson.

Lina Shtern (Figure 5) was the first Soviet woman-academician and first woman professor of the University of Geneva (Switzerland), several new directions in biological chemistry and physiology are concerned. Her works on tissue respiration, in particular, the discovery of enzymes - dehydrogenases together with Prof. F. Batelly, on study of blood-brain and blood-tissue barriers put forward Shtern as one of the leading scientists of Europe. Studying tissue respiration together with Jan Lui Prevot (Prevost) at Geneva University, Lina Shtern carried out series of experiments in which she studied influence of asphyxia on a regulation of respiration and circulation. The results of these works have allowed them to reject a hypothesis of L. Mosso about the existence of spinal respiratory centers. Later, during Stalinism she was subjected to repression and spent several years in prison [Rosin & Malkin, 1987].

Figure 5. Lina Shtern (1878–1968), the first Soviet woman-academician and
the first woman professor of the University of Geneva (Switzerland).

From far Russia in Langley's laboratory Leon Orbeli (1882-1958), the founder of Soviet aerospace physiology in future, has arrived on training [Orbeli, 1971; Ginetsinskii et al., 1957]. Having worked with Langley, Orbeli then joins to Barcroft and carries out with him experiment of lactic acid influence on a hemoglobin dissociation curves. The paper with the results was published in *Journal of Physiology* [Barcroft & Orbeli, 1910].

The revolution of 1917 and subsequent civil war has interrupted the scientific development in Russia and Ukraine. For the scientists there was a serious situation. Many professors of universities were compelled to emigrate. In the period of 1918-1920, twenty one professors of the Kiev University only were lost from typhus, starvation, or were killed.

After the termination of civil war in USSR, the physiological faculties and laboratories at the newly organized universities, medical and veterinary institutes were built. In the beginning of 1930s many young talented scientists were sent again on training abroad. One of them was Eugenie Kreps, an outstanding physiologist and biochemist, encyclopedically educated scientist, one of founders of the comparative and evolutionary directions in physiology and biological chemistry, and an expert in underwater physiology. As a result of his common works with Leon Orbeli in underwater physiology in 1927-1930, the depth and duration of diving were enhanced [Kreps, 1975;1989].

The first scientific victims of Stalin reprisals appeared in 1929-1930. People in the dock were mostly physicians by education and scientists as to their activities. Most of them were old intellectuals and in the opinion of the communist party nomenclature, they were bourgeois and were to be treated as alien elements. The accusations brought against scientists were absurd, inept and absolutely incompatible.

But despite of this dreadful situation the scientists continued to work. At the end of 1930s, the first soviet barometric laboratory was founded in the Leningrad Military Medical Academy [Gurvich & Fainberg, 1938; Krotkov, 1939]. The research works in this facility were not stopped even during the Second World War. In 1946-1949 a detailed study of the central nervous system (CNS) activity during hypoxia was carried out by O. Gazenko and V. Zvorikin, who both investigated the disturbances of CNS activity at various degrees of hypoxemia, as the mechanisms of hypoxic cramps. The large attention was given to research of high-altitude acapnia and mutual relation between oxygen and carbon dioxide (A. Panin, O. Sydorov, V. Skripin, etc.). At that time investigations of hyperbaric influences on respiration and also changing of nitrogen in gaseous mixture on helium were accomplished [Sergeev, 1962; Brestkin et al, 1984]. On the ground of these investigations the fundamental principles of establishment of artificial atmosphere for space vehicles were worked out [Parin & Gazenko, 1963; Gazenko, 1997]. The new stage of aviacosmic biology and medicine is connected to the names of such outstanding scientists as A. Lebedinsky, V. Parin, and O. Gazenko [Grigorjev & Fedorov, 1998]. The brilliant completion of this work was the space flight of the first cosmonaut Juri Gagarin.

There are two viewpoints on the problem of hypoxia. The first concept, belonged mostly to Western scientists, is perfectly expressed in Barcroft's words: "*Hypoxia not only intercepts the machine, but also damages the mechanism*". The second viewpoint is that hypoxia (even severe but brief and intermittent) causes beneficial effects on an organism. The Ukrainian scientists, first of all, Nikolai Sirotinin (Figure 6), were the first to pay a serious attention to the constructive and curative actions of adaptation to hypoxia, remembering the ancient wisdom - "*All is a poison and all is a medicine*". The complete isolation from Western science during that time period of history may have served as the cause of original development of the given direction in Ukraine.

Figure 6. Nikolai Sirotinin (1896–1977). In 1934, he conducted the first research in the field, seeking effective methods for pre-acclimatization. He proposed that only a few days at altitude would increase tolerance to subsequent hypoxic exposure. From such studies the concept emerged that intermittent, repeated exposures to hypoxia could induce acclimatization.

The concept of repeated hypoxic training arose before the Second World War because of the need for altitude acclimatization of Soviet pilots, who flew in open cockpits to altitudes of 5000 to 6000 meters (16000-19700 feet) [Streltsov, 1939]. In 1934 N. Sirotinin conducted the first research in the field [see review, Ivashkevich and Serebrovskaya, 2000], seeking effective methods for pre-acclimatization. Although Sirotinin did not perform experiments using intermittent hypoxia, he proposed that only a few days at altitude would increase tolerance to subsequent hypoxic exposure [Sirotinin, 1940, 1975]. From such studies the concept emerged that intermittent, repeated exposures to altitude could induce acclimatization. In 1930s the methods to increase the endurance to high-altitude flights included a stay at high altitude camps for several weeks, regular high-altitude flights by airplane, training in altitude chambers, and inhalation of low oxygen mixtures [Gurvich, 1938; Krotkov, 1939]. Numerous researches showing the efficacy of repeated decompressions in a chamber were also carried out at that time by Appolonov, Mirolyubov, Egorov, Ctreltsov, Kudrin [Rozenblyum, 1943]. As was usual, the subjects were exposed to 5000 m for one hour per day, over several days for a total of 7 to 11 exposures. During successive altitude exposures, compared with the initial exposure, the higher ventilation and blood arterial oxygen saturation, together with the lower blood PCO_2, implied that ventilatory sensitivity to hypoxia had been increased. Furthermore, the residua of these effects were detected for up to four weeks. Fainberg and Osypov [Gurvich & Fainberg, 1938] reported that 30 minutes to three hour exposures every two to three days for a total of nine exposures, increased the concentration of hemoglobin by up to 12% and red blood cells by up to 22%. Soviet studies such as these led to altitude training of paratroopers, and jumps by a man, Kaitanov, and two women Pyasetskaya and Shishmariova, from the record high altitudes. Later, in 1970s, Agadzhanyan & Mirrakhimov [1970], Katkov et al [1979, 1981], Kovalenko et al [1981] and others showed that a gradual adaptation to hypobaric hypoxia not only facilitated acclimatization, but also improved working capacity and endurance of athletes and spacemen [reviewed by Gippenreiter & West, 1996; Grigorjev & Fedorov, 1998].

Because transport of pilots to mountain environments or utilization of chambers proved expensive and inconvenient, as early as 1938, N. Golubov, R. Levy, and L. Shik [Vorontsov et al, 1959] utilized inhalations of hypoxic gas mixtures for training pilots. Egorov and Alexandrov on the basis of Paul Bert's method of rebreathing with CO_2 absorption, created their own equipment, a device named EA-4, adding oxygen to maintain the O_2 level constant [Gurvich & Fainberg, 1938]. In the intervening years to the present, intermittent hypoxia has been used extensively in the former Soviet Union and the CIS not only for altitude pre-acclimatization [Gorbachenkov et al, 1994], but also it has been proposed for treatment of a variety of clinical disorders [Kolchinskaya, 1993]. Successful development of molecular biology and genetics has created the possibility of more profound researches in Russia and Ukraine. The recent achievements in this field of knowledge are reflected in the different chapters of this book.

It should be mentioned that, in addition to the former Soviet Union, the scientists from other East European countries such as Czech Republic have also made significant and original contributions to intermittent hypoxia research. In fact, the investigators from Prague were among the first groups who studied the effects of intermittent hypoxia on myocardial anoxia resistance and pulmonary circulation [Poupa et al., 1966; Widimský et al., 1973]. Since late 1990s, the Czech scientists expanded their research with a rodent model of anti-ischemia cardioprotection through adaptation to chronic intermittent hypobaric hypoxia [Asemu et al., 1999]. The Chapter 7 of this monograph represents some recent accomplishments by these investigators.

INTERMITTENT HYPOXIA RESEARCH IN ASIA, OCEANA, WESTERN EUROPE, AND USA

The very first PUBMED-retrievable research article referred to intermittent hypoxia was published in June 15, 1945 in *Science* by Ward C. Walstead from University of Chicago, USA. In his article, this pioneering investigator described a marked and progressive impairment in peripheral vision in 65% of the 20 male pilot trainees who were chronically exposed to moderate intermittent hypoxia (*i.e.* simulated altitude of 10000 feet/3000 meter, 5-6 hours per day, 6 days per week, for 4-6 weeks) [Walstead, 1945]. The following Table 1 is an approximate representation of the individual country’s contrition to the body of literature on intermittent hypoxia research. These data should be cautiously interpreted, because their accuracy may be affected by the various forms of key words, which the authors used in their original publications. To our knowledge, many authors (particularly those from the former Soviet Union countries) had used the terms as “repetitive”, “periodic”, or “interval” hypoxia, instead of intermittent hypoxia. The PUBMED search may simply miss or underestimate these relevant and valuable contributions.

Table 1. List of the top 20 ranked countries with PUBMED-indexed publications on intermittent hypoxia (PUBMED search date was February 25, 2009).

Ranking	Country	Total No. of Publications	Years of Publication
1	USA	443	1965-2009
2	Russia	122	1978-2008
3	Germany	106	1985-2008
4	China	80	1979-2009
5	Canada	56	1988-2009
6	Ukraine	55	1992-2008
7	Japan	52	1988-2009
8	France	51	1979-2009
9	Australia	40	1978-2008
10	UK	40	2001-2009
11	Czech Republic	35	1966-2008
12	Italy	29	1989-2008
13	Taiwan, ROC	22	1995-2008
14	Chile	19	1994-2008
15	Sweden	18	1988-2007
16	Ireland	17	1995-2009
17	India	16	1976-2008
18	Spain	16	1991-2008
19	Israel	15	1990-2009
20	Columbia	14	1991-2008

The American researchers have primarily focused on the detrimental effects of intermittent hypoxia since 1970s. For example, James McGrath and his colleagues in United States and at the Czechoslovak Academy of Sciences had shown the significant right ventricular hypertrophy and paradoxically enhanced anoxic tolerance of the right ventricular muscle in the rats exposed to chronic intermittent hypoxia [McGrath & Bullard, 1968; McGrath et al., 1973]. Other researchers later found in anesthetized, chest-open canine models that intermittent global or alveolar hypoxia potentiates pulmonary vasoconstrictor response to hypoxia [Unger et al., 1977; Miller & Hales, 1980]. However, this potentiation effect was not confirmed in the subsequent study in chest-closed dogs [Chen et al., 1985]. There were few studies demonstrated the time course of plasma erythropoietin levels following various modes of intermittent hypoxia in humans [Knaupp et al., 1992] and mice [Seferynska et al., 1989].

As clearly indicated in Figure 7, there was a sharp surge in the number of publications on intermittent hypoxia has started from the time point between 1999 and 2000. This “millennium effect” is most likely related to a doubling increase in research funding levels of National Institutes of Health in USA during the second term of President Bill Clinton. This could be another good example how the governmental policies and financial support towards biomedical research can substantially influence the productivity and quality in a particular scientific area.

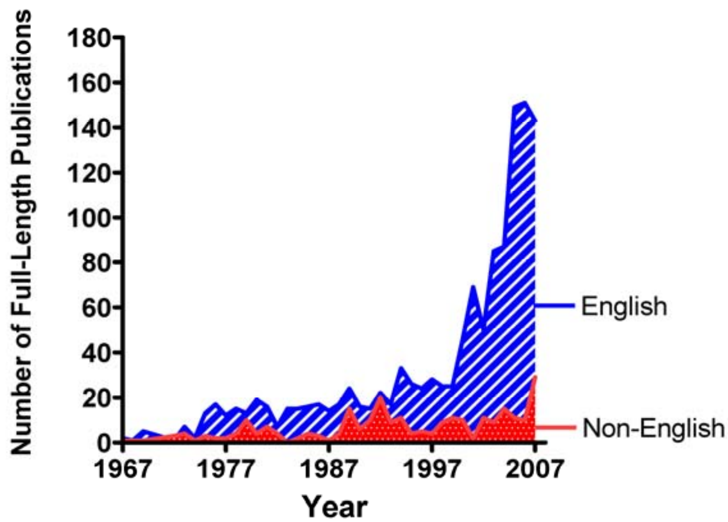

Figure 7. A forty-year trend of intermittent hypoxia research in terms of the number of publications indexed in PUBMED under the keyword "Intermittent Hypoxia".

In particular, on November 29, 1999, the National Heart, Lung, and Blood Institute of USA had announce a Request for Applications (RFA) titled as "Oxygen Sensing During Intermittent Hypoxia", which aimed to improve our understanding of how intermittent hypoxia contributes to the pathophysiology of cardiopulmonary, vascular, hematological, and sleep disorders. The NIH committed $3.6 million in Fiscal Year 2000 to fund up to 14-16 new grants in response to this RFA. Most likely, this unprecedented governmental support in this specific field had produced the sharp increase in the number of publications after 2000 indicated in Figure 7. Notably, the *Journal of Applied Physiology* published a series of review articles and original studies on this topic in 2001 [Mitchell et al., 2001; Prabhakar, 2001]. In addition, a new journal named *High Altitude Medicine and Biology* has launched in 2000 under the chief-editorship of Prof. John B. West from the University of California at San Diego. Since then this journal has published a number of review and original articles intermittent hypoxia [*e.g.*, Powell & Garcia, 2000; Serebrovskaya, 2002; Tin'kov & Aksenov, 2002; Brito et al., 2007], with a more balanced international coverage on both of beneficial and injurious effects. All of these efforts and interests had undoubtedly revitalized the intermittent hypoxia research. This book has also collected some most recent advances from the leading U.S. researchers (e.g. Chapters 9, 17, 18).

However, for the purpose of this RFA, intermittent hypoxia was defined as repetitive hypoxic episodes lasting up to 2 min. Due to this policy restriction, the increased NIH funding had barely distributed to support the studies on the beneficial effects of other modes of intermittent hypoxia. Consequently, only a few laboratories in USA have maintained the studies on the beneficial side of intermittent hypoxia. There are two areas worth to mention. The first area is the "living high-training low" principle, which was first proposed by U.S. investigators in late 1990s [Levine & Stray-Gundersen, 1997], for a more effective enhancement of sea-level exercise performance. Another area is on the cardioprotective effects elicited by systemic intermittent hypoxia. The researchers from Johns Hopkins

Medical Institutions [Cai et al., 2003], University of North Texas [Zong et al., 2004], and Virginia Commonwealth University [Xi et al., 2002] had established various rodent and canine models of acute or chronic intermittent hypoxia to study the novel cellular and molecular mechanisms underlying the cardiac ischemia-resistant phenotype induced by intermittent hypoxia.

On the other hand, the intermittent hypoxia research in Western Europe had primarily focused on its detrimental effects, particularly under the pathological conditions such as sleep apnea. For example, in 1990s investigators from France, Italy and Ireland [Freminet et al., 1990; Benzi et al., 1993; Savourey et al., 1994; McGuire & Bradford, 1999] had published several studies related to intermittent hypoxia. More recently, a German research group demonstrated that habitual snoring (i.e., snoring frequently or always) was associated with poor academic performance in the 1144 third grade primary school children who participated this study [Urschitz et al., 2003]. Interestingly, such a relationship between snoring and poor academic performance was also found in children without intermittent hypoxia and intermittent hypoxia alone did not show an independent association with poor academic performance. However, a later study by the same group suggested that the nadir of pulse oximeter saturation (SpO_2) values in a population-based cross-section of 995 primary school children was significantly associated with impaired academic performance. Both the mild (SpO2 91%-93%; odds ratio: 1.65; 95% confidence interval: 1.06-2.56) and moderate hypoxemia (SpO2 < or =90%; odds ratio: 2.28; 95% confidence interval: 1.30-4.01) were associated with impaired performance in mathematics. [Urschitz et al., 2005]. Researchers from Germany also recently reported that a daily 1 h exposure to intermittent normobaric hypoxia (10-11% O_2) for 15 consecutive days had no effect on aerobic or anaerobic performance in 20 endurance-trained subjects [Tadibi et al., 2007]. Similar negative results were previously published by British investigators [Morton & Cable, 2005].

To the contrary, a well-established hypoxia laboratory in University of Oxford demonstrated the anti-hypoxic cardioprotective effects induced by chronic intermittent hypoxia (8% O_2, 12 hours per day, for 21 days) in guinea-pigs [Mohan et al., 2001]. Similar beneficial effects of acute intermittent hypoxia were confirmed by a group of investigators from University of Grenoble, France, who have been quite active in this field since 2005 [Béguin et al., 2005; also see Chapter 1 of this book]. Such different results could be explained by different regimens of hypoxia exposure and variability of individual reactivity to hypoxia. These are very important factors since low doses of hypoxic exposure cannot intensify adaptive/beneficial mechanisms, whereas excessive exposures to severe intermittent hypoxia may provoke dangerous pathological processes.

Coincidentally, a similar abrupt increase in intermittent hypoxia related publications from China, Japan and Taiwan was also evident for the same time period (started from late 1990s). Although intermittent hypoxia related literature was published by Chinese investigators as early as 1979, right after the end of infamous “Cultural Revolution” (1966-1976), which severely disrupted the biomedical research activities in China. The real take-off for the investigations specifically focused on intermittent hypoxia occurred around the beginning of 21^{st} century. There is a very active research laboratory headed by Zhao-Nian Zhou from the Shanghai Institute of Physiology, Chinese Academy of Sciences. These investigators have published more than 23 papers since 2000 [Zhong et al. 2000] and become a driving force in elucidating the molecular mechanisms of intermittent hypoxia-induced cardioprotection [Zhu et al. 2006]. In Japan, the earlier studies on intermittent hypoxia were related to its regulatory effects on systemic and pulmonary blood pressure [Iwase et al., 1992; Okabe et al. 1995]. Since 1998, a research group led by Miharu Miyamura at Nagoya University has become very active in intermittent hypoxia studies [Katayama et al., 1998]. They have published more than a dozen of original research articles to characterize the effects of in sedentary subjects and endurance athletes. Their key findings are well described in the Chapter 11 of this book, contributed by one of the leading Japanese researchers in this field – Keisho Katayama.

For the rest of Asia, several investigators in Taiwan have shown impressive productivities since 2001, particularly in the area of intermittent hypoxia-induced neuroprotection [Lai et al., 2001; Lin et al. 2002]. The Chapters 15 and 25 of this book are contributed by two of the Taiwanese principle investigators. A number of research groups in India also contributed in innovative ways to the literature. Notably, the researchers from the Nutrition Division of the Defence Institute of Physiology and Allied Sciences in Delhi have consistently published since 1990, primarily focused on the hematological, endocrinal, and skeletal muscular adaptation to intermittent hypoxia [Sawhney et al., 1990; Vats et al., 2001; Dutta et al. 2008]. In addition, a researcher from the All-India Institute of Medical Sciences in New Delhi was the first to demonstrate an inhibitory effect of intermittent hypoxia on male reproductive system in primates [Saxena, 1995].

Intermittent hypoxia research in Australia was pioneered by a group led by an internationally renowned respiratory physiologist - Colin Sullivan, who established the first clinical sleep laboratory in that country in 1979. His invention in 1980 of nasal continued positive airway pressure (CPAP) has revolutionized the treatment of obstructive sleep apnea. Sullivan and colleagues were also among the first to identify an augmentation of normoxic ventilation following repetitive exposures to hypoxia in conscious dogs [Cao et al., 1992]. More recently, his colleagues at The University of Sydney also had sustained interests and innovation in the areas of intermittent hypoxia related to pediatric sleep apnea [Machaalani & Waters, 2003] and athletic training [Townsend et al., 2002]. Four Australian researchers have also contributed to this monograph (Chapters 26, 30).

CONCLUSION

Similar to what happened in all other scientific disciplines, it has taken a global effort to fundamentally advance the intermittent hypoxia research. Historically, scientists from East European countries were the pioneers for discovering and utilizing the beneficial effects of intermittent hypoxia to pre-adapt or precondition the human body against environmental stressors and various diseases, whereas the majority of their counterparts in West Europe and North America were primarily aware of the injurious effects of chronic intermittent hypoxia associated with sleep-disordered breathing. However, during the past decade, such a gap of division between East and West has been shrinking. The tremendous technological advances with Internet and political transformations have fundamentally changed the way and efficiency of communication among scientists from any corners of the world. We are expecting this trend of vigorous research on intermittent hypoxia continues in the years to come and certain new discoveries in this field would eventually benefit the health and well-being of entire humanity.

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