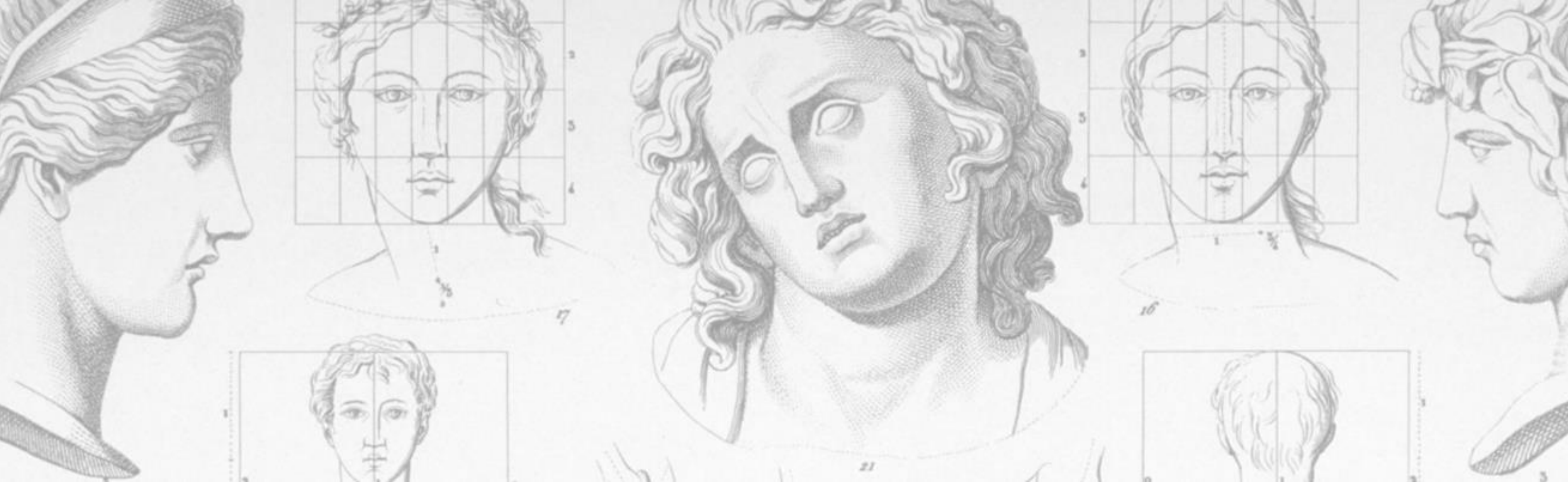

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Jan Bures

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Jan Bures

BORN:

Ctyri Dvory, Ceske Budejovice, Czech Republic
June 13, 1926

EDUCATION:

Faculty of Medicine, Charles University, Prague, M.D. (1950)
Czechoslovak Academy of Sciences, Prague, Ph.D. (1955)
Czechoslovak Academy of Sciences, Prague, D.Sc. (1963)

APPOINTMENTS:

Institute of Physiology, Czechoslovak Academy of Sciences (1952–present)

HONORS AND AWARDS (SELECTED):

Central Council of the International Brain Research Organization (1964–1979)
Governing Council of the International Brain Research Organization (1992–1998)
Council of the European Neuroscience Association (1992–1996)
Member of Academia Europea (1992)
Honorary Doctorate, University of Lethbridge, Canada (1992)
Foreign Associate, National Academy of Sciences, USA (1995)
Foreign Member of the Polish Academy of Sciences (2000)
Honorary Member of European Brain and Behavior Society (2000)
Honorary J. E. Purkynje Medal, Czech Academy of Sciences (2001)

Jan Bures pioneered the reversible ablation technique by programmatic analysis of the morphological, physiological, and behavioral effects of spreading depression. He further studied the neurophysiology of vertebrate learning, adopting an integrative and systems-level approach to the analysis of animal cognition.

Jan Bures

The aim of an autobiographic chapter is to assess the significance of various factors which may have oriented the subject to science. The two main factors usually considered are genetic endowment and environmental influences. In my case, there is no evidence of intellectual activities in my remote paternal and maternal ancestries. Not much clearer are the environmental factors arousing my early interest in science. But environmental factors in the politically hot climate of Central Europe created situations that tested the resilience of my decision to pursue science and demonstrated the support offered by the international scientific community to the individual scientist.

My father, Rudolf Bures, was born in 1874 at a small farm in central Bohemia. As a younger son he had no chance to stay at the farm and decided, therefore, after termination of his military service in the Austrian army to join police work in gendarmerie. He learned German, passed a number of examinations, mastered good knowledge of the Austrian Law, and became a junior police officer in Trhove Sviny, a small town in South Bohemia. Here in 1904 he met my mother, Marie Pislova, a 20-year-old daughter of a local wheelwright. She had just returned from Vienna and Prague, where she had been working for a year as a maid. Her father, who died before I was born, was a known artisan. Unfortunately, his plans to modernize the workshop were frustrated by the premature death of his eldest son who died as a prisoner of war in a Russian camp during World War I. His two younger sons, Peter and Josef Pisl, were the first members of the family to receive a high school and university education: Peter as a lawyer, working later as a small town notary, and Josef as geodetic engineer, who graduated at the Prague Technical University and was working there as an Assistant Professor until 1934, when he retired because of health problems and returned to his home. He was a true scholar with encyclopedic knowledge and vast files of excerpts from all fields of science, spoke four foreign languages (German, French, English, and Russian), and was always prepared to help children in the neighborhood to master difficult problems in mathematics, physics, and foreign languages. On the other hand, he was a very impractical person, unable to manage the small fields he owned and the old house in which he was living. He never married and was until his death dependent on the help of his older sisters, Cecilia and later of my mother. This was probably the reason why I admired him, but did not find him an attractive example.

My brothers Rudolf and Charles were born in 1906 and 1910 when my father's gendarmerie unit was stationed in Borovany, a small village close to Trhove Sviny. After the end of World War I, which led to collapse of the Austrian empire and the birth of independent Czechoslovakia, he advanced to a more senior position in the Czech gendarmerie and was moved to Ctyri Dvory, now a suburb of the large town Ceske Budejovice, better known to Americans under the German name Budweis, from which the name Budweiser beer is derived. Famous beer has been produced in this locality since the 15th century. The closeness of the city and the many high schools simplified access for my brothers to education. They both attended Jirsik's gymnasium in Ceske Budejovice and after graduation went to study medicine at the Medical Faculty of the Charles University in Prague, the oldest university in Central Europe, which had been founded by the Czech king and Roman emperor Charles the IVth in 1348. When I was born in 1926, Rudolf was already a medical student and Charles was in the last years of high school. The history of my family illustrates rapid transition from a farmer-artisan status to intellectually active middle class, characteristic for the Czech population in the first half of the 20th century.

What could be the important environmental factors attracting me to science in my childhood? Although infantile amnesia seems to block reliable recollection of episodic memories from the first four years of my life, some information can be obtained from my relatives. I was born to old parents, but this did not put me at a disadvantage, because my mother exposed me as much as possible to the company of other children in the neighborhood and spent a lot of time reading me books, which were probably intended for considerably older boys, but which surprisingly aroused my interest and motivated me to hear more. My brothers advised my mother not to read me the standard fairy tales, but something they considered more interesting—adventure stories, geographical discoveries, and science fiction. Taking into account what was available at the time in the Czech language, my mother's choice was Jules Verne. In my preschool years, I was exposed to at least 20 books by this wonderful author, some of them repeatedly, because I insisted that the particularly interesting passages be read to me again and again. The admirable patience of my mother was soon rewarded by my motivation to be independent of her reading. As soon as I learned to read, I attempted to use this new skill for rereading the already known books and for exploring the content of other promising volumes. In fact, this early experience, akin to imprinting, made me addicted to books. I still remember how deeply impressed I was during my first year in the high school in Ceske Budejovice by visiting the municipal library which allowed the juniors like myself to visit the shelves with thousands of books and select those they wanted to borrow for home reading. I learned that books in a public library can be appreciated, not only according to their content, but also according to the traces left on them by their readers. Impact factors and citation rates of the electronic era were reflected in the worn down look of the most popular books.

Another less apparent consequence of the early reading was that I accepted and identified myself with the Jules Verne's philosophy. Some of his books were an impressive glorification of knowledge and of creativity supported by knowledge. Cyrus Smith, the hero of his book *Mystery Island*, is an engineer whose balloon carrying four other passengers wrecked on a deserted island. Although they have nothing more than the content of their pockets, engineer Smith finds a solution for all their problems. He shows his friends how to make fire, what to eat, and where to find safe dwelling. He shows his friends how to make fire, to find safe dwelling, to prepare bricks from baked clay, to produce iron by melting iron in a blast furnace, to domesticate wild animals, to start a plantation from a seed found in a pocket, to synthesize nitroglycerine and use it for construction purposes, to estimate the geographical location of the island and find ways to leave it. Cyrus Smith demonstrates that man can do something from nothing, provided that he has the necessary knowledge. It seems that the possibility of applying knowledge to solving problems of vital importance impressed me already at this age and that I accepted that changing the world for the benefit of mankind was the ultimate purpose of knowledge and science.

In 1931 my father retired from the gendarmerie and our family moved from Ctyri Dvory to Trhove Sviny to live in the house of my aunt Cecilia, who had recently died. Beginning in the autumn of 1932, I attended here the first four classes of primary school. I was good in reading and counting, but had problems with calligraphy and drawing, which has persisted throughout my life. At the age of 10, I prepared for the entrance examination to the Jirsik's gymnasium in Ceske Budejovice, the high school attended by my brothers. I passed the exam and in September 1936 started to study there. I was living in a rented room within walking distance of the school and returned on Sundays by train and bus to my parents in Trhove Sviny. This was a very dramatic time in international politics: Hitler occupied Austria and insisted on annexing the Sudeten, regions of Czechoslovakia at the border of Germany and Austria with majority of German population. Our government, relying on French and British support, invested enormous effort into fortifications and weapons for defense of the Czechoslovak territory, but in the critical negotiations between Germany, Italy, France, and Great Britain taking place in September 1938 in Munich, the Western powers agreed with the German demand and recommended to the Czechoslovak government to yield all territories with German majority to Germany. Because all the fortifications were close to the German border, this made the remnants of Czechoslovakia not defensible. Within several weeks, the Czech population was forced to leave the to-be-occupied regions and find resettlement in the central parts of the country. It was obvious that this was only a temporary solution. On March 15, 1939, the German troops occupied the rest of Czechoslovakia and split it into the Protectorate of Bohemia and Moravia and into independent Slovakia. The democratic Czechoslovakia was destroyed, and the legal basis of personal security, equality, free speech, and foreign travel suddenly disappeared. Most students in my class were affected by the takeover in some personal way. My older brother Rudolf, who ran a medical practice in Ctyri Dvory, was imprisoned by Gestapo on the first day of occupation because he was the chairman of the local organization of Friendship with the Soviet Union. He spent several months in Czech prisons before being finally transported to the German concentration camp Buchenwald. He had the good luck to be released two years later, shortly before the German invasion of the USSR. There were other more sad fates. A number of Jewish students were at first forced to leave schools and start working at menial jobs. Later they disappeared when their families were shipped to concentration camps. Gestapo had a large network of confidants who reported all forms of anti-German attitudes, which were punished in the most severe way (death penalty for listening to the Czech transmission of the BBC). The pervasive atmosphere of terror made even 13-year-old boys and girls very reticent in the company of unknown people.

In spite of the stressful conditions, school followed the traditional curriculum. There were more hours of German language, other disciplines (Czech history, literature, and art) were purged of topics unacceptable for the occupants, and some books were removed from the school and public libraries. But mathematics, physics, chemistry, geography, and languages (Latin and French) remained untouched. I became most interested in mathematics and physics, and in anticipation of future development, I attempted to improve my language education by learning English and Russian. I passed the final examination (which had to be done in the German language) in June 1944. There was no opportunity to continue study because the Czech universities had been closed since 1939 after students' protests against occupation. We had to work in factories or in agriculture, constructing runways at the military airport and repairing damage caused by Allied bombers. I acquired a number of useful skills during this period (working on a turning lathe and using tools for fine mechanics) and came to know different people, all hating the war and hoping that they would be lucky enough to survive and to do something to prevent a relapse of this nightmare.

The war ended in South Bohemia, the southern part of which was taken by the American army and the northern part by the Soviet army. Many lives were lost in the last days of war because the retreating German troops, particularly the SS divisions, fought desperately to escape the Russians and to surrender to the Americans.

With the end of war, the University opened and started to compensate the losses. The priorities were to allow students whose study was interrupted in 1939 to finish their education as fast as possible and to prepare the University for accepting into the first years of undergraduate studies all students accumulated over the six years of university closure. I arrived in Prague already in June to study mathematics in the extraordinary summer semester. This proved to be a wrong decision, because the introductory lectures I attended in the overcrowded lecture halls of the Faculty of Mathematics and Physics were explaining the philosophy of basic mathematical operations and appeared to me trivial and uninteresting. I believed (probably correctly) that my failure to appreciate mathematics was due to a lack of talent and decided to try my luck in a field that was successfully mastered by my brothers, i.e., medicine.

Medical Faculty of the Charles University in Prague

In September 1945, I became a student of the Faculty of Medicine. The first-year lectures were attended by several thousand students and were given in the big entertainment center Lucerna, seating more than 1000 people. The textbooks were another difficulty that could be only partly overcome by the use of German books. The first two years of medical study were devoted to preclinical disciplines, including physics, chemistry, biology, embryology, histology, anatomy, and physiology. In spite of the overcrowded lectures, the teaching done by the best professors we had was interesting and sometimes exciting. Thus, the fact that liquids are incompressible was demonstrated in the course of medical physics by a pistol shot into a cardboard box filled with water. Whereas the totally filled closed box exploded upon the impact of the bullet, a partially filled box was only penetrated by two small openings. It is regrettable that this demonstration was later removed from the course program as too dangerous for the audience, although it could be nowadays included in the psychology course to demonstrate facilitation of memory acquisition by emotional experience.

I was particularly impressed by lectures in biology, delivered by Professor J. Belehradek (who later emigrated to Great Britain, and lectures in physiology, delivered by Professor V. Laufberger. The two courses were very different in style. While Belehradek based his teaching on his textbook published before the war, which contained an excellent survey of pertinent international literature, Laufberger offered students improvised mimeographed texts prepared by his assistant professors and concentrated his attention on creating a practical course in physiology, giving a detailed step-by-step description of the theoretical principles, technical tools, practical procedures, and expected results of the experiments the students had to perform. Similarly different was the content of their lectures. Whereas Belehradek described systematically the theoretical and philosophical issues and the current trends of world research, he did not speak much about the work done in his laboratory. Laufberger's lectures did not attempt to explain physiology, but to describe what he found interesting and on what research problems he was currently working. In the first years after the war, he was interested in neurophysiology; in the work of Norbert Wiener; in recording electrical activity of nerves, brain, and heart; and in the design of simple robots. His lectures were often difficult to understand, but they conveyed clearly his enthusiasm, explained his hypotheses, and described the experiments by which he wanted to confirm them or to falsify them.

During the second year I participated with a group of students in a two-month-long public health service operation aimed at the inoculation of children in North Moravia against tuberculosis and other contagious diseases. Here I met an attractive and pleasant girl, Olga Komoradova, an optimistic and energetic colleague, interested not only in clinical medicine, but also in science. We were both members of the Communist party and participated actively in the political life of university students. We rapidly found that we shared many important views and that we would like to live together. Three years later we married, and on December 23, 1949, our daughter Olga was born while we both were in the last year of medical study.

When studying the preclinical disciplines, I paid attention not only to the lectures, but also to the possibility of joining some ongoing research. This was most common in anatomy, which needed demonstrators for practical courses in osteology, for dissections, and for preparation of schematic illustrations for teaching. Several years of such student work in anatomy was an excellent recommendation for surgery or pathology and was popular among students with clear ideas about their future medical career. This was not my case, because the first two years of medicine had increased my interest in biomedical research and reduced my motivation to become a physician. I wanted to join a field offering the possibility of independent experimental work under the guidance of an experienced colleague, but I knew that the choice of the field would be determined by the available opportunities. Thus, my decision for neuroscience was a result of rational assessment of the advantages and disadvantages offered by the various laboratories I explored.

The most attractive opportunity was the Laboratory of Experimental Neurophysiology, organized in the newly established Central Institute of Biology. Its head, Assistant Professor Zdenek Servit, was a young neurologist who believed that advances in diagnosis, prevention, and therapy of diseases can only be achieved by strong basic research. His primary target was epilepsy, a common neurological disease due to disturbed interaction of excitatory and inhibitory mechanisms, which he wanted to study by using an evolutionary approach, comparing epileptic seizures at different levels of phylogenetic and ontogenetic development. He was a pleasant, eloquent man with limited experimental experience, but with excellent knowledge of pertinent literature and with the skill to prepare and write research reports. He was offered two large rooms on the second floor of the Institute of Physiology of the Medical Faculty, salaries for two technicians, and the possibility of recruiting students who would like to stay as employees after graduation. In early spring 1948 I became, as a third-year medical student, a member of his group.

First Steps in Science

The laboratory was not yet equipped for experimental work, but because Servit considered it important to announce its existence by some published paper, he suggested that I help him prepare a statistical study evaluating medical records of almost 4000 epileptic patients treated during the previous 15 years by the Neurological Clinic. The vast material was collected by students who transcribed the relevant information from the case sheets into prepared questionnaires. My task was to organize the collection of data and to perform statistical analysis of the results. The first part of the study was published two years later (Servit and Bures, 1950), and the second part was published in 1952. Animal experiments, started in 1949, were aimed at testing the hypothesis that the grand mal epileptic seizure is similar in various representatives of vertebrates. The seizure was elicited by transcranial electroconvulsive shock applied to mice (*Mus musculus*), lizards (*Lacerta viridis*), and frogs (*Rana temporaria*). The similar size of these animals simplified the question of whether differences in threshold current eliciting clonic-tonic convulsions of the limbs could be explained by brain volume or should be ascribed to evolutionary factors. I addressed this problem together with Mojmir Petran, another medical student who preferred basic research to medical practice and joined Servit's laboratory. Mojmir, who was an expert in physics (he contributed later to the invention of the confocal microscope), introduced me to the use of measuring instruments and cathode ray oscilloscopes. After several months of preliminary experiments, we proposed the density of the quantity of electricity passed between an intraoral electrode on the palate and a cranial electrode on the occiput as the best estimate of threshold, which was 92 uAsec/mm^2 in mice, was 3 times higher in lizards, and was 15 times higher in frogs. Still more important was the fact that mice and rats had the same threshold, 92 uAsec/mm^2, although rats were 10 times heavier than mice (Bures and Petran, 1952). Several other papers studied the effect of hypothermia, the effect on seizure threshold of hydration of the brain, and the effect of positive or negative DC current, which was applied on the head against a large indifferent electrode on the belly.

Ph.D. Dissertation

Simultaneously with the examination of the phylogenetic development of epilepsy, directed by Professor Servit, I was working on an independent project that was the subject of my Ph.D. thesis. In fact, this degree was called at that time "candidate of science" (CSc.) because Czechoslovakia and other countries of the East Block modified the system of academic degrees according to the Soviet model. After consultations with Professor Servit, who was my supervisor, I decided to study an interesting form of epilepsy, the so-called audiogenic seizures, which can be elicited in rats and mice by strong acoustic stimuli, e.g., by jingling a bunch of keys or by exposing the animal to a 120-dB bell. The advantage of this model was that unlike spontaneous epilepsy, the acoustic reflex epilepsy could be elicited by a defined stimulus that made it possible to trace the spread of excitation from the acoustic projection to mesencephalic and prosencephalic structures mediating the generalization of the seizure, manifested by convulsions and by high amplitude spikes and waves in the EEG. This seemed to be a feasible task, but difficulties soon emerged. The incidence of audiogenic epilepsy in the Wistar rats available in Prague was rather low and not reliably reproducible. The first thing was to introduce a sensitizing procedure, increasing the susceptibility of the animals to the acoustic stimulus. This was easy, because a subconvulsive dosage of pentamethylentetrazol (50 mg/kg) increased the percentage of susceptible animals to 50%. A more serious difficulty was the EEG recording. The only EEG apparatus in Prague was an eight-channel Grass device donated to Czechoslovakia by the United Nations Relief and Rehabilitation Administration (UNRRA). It was used for the examination of patients at the Neurological Clinic of the Medical Faculty. Its use for animal experiment was an almost clandestine operation made possible by cooperation with staff employees of the clinic.

In spite of the above technical and organizational problems, I succeeded in finishing in three years (1950–1952) six experimental studies related to the theme of my dissertation, which was completed and submitted in December 1952. The individual papers were published in 1953 in Russian or English in *Physiologia Bohemoslovaca*, and their English summary appeared 10 years later (Bures, 1963). The main results illuminated behavioral, integrative, and electrophysiological aspects of reflex epilepsy.

Since the electrophysiological experiments had to be done on restrained animals, it was necessary to examine the effect of restraint on seizure susceptibility. It was found that gentle fixation of the forelimbs and one hindlimb reduced the incidence of audiogenic seizures in sensitized rats or mice from 70 to 10%, but that longer lasting restraint (10 min) lost its inhibitory effect and rather increased seizure susceptibility. If the animal exposed to the auditory stimulus, made ineffective by restraint, was re-exposed to the auditory stimulus when free, no seizure was elicited. This blockade was not due to the duration of the preceding restraint, but to the duration of the preceding acoustic stimulus, which probably left some persisting inhibition in the auditory system. The subsequent study compared the effect of restraint and of other strong stimuli on the blocking of audiogenic seizures. Similar inhibition elicited by electric shock to the lower part of the body started 30 sec after the shock and disappeared 3 min later. Audiogenic seizures were also blocked by forced swimming. It was also demonstrated that repeated presentations (six to eight) of the inhibitory stimulus decreased its efficiency to control level.

Attempts to identify the anatomical substrate of audiogenic epilepsy showed that the first seizures in rats coincided with the maturation of cerebral cortex, i.e., with the appearance of cortical postural reactions and of acoustic evoked responses in auditory cortex. Another study indicated that elimination of the major sensory modalities (vision, olfaction, audition) as well as blockade of most somatosensory and visceral sensations by myelotomy decreased seizure susceptibility. Finally, analysis of the effects of hypothermia on seizure susceptibility indicated that while susceptibility to electroconvulsive shock is not changed by reduction of body temperature to 20°C, audiogenic seizures cannot be elicited at temperatures below 27°C. This is not due to blockade of auditory responses in the cortical projection area where evoked potentials remain preserved at 21°C, but rather at some subcortical level.

Postdoctoral Period

I found the work on the dissertation very stimulating—I could ask questions that I considered interesting, find the best way to solve them, and decide how to interpret the results. Although Professor Servit was a very liberal boss who liked to discuss research with his co-workers, he usually prepared an outline of the project and took responsibility for the formulation of the final version of the manuscript. I believed that the dissertation had qualified me for a more independent position. We discussed the problem in detail and although Professor Servit was not quite enthusiastic about it, he agreed to give me more freedom. This was not too painful for him, however, because this was a period of rapid growth of our science. The Central Institute of Biology became one of the institutes of the newly organized Academy of Sciences, and it was expected that it would rapidly grow by training dozens of new scientists. Ernest Gutmann, the most qualified neuroscientist in the country, was asked to form a Department of Muscle Physiology. He emigrated before the war to England, studied biology in Oxford, and got a British Ph.D. with J.Z. Young as supervisor. He had extensive experimental experience and understood how modern science should be done. It was very fortunate that he was around when *Physiologia Bohemoslovaca*, the foreign language output for Czech research, was started and when the institute library was organized. Another mature scientist who appeared in Servit's group was Friedrich Eckert, a specialist in comparative physiology of invertebrates. He was a former Assistant Professor at the German University in Prague, who married before the war a Jewess and after German occupation of Czechoslovakia refused to divorce her. His moral integrity saved her life for which he paid several years of imprisonment in a concentration camp.

Servit had a number of new graduate students, some of them (Josef Zachar, Daria Zacharova, and Domin Svorad) coming from Slovakia and others from Bohemia (Olga Hudlicka, Vera Novakova, Zdenek Martinek, Libuse Chocholova, Jaroslav Sterc, and Zdenek Lodin). He allowed me to find, investigate, and publish my own research projects; to collaborate with my wife Olga, who left the position of Lecturer at the Physiological Institute of the Medical Faculty and was concluding her Ph.D. dissertation under Servit's supervision; to use the help of two technicians for our experiments; and to find additional postgraduate students whose Ph.D. dissertations would be related to our program.

While the above negotiations were proceeding, we started to look for an interesting, promising, and feasible theme that could serve as a reliable basis for team research. The possibility appeared in one of the joint papers (Servit et al., 1953) that examined the effect of DC current on the duration of anesthesia. Later analysis (Bures, 1954a) of EEC changes, observed in the polarized hemisphere, indicated that the current onset is accompanied in the cortex adjacent to the polarizing electrode by a striking decrease of EEG amplitude which spreads during several minutes over the entire neocortex. The properties of this phenomenon closely resembled spreading EEG depression (SD), described 10 years earlier by Leao (1944). To identify it as SD required recording the negative slow potential wave accompanying the wavefront of the EEG depression and determining the velocity of propagation (3 mm/min), the two characteristic markers of SD. Convenient DC recording was achieved by the chopper technique (Goldring and O'leary, 1951), which made it possible to record the slow potential directly in one EEG channel, the input of which was short-circuited and only once per second briefly connected to a 1 μF condenser placed between the non-polarizable calomel cell electrodes that were applied to the points where the potential difference was measured. This was demonstrated in a subsequent paper (Bures, 1954b), which also reported that SD can be elicited in non-anesthetized rats and that its properties are not different from those seen under anesthesia. These findings seemed to us sufficient for considering SD as a suitable theme for collective multidisciplinary research. In fact, I am still surprised that our plan to study the very abstract, academic problem of SD did not meet opposition, but was well accepted. The reason was probably the atmosphere of intellectual preparedness for phenomena mediated by non-synaptic interaction of neurons. SD fitted well into the vague, but plausible concept that besides nerve impulses the brain employs other means to integrate its activity. While most examples of ephaptic transmission, propagation of nerve signals across cuts and field-mediated synchronization of activity of large neuronal populations, were poorly reproducible, SD remained the only robust and reliable example of phenomena of this class. This was true not only for Western science, but perhaps still more for Soviet neurophysiology, paying much respect to the mysterious concepts of dominant state, parabiosis, and perielectrotonus. Particularly the dominant state, wherein activation of a nerve center increased its responsiveness to a wide range of nonspecific stimuli, seemed to be related to the problems of neural plasticity. Although skepticism prevailed, the underlying beliefs, expectations, and doubts kept the idea of non-synaptic integration alive and gained support for projects offering reasonable chances to address the above questions.

Laboratory of Physiology of the Central Nervous System

Ten years after the discovery of SD, the field was well surveyable, and it was not difficult to accumulate in a couple of years reprints of pertinent papers and to establish contact with the most active research groups. On the basis of such a survey, we tried to formulate the list of the principal research directions connected with SD.

1. Manifestations and concomitants of SD
2. SD eliciting stimuli and conditions blocking SD development
3. Morphological substrate of SD; SD-prone and SD-resistant structures of the vertebrate brain; and phylogenetic and ontogenetic aspects
4. Metabolic nature of SD and SD-related phenomena
5. Electrophysiological consequences of SD in remote brain structures
6. Behavioral manifestations of SD and its effect on innate reactions and on acquisition, consolidation, and retrieval of conditioned reactions

We have split our effort and attempted with Olga to cover in the next two years the above six directions and to explore the possibility of their detailed investigation. Olga took responsibility for point 6, in particular, for developing her idea to use SD as a functional ablation procedure allowing examination of the role of the depressed cortex in different stages of memory trace formation and retrieval. I concentrated on electrophysiological and other technical problems, and we both participated in individual papers according to the time we had spent on them.

The start of the SD project was made possible by another technique of SD initiation: application of DC current to exposed cerebral cortex was replaced by chemical stimuli applied on filter papers to the dura-covered bottom of trephine openings (4 mm in diameter) prepared in the parietal bones. While 1% KCl solution elicited usually a single SD wave, 25% KCl evoked a train of SD waves accompanied by continuous EEG depression lasting 2–3 hr (Bures and Buresova, 1956b). Such prolonged depression was well suited for examination of long-lasting consequences of functional decortication, e.g., for demonstration of reduced excretion of a 5% water load (Buresova, 1957a), of reduced metabolic thermoregulation (Buresova, 1957b), and of blockade of unconditioned reflexes and natural conditioned reflexes (Buresova, 1956). The latter studies were included in Olga's Ph.D. dissertation entitled "Physiological Consequences of Stimulation of the Central Nervous System by Direct Current and by Potassium Ions." Application of chemical substances to the cerebral cortex could also be used for estimation of the threshold concentrations of SD-eliciting compounds or of drugs blocking SD initiation or SD propagation (Bures, 1956; Bures and Buresova, 1956a). Important contributions to the SD-related phenomena were the papers describing the terminal anoxic depolarization of the cerebral cortex and its modification by local treatment of the cortex (Bures and Buresova, 1957) or by systemic application of drugs (Benesova, Buresova, and Bures, 1957). The metabolic aspects of SD were addressed in a study comparing the metabolic effects of 0.1 M KCl on brain slices with the mechanism of the metabolic processes leading to SD initiation by the same KCl concentrations (Bures, 1956). Similarly, the dependence of SD on the body temperature of rats indicated that between colonic temperatures 20° and 40°C the amplitude of the negative slow potential changes with Q10 = 1, and the SD propagation rate and the duration of the slow potential change with Q10 = 1.7 to 2.0 (Bures et al., 1957). Finally, the morphological aspects of SD were addressed in a study describing the development of SD and of terminal anoxic depolarization during the first 20 days of postnatal life in rats (Bures, 1957).

The results obtained in the three years 1953–1956 confirmed the expectation that the SD project can support meaningful research into the mechanisms of cerebral functions and is closely related to investigations performed in a number of international neuroscience centers. In addition, five papers were published in refereed international journals and thus proved their capability to compete with international production. On the basis of these results, we were given three positions for graduate students who would cover the most promising areas of our SD research: metabolism (biochemist Jiri Krivanek), morphology (anatomist Eva Fifkova), and functional organization of the brain (Tomas Weis). We were also given the positions of an electronic engineer and of three technicians specialized in biochemistry, histology, and electrophysiolgy. In 1958, our team was officially declared the Laboratory of Physiology of the Central Nervous System, and I was nominated its head.

The new employees were coming between 1956 and 1958. The first was Jiri Krivanek, who started immediately with a demanding biochemical program. His main task was to support the electrophysiological analysis of SD by finding the chemical concomitants of the slow potential shift and of the EEC depression. Already during his first year he found that the depolarization of cerebral cortex during SD and anoxia is accompanied by a dramatic decrease of phosphocreatine in the depolarized cortex (Krivanek, Bures, and Buresova, 1958). Soon followed papers describing the decrease of glycogene and glucosis and the increase of lactate in the SD-affected tissue (Krivanek, 1958). His not less important task was to verify Grafstein's (1956) hypothesis that the SD spread is mediated by diffusion of potassium ions liberated from depolarized neurons. This was studied by washing the exposed cortical surface with isotonic NaCl and by comparing the leakage of potassium ions from the normal cortex and from the depolarized cortex into the washing fluid. Although it took at least 2 min to accumulate sufficient volume of the superfusion fluid for measuring the K^+ concentration in the sample with a flame photometer, the method was sensitive enough to show that SD presence is accompanied by a fivefold increase of potassium in the washing fluid (Krivanek and Bures, 1960). This indicated at least a fivefold increase of potassium concentration in the extracellular space during the negative slow potential. The assumption that the real increase can be several times higher was confirmed only 15 years later after ion-sensitive electrodes became available.

Eva Fifkova, an assistant in the Institute of Anatomy of the Medical Faculty, started to work with our group as an externist. She prepared with J. Marsala from the same Institute the first version of a Czech stereotaxic atlas and later performed histological controls for individual electrophysiological studies. She joined our department in 1958, and her main task was to study the morphological substrate of SD, particularly the boundaries of SD propagation in the neocortex, hippocampus, caudate nucleus, thalamus, and cerebellum of rats and in the striatum of pigeons. The above studies formed the basis of her later Ph.D. dissertation.

Tomas Weis started to work in our laboratory as a medical student and returned to us several years later after completion of his medical training as a graduate student. Since he was not technically specialized, he concentrated on electrophysiological analysis of remote effects of cortical or hippocampal SD on subcortical structures and on integrative functions, e.g., sleep.

First International Contacts

The Academy of Sciences was aware of the necessity to establish direct contacts with scientific institutions abroad and between individual scientists, but foreign travel was extremely limited in the first postwar decade. In autumn of 1954, the Academy arranged for me and Jiri Krecek, our colleague working in developmental physiology, a two-month visit to Soviet research centers in Moscow and Leningrad. I wanted to visit laboratories performing electrophysiological experiments in animals, and my hosts did their best to show me all they had. In Moscow I visited the Institute of Higher Nervous Activity and saw the laboratories of Academician V.S. Rusinov, met his co-workers G. Kuznetsova and I. Kozlovskaya, and thoroughly studied his recording equipment that was even according to the Czechoslovak standards desperately obsolete. In spite of the technical shortcomings, experiments showing that the dominant focus produced by polarization of motor cortex attracts acoustically elicited responses were interesting and impressed me as a useful model of plasticity. On various occasions I was asked to give seminar talks describing our current research. The seminars were well attended, but the discussion indicated that most participants were not aware of the existence of SD and were surprised that I did not use Pavlovian terminology to interpret it. I had to explain that there were no reasons to consider the decrease of EEC as a sign of some form of Pavlovian inhibition and that reliable electrophysiological markers of behavioral inhibition were yet to be found. My attitude was not understandable to an audience accustomed to accepting explanations based on old concepts that had never been sufficiently proven, but whose authority should not be questioned. Poor knowledge of non-Russian literature was due to the low percentage of scientists able to use foreign languages and by the absence of English journals in the libraries of the institutes. However, even access to Russian literature was limited by ideological considerations. During one month in Leningrad I was hosted by the Institute of Physiology of the Academy of Sciences. I spent a lot of time in the library of the Institute trying to look up Russian journals not available in Prague and was deeply shocked to find that many volumes had been obviously censored in a very crude way, by removing whole pages or by gluing them together so that they could not be read or by blackening names or whole lines or paragraphs that mentioned scientists who were prosecuted in some political process. Attempts to find an explanation were not answered.

I was later advised by the Russian colleague responsible for my scientific program not to ask questions that cannot be answered or that could expose the questioner to unpleasant interrogation later. The main conclusion drawn from the two months spent in Russia was that in the coming years our field could expect from this country neither technical innovations nor theoretical advances. On the other hand, I found among the people I met in the Russian institutes a number of talented, enthusiastic researchers who wanted to work in Prague and who later succeeded to visit us for shorter or longer periods.

An important consequence of my visit was increased visibility of our group in Russia. We were put on the list of potential foreign partners for collaborative projects, which could not be implemented in the Soviet Union alone. This was illustrated by collaboration with Kh. S. Koshtoyants, an Armenian scientist and Professor of the Moscow State University, who learned about our experiments demonstrating that the SD-eliciting potency of KCl can be counteracted when adding to the KCl solution a definite concentration of $CaCl_2$. He wanted to find some way to test the detoxicating effect of glutathion on the toxicity of $HgCl_2$ and suggested he perform a simple experiment during his several months-long stay in Prague which could (1) test the possibility of eliciting SD by local application of the thiol group poison $HgCl_2$ on the exposed cerebral cortex and (2) test the possibility of blocking the $HgCl_2$-elicited SD by supplying reactive SH groups with an appropriately concentrated solution of glutathione. The experiments performed in a few weeks showed that 5% $HgCl_2$ elicits a train of six SD waves when applied on intact neocortex, but that it remains ineffective when applied on cortex pretreated for 5 min with 10% glutathione. This effect of glutathione was limited to $HgCl_2$ and left the SD waves elicited by KCl unchanged. The results were published in *Proceedings of the Soviet Academy of Sciences* (Bures and Koshtoyants, 1955).

International Congress of Physiology

Perhaps the most important international contact in this period was my participation in the XXth International Congress of Physiology in Brussels. The Czechoslovak Physiological Society sent an official delegation including 17 scientists from the universities and Academy of Sciences and helped the delegates with the language editing of their papers. Our English journal, *Physiologia Bohemoslovaca*, prepared a supplement containing extended versions (3–7 pages) of the 17 contributions of the Czechoslovak delegates. Our abstract in the Congress proceedings (Bures and Buresova, 1956b) and its three-page version in the supplement (Bures and Buresova, 1956c) were the first English reports describing the use of SD as a functional ablation procedure.

Entering Big Science

In autumn of 1957, I was invited by the Georgian Academy of Sciences to participate in the Third Gagra Conference on the Mechanism of Conditioned Reflexes. The conference took place from January 13 to 24, 1958, in a recreation center of Soviet VIPs in the Black Sea resort of Gagra. These conferences organized by Academician I. S. Beritashvili were the most influential meetings of Soviet specialists dedicated to open discussion of controversial problems in the ideologically sensitive field of higher nervous activity. The first conference on bioelectrical phenomena in 1948 was followed by a longer interval due to administrative persecution of Beritashvili by the Stalinist leaders of the Academy who accused him of not being loyal to the materialistic interpretation of Pavlov's ideas. Beritashvili refused to denounce his belief that the behavior of animals is determined not only by conditioned reflexes but also by so-called images, complex representations of the world surrounding the animal, and of corresponding expectations of possible consequences of specific behaviors. After Stalin's death in 1953, Beritashvili's situation gradually improved, and this was manifested in the second Gagra conference on excitation and inhibition in 1955 and in the third conference that should have included also several scientists from Poland, Hungary, and Czechoslovakia. Since the other invited guests were not able to come, I remained the only foreign participant at the conference. Because I had a very junior position in the Czechoslovak Academy of Sciences, the invitation was a surprise not only for me, but also for my superiors. The mystery was solved only during the conference.

The most talented co-worker of Beritashvili, A. I. Roytbak, had written in 1955 a book, *Bioelectric Phenomena in Cerebral Hemispheres*, with a pertinent review of relevant literature. A chapter of this book was devoted to the SD phenomenon, and its properties attracted scientists studying mechanisms of nervous integration. Among the papers quoted by Roytbak were also my two articles on SD published in *Physiologia Bohemoslovaca* in 1954. The paper describing the possibility of eliciting SD in the cortex of non-anaesthetized intact rats was considered particularly important because it opposed the assertion of Professor Gedevani, a Georgian rival of Beritashvili, that the slowly spreading inhibition in the cerebral cortex can only be observed in deep barbiturate anesthesia. In this way I became, without knowing about it, an ally of the Beritashvili clan and a person whose invitation seemed desirable. In addition, Roytbak's assessment of my qualification was wrong. Roytbak had sent in September 1955 a copy of his book "to professor Jan Bures." This dedication suggested that he believed me to be a rather senior person and prepared Beritashvili and the conference organizers for receiving an important representative of the Czechoslovak Academy. I realized all this suddenly in the first minutes after landing at the airport in Adler, the closest airport to Gagra. Although there were only a few passengers disembarking from the plane, it took almost 30 min before the members of the welcome committee who came in two cars to take me to the conference place in Gagra decided that the young boy not at all corresponding to their expectations was the person they should take to the conference. It seemed, however, that as soon as the disappointment was overcome, they were quite happy that I was not a stuffy professor but somebody prepared to answer all their questions and to learn about their problems and plans.

I learned only during the conference about still another reason for my invitation to Gagra. Representatives of the Soviet Academy of Sciences were negotiating with a group of Western scientists about the possibility of organizing an international scientific forum that could help governments find peaceful solutions to the problems of the Cold War period. Study of the brain, psychology, and education seemed to be the fields best suited for this purpose, and the plan was to start this venture with an international conference to be held in October 1958 in Moscow. A Soviet scientist entrusted with the organization of the Soviet block participation in this conference was G. D. Smirnov, whom I had briefly met during my visit to Moscow in 1954 and who was also a participant at the Gagra conference. He explained to me that Gagra was one of the last preparations for the Moscow meeting and that the Soviet speakers would be selected from the Gagra speakers. It seemed that I was invited to Gagra to demonstrate what I could present in Moscow and to discover how I would manage the stresses of the lecture and subsequent discussion.

The first days of the conference were devoted to study of the 16 papers to be presented. The actual lectures and discussions took place from 11:00 AM to 6:00 PM so that the participants had plenty of time to prepare their discussion and edit their contributions that had been prepared by the organizers for later publication. Presentation of the paper (not more than 1 hr) was followed by questions, which were immediately answered by the speaker, and by general comments, summarily answered in the concluding statement of the speaker. The discussion was sometimes very critical, but was always motivated by a sincere effort to find the proper solution to controversial problems. Our paper, "Application of Spreading EEG Depression in Research into the Mechanisms of Conditioned Reflexes," elicited a number of technical questions and critical comments by the representatives of the Vvedenski's school (N.V. Golikov) who wanted me to use Vvedenski's terminology when describing and explaining SD. To this request I replied in a rather harsh way: "I appreciate the historical significance of Vvedenski's contribution to electrophysiology, but I am also aware of the fact that his main discoveries were made 70 years ago. I believe that dogmatic acceptance of his ideas and hypotheses hinders the development of contemporary methodological approaches, which make it possible to understand the nature of the studied phenomenon. This is why we refused to explain SD using Vvedenski's terminology and concentrated our effort on metabolic, physicochemical, physiological and morphological analysis of this phenomenon." I was glad to see that this position was shared by most participants at the conference, who refused the tendency to reduce research problems to a terminological level.

After the conference I was invited to visit Beritashvili's institute in Tbilisi to learn more about his current research, which was concerned mainly with the problems of spatial orientation of animals and humans. He was interested in our plans to concentrate on the physiology of memory and to use SD as a research tool for this purpose. Although he was already quite old at that time, he was very well informed about the recent development of the field and advised me how to do various experiments of a cognitive character. During the conference I met not only the present, but also the future leaders of Soviet neurophysiology, among them P. G. Kostyuk, who became my good friend.

The Gagra conference showed me some weak points in our research. One of them was the absence of unit activity recording required for assessment of remote effects of cortical or hippocampal SD on subcortical structures. To fill this gap, I obtained an Academy fellowship for a three-week visit to the Institute of Physiology of the University in Pisa, where Professor G. Moruzzi had established one of the best microeloectrophysiological laboratories in Europe. I arrived in June 1958 and was accepted in a friendly way. After detailed discussion of my plans with Professor Moruzzi, I was offered an equipped laboratory with a stereotaxic apparatus and microdrive, a two channel preamplifier, and an oscilloscope. I was shown how to prepare tungsten microelectrodes and how to introduce them into the reticular formation of rats and record activity of reticular neurons. In two weeks I was able to obtain reliable recordings and to demonstrate to Professor Moruzzi a marked increase in the firing rate of reticular neurons shortly after elicitation of cortical SD.

While unit activity recording was the main goal of my stay in Pisa, I was less impressed by the organization of the research. The Institute had only three staff employees: Professor Moruzzi and two assistant professors, Arduini and Mollica. Research was mainly done by foreign or Italian students who worked in the Institute for one to three years. During my stay there were four foreign students from Canada, Japan, West Germany, and Chile, as well as five Italian students. Research was organized around the three staff employees. In the autumn, groups consisting of one to two foreigners and one to two Italian students were formed around the three oldest employees. They started to work on agreed projects and tried to complete parts of them in a way that would allow preparation of manuscripts in July. The project continued the following autumn with a partly changed team and somewhat updated goals. I was impressed by the excellent results produced by this simple informal system, based on the prestige of Professor Moruzzi and on the motivation of the visiting scientists, who worked very hard to obtain in the short time available results that would give them the opportunity to become co-authors of publications and confirm their affiliation with a leading research center. I hoped that our laboratory in Prague would one day be able to follow this wonderful example and become similarly attractive for visitors who would come to learn something interesting while contributing to an exciting research project.

After returning to Prague, I spent all summer recording reticular units in our laboratory. The amplified spikes were detected by a Schmitt trigger circuit and converted to standard rectangular pulses which were passed through a diode to a condenser. After 30 sec the condenser was discharged by a relay and started to be charged again. This simple integrator made it possible to record slow changes in unit activity produced by spreading depression waves in the ipsilateral cerebral cortex. Shortly before the Moscow colloquium, our Institute was visited by two American participants at the meeting, M. A. Brazier and H. W. Magoun, who wanted to see our laboratories and speak with people doing this research. They spent almost the whole day in our laboratory, seeing the experiments with SD in freely moving animals, slow potentials in cerebral cortex, and accompanying unit activity changes in remote brain structures. They asked many pertinent questions, offered much useful advice, and seemed to be impressed by what they saw.

The Moscow Colloquium

The meeting in the House of Science from October 6 to October 11, 1958, was attended by 26 scientists from the USSR, 7 scientists from the Central and Eastern Europe, and 1 scientist from China. The Western participants were from the United States (4), France (3), and one each from Belgium, Netherlands, Italy, England, India, Japan, Mexico, and Canada. The Eastern participants presented 16 lectures coinciding in 11 cases with the talks given at the previous Gagra conference. The Western participants presented 13 talks. The proceedings of the conference, including also the discussion following individual talks, were published in 1960 as a supplement of the journal *Electroencephalography and Clinical Neurophysiology* and are rather well known. The main theme of the conference was the dispute about the locus of the plastic changes underlying the formation of conditioned reflexes. While the representatives of the Pavlovian school (Livanov, Trofimov, Anokhin, and Voronin) insisted that the CS-US association proceeds in the cortex, Gastaut suggested that the closure takes place in subcortical structures, especially in the reticular formation and in the non-specific thalamic nuclei. The attempts to find support for either position by electrophysiological evidence did not yield convincing results. Our lecture was well accepted because it approached the same problem in a different way, i.e., by using an easily identifiable electrophysiological phenomenon precisely located in space and time as a functional ablation procedure, testing the brain regions that are in a definite time window indispensable for elicitation of the conditioned reaction. I received flattering commentaries from Professors Magoun, Chang, and Bremer. When Professor Voronin wondered why blockade of the preferred forepaw by SD does not lead to an immediate switch of the habit to the contralateral limb, Professor Jasper mentioned his earlier experiments showing by other functional ablation procedures (local cooling or Novocain anaesthesia) similar effects on handedness. Professor Sarkisov considered rats unsuitable for research of this kind, because their cortex is insufficiently differentiated, and suggested that we pay more attention to the role of subcortical structures in the organization of conditioned reflex activity.

An important result of the Moscow colloquium was the unanimous resolution of its participants to form a permanent international organization for the study of brain, facilitating contacts between scientists interested in brain research. Owing to the efforts of Professors A. Fessard and H. Jasper, this goal was included in the UNESCO program and soon led to the birth of the International Brain Research Organization (IBRO). One immediate consequence for myself was an invitation to visit the United States and to participate in a conference in some respects analogous to the Gagra meetings.

Conference on Central Nervous System and Behavior

I was invited by the Josiah Macy Jr. Foundation to take part in the second conference of the Central Nervous System and Behavior series. This series of 5 yearly conferences was attended by a stable group of about 20 prominent scientists who were each year joined by an additional 10 visitors invited to report on topics relevant to the program. I had to speak about reversible decortication and behavior, V. S. Rusinov spoke about manifestations of conditioning in the human EEG, and E. Grastyan spoke about hippocampus and conditioning. An unusual feature of the Macy conferences was the stress placed on the discussion between the participants. The organizers believed that formal talks taking 90% of the time at standard conferences gave the speakers too much influence on the course of the conference. To give the audience a better opportunity to influence the conference program, it was recommended that the main talk be interrupted by questions, objections, and comments. It was hoped that in this way it would be possible to direct the attention of the conference to problems more important than those covered by the speaker. Although this expectation was not always confirmed, the approach led to rapid clarification of controversial points and increased attention by the audience. In fact, the lecture sometimes resembled a cross-examination in a courtroom rather than a scientific discourse, but the moderator usually succeeded in giving the speaker enough time for presentation of the main points of his talk. This can be quantitatively documented by my talk that was interrupted 94 times by 13 discussants, among whom the most active ones were Jim Olds, Paul MacLean, Frank Fremont-Smith, Dominick Purpura, and Karl Pribram. I learned from this form of discussion how many inaccuracies and ambiguities were present in my presentation and how important it was to try to reduce their frequency. I also found how superficial my preparation was for entering new areas of research (e.g., the anatomical and functional relations of neocortex and the hippocampal formation) and how important it was to lay firm ground to study the morphological boundaries of SD.

After the conference I was given an extremely well selected and efficiently organized tour through neuroscience centers related to my research interests. During four weeks I had the opportunity to visit the following places: the laboratories of H. C. Magoun and J. D. Green at the University of California, Los Angeles; the laboratories of R. W. Sperry and A. van Harreveld at the California Institute of Technology, Pasadena; the laboratory of J. L. O'Leary at Washington University, St. Louis; the laboratory of Jim Olds at the University of Michigan, Ann Arbor; Xavier University, Cincinnati; the laboratory of R. E. Myers, Walter Reed Army Institute, Washington, DC; the laboratory of W. H. Marshall at the National Institutes of Health, Bethesda; and the laboratories of H. Jasper and D. L. Burns at McGill University, Montreal. Particularly important for me was the opportunity to meet the leaders of contemporary SD research, Marshall and Van Harreveld, as well as other scientists who had made important contributions to the field (Burns and O'Leary). This formed a safe basis for future contacts based on personal friendship. Not less important was the opportunity to establish contacts with Sperry and his former student Myers, whose split brain work we tried to replicate and to expand in our reversible split brain studies. The one-week visit to Jim Olds started an intercontinental collaboration examining the influence of cortical SD on self-stimulation of various subcortical motivation centers. The resulting paper (Bures et al., 1961), the electrophysiological part of which was done in Prague and the behavioral part in Ann Arbor, led to the conclusion that cortical operant mechanisms are greatly suppressed during SD and that this effect blocks all approach behavior and the operant components of aversive behavior.

My trip to America had not only scientific, but also political aspects. The possibility of meeting a large sample of American scientists and discussing with them not only science but also everyday social and economical problems of the world convinced me that political confrontation of East and West is counterproductive and that it is necessary to seek goals on which the two systems can agree. A similar attitude was shared by many American colleagues. Perhaps this was best expressed in a joke often told by Frank Fremont Smith, who suggested that when seeking a slogan which would be acceptable to all races, religions, and political factions, it is best to start with a moral that is understandable even to animals. According to his opinion, the best slogan corresponding to such criteria is "Kids are O.K." He believed that exchange visits of large samples of the young population between countries may considerably improve international relationships. Something confirming this view happened during my short visit to Xavier University, the purpose of which was not quite clear to me, because no SD-related research was conducted there. I was asked, however, to explain to the biology students, assembled in a large lecture hall, what research I was doing, what its purpose was, and what benefits it may bring to people. I did my best, stressing the importance of biomedical research and the hope it brings to patients and to their families. In a subsequent discussion I answered a dozen questions concerning university education, medical care, social conditions, financing of research, etc. After the lecture, the professor who had introduced me explained how happy he was to have me as a living example of the fact that people on the other side of the Iron Curtain are much the same as here, have similar problems, and try to use the same means to solve them. Since Xavier University is one of the Jesuit Universities in the United States and he was a priest, his statement impressed me as a sincere expression of a feeling of the need to overcome the antagonisms of a bipolar world by belief in the force of common human values.

Second International Meeting of Neurobiologists, Amsterdam, 1959

The series of meetings started in Gagra in 1958 was concluded in the autumn of 1959 in Amsterdam by a conference on Structure and Function of the Cerebral Cortex to which I was invited to deliver a talk about metabolic aspects of SD. The paper summarized the chemical substances, the local application of which elicited SD, and the metabolic interventions (anoxia, hypoglycemia) facilitating subthreshold SD-evoking stimuli and described biochemical changes occurring in the cortical regions invaded by SD. Among the discussants were B. Grafstein, A. Van Harreveld, and McIllwain.

The First Book

The first years of electrophysiological research performed with limited access to expert instruction forced all students working in Servit's department to read very carefully the technique sections of the articles they used as the basis for their planned experiments. Of course, quite often we were not able to get some important detail and then had to go to other papers of the same author or had to try a different approach that was described in a more accurate and reliable way. Sometimes it was easier to substitute the missing information by trying a tentative solution that mostly did not work as expected, but helped us understand the theoretical principles involved. All these efforts were informally discussed among three technically minded investigators, M. Petran, J. Zachar, and myself. Petran was an expert in physics and electronics, Zachar was an expert in the muscle and peripheral nerve electrophysiology, and I specialized in electrochemistry and electrophysiology of the central nervous system. After five years of collaboration, we came to the conclusion that the experience we had accumulated in the course of our work could be described in a book, which might serve as an introduction to electrophysiology for graduate students and biomedical researchers. The idea was to write a book that would combine the necessary technical information with detailed description of individual experiments to be performed, covering the principles involved, apparatus and material, animal preparation, procedure, results, and their interpretation. Muralt's *Practical Physiology* for medical students served as an example of a similar book. It was required that the simple experiments be described at a level guaranteeing reproducible results.

After we decided to write and agreed on the general plan of the book, we started to explore the possibility of its publication. Our first choice was Academia, the publishing house of the Academy of Sciences, which was supposed to publish scientific monographs coming from the institutes of the Academy. A preliminary assessment of the proposed manuscript was done by the publication committee, which was chaired by the Vice President of the Academy, Professor V. Laufberger. He rejected the original plan to write the book in Czech because according to his opinion "nobody will read such a book written in Czech" and suggested to Academia that they offer an English version to foreign publishers interested in possible co-editions of attractive titles. He probably liked our cookbook idea of recipes for specific experiments, because he used Muralt's book as a model for his *Practical Physiology*, but I was never sure whether he believed that our book could succeed in international competition or whether he wanted to show three obviously immodest youngsters that they had overestimated their creativity. Surprisingly, Academic Press was interested in a co-edition; we found an English-speaking physiologist, our colleague Peter Hahn, to serve as translator and language editor and two anatomists from the Medical Faculty of the Charles University in Prague, Eva Fifkova and Josef Marsala, to serve as authors of sterotaxic atlases of the brains of rat, rabbit, and cat, which would form a part of the book. The book was ready for publication in 1959 and appeared simultaneously in Prague and in New York in 1960.

In the last year before publication, we wanted to obtain preliminary reviews of various chapters of the book from experts familiar with the subject. While in most cases we got very positive comments and constructive recommendations, some of our invited advisors tried to dissuade us from writing the book. One of them was Professor H. Grundfest, who read during a short stay in Prague several chapters and told us in subsequent discussion that he appreciated very much our effort, but believed that the experiments could be described much better by more experienced scientists who were sensitive to possible pitfalls and who could provide wider interpretation of the results. Needless to say, we were rather worried by such outspoken skepticism. We tried to explain that it was not our intention to write a fundamental treatise, but a practical handbook which would summarize the minimum information necessary for running typical experiments. We hoped that the readers would decide whether this form was what they wanted. And the readers did. The book was sold out in a year. A new printing was published in 1962, and an extended new edition was published in 1967. A Russian translation appeared in 1962 in a huge number of copies. A year later the book was translated into Chinese and published 3200 copies.

Countless discussions with the readers revealed the most probable reasons for the popularity of the book. The students usually stressed the fact that the book contained the information sufficient for simple experiments that are easy to do and that correspond well to their interests. The teachers using the book in practical courses asked the students to follow the book and to contact their instructors only when something does not work as expected. They believed that the book not only saved their time, but that independent attempts of the students to find the correct solution considerably improved their understanding of the problem.

Research Orientation in the 1960s

The series of conferences was followed by a more quiet period in 1960. Contacts with French colleagues led to invitations to two interesting symposia in 1961. One was concerned with audiogenic epilepsy, a field I had left almost 10 years ago, but for me it was the first opportunity to discuss my results with colleagues who could give me useful advice. The second Conference on the Physiology of Hippocampus, organized in August 1961 in Montpellier, corresponded more to my current interests. It was attended by a number of leading specialists I had met earlier (Albe-Fessard, Fessard, Gastaut, Grastyan, Jasper, Lissak, MacLean, and Marshall). I appreciated the talks by Per Andersen, Brenda Milner, and Eric Kandel and the informal discussions with them. Since I knew Kandel's paper (Brinley, Kandel, and Marshall, 1960) on the role of potassium ions in the mechanism of SD, I asked about his further plans and was surprised by his decision to leave not only the SD research but also the promising electrophysiology of hippocampus described in his contribution to the conference and to start investigations of the plastic changes underlying learning in the simple nervous system of the *Aplysia*.

In January 1962, I participated in the Fourth Gagra Conference with a talk describing the use of cortical SD in rats for the study of the tonic influences of the neocortex on the subcortical centers. Further results of this research were reported in September 1962 on the XXII International Physiological Congress in Leyden, Netherlands, where our group contributed three papers (delivered by Bures, Buresova, and Weiss) describing the effect of cortical SD on spontaneous unit activity and evoked responses in thalamic and hypothalamic centers. In March 1963, I was invited by the British Biological Council to the symposium Animal Behavior and Drug Action, taking place in London. In my talk I reviewed results of our experiments describing the effect of atropine and physostigmine on EEC activity and on the acquisition and retrieval of the passive avoidance reaction. After the end of the symposium, most of the participants were invited to continue the discussion in a Ciba symposium that, among other things, paid attention to the possible use of SD as a functional ablation procedure in pharmacological experiments. From late August to early October, due to an invitation of the American Psychological Association, I spent almost seven weeks in the United States, where I attended the XVIIth International Congress of Psychology in Washington, the 71st Annual Meeting of the American Psychological Association in Philadelphia, and the First Conference on Learning, Remembering, and Forgetting in Princeton. At the International Congress, I gave in the symposium Neurophysiology of Learning, organized by R. Galambos, a lecture "Functional Dissection of the Mechanisms of Learning," which was discussed in detail by Larry Weiskrantz. In the intervals between the above meetings I visited, according to a plan carefully prepared by my hosts, a number of neuroscience laboratories in Bethesda, Boston, Cambridge, Providence, New Haven, New York, Rochester, and Houston. The most important new contacts established were with Professor H.-L. Teuber and his group (Chorover, Schiller, and Altman); Dr. Gerstein at MIT; David Hubel and Torsten Wiesel at the Harvard Medical School in Boston; Pfaffman at the Brown University, Providence; Neal Miller at Yale University; and Professor Roy John at Rochester.

The international conference Reflexes of the Brain organized by the Soviet Academy of Sciences and by the IBRO to celebrate the 100-year anniversary of the publication of Sechenov's book of the same name was the last important meeting of the year. Our contribution described the progress made by applying SD to the analysis of the mechanisms of conditioning. I paid special attention to the boundaries of SD propagation, to the duration of unit inactivity during an SD episode, and to the possibility of disrupting conditioned responses seen in the activity of subcortical neurons by cortical SD. Unlike the case of the Moscow colloquium, SD was discussed in two other papers by Meshcherski and Narikashvili, who worked on rabbits and cats, respectively. This led to disagreement about results concerning the effect of cortical SD on evoked responses in specific thalamic nuclei, probably due to incomplete invasion of different cortical layers in cats and rabbits. International recognition of our group was manifested in 1962 by my election to the Central Council of the IBRO. The fact that I was elected as a member at large by postal ballot of the IBRO membership probably reflected publications in journals and participation in international conferences attended by the IBRO members.

The next year, 1965, was very busy. It started with the symposium "Cortico-Subcortical Relationships in Sensory Regulation" organized in February in Havana by the Academy of Sciences of Cuba for 30 participants from 13 countries. We contributed two papers, one describing the use of thalamic SD as a tool for differentiation of cerebral cortex by thalamic spreading depression and the other describing the modulation of reactions of colliculus inferior neurons to acoustic stimuli by changes in their spontaneous firing rate by polarization or by microelectrophoretic application of glutamate. After the conference, I was asked by the local organizers to come next year to deliver a practical course in electrophysiology to a group of graduate students. We made a plan for the course and agreed on technical requirements (apparatus, laboratory space) for it. On September 1 the 23rd International Congress of Physiological Sciences in Tokyo began, and in the symposium "Neural Mechanisms of Conditioned Reflex and Behavior," I delivered a paper on conditioning of isolated neurons by using direct stimulation of the recorded cell as the unconditioned stimulus (Bures and Buresova, 1965).

I also participated as a discussant in the symposium "Structure and Function of the Limbic System" which took place in Hakone from September 10 to September 20. An unexpected bonus to the trip to Japan was an unplanned week-long stay in Cambodia: due to the war between India and Pakistan we had to wait one week for a connecting flight to Europe in Phnom Penh, and this gave us a marvelous opportunity to visit Angkor Vat and other jewels of Indochina architecture.

In 1966, after participation in the Fifth Meeting of the Collegium Internationale Neuro-Psychopharmacologicum in Washington and after a series of lectures in the United States and a brief visit to Mexico, I arrived in Havana to organize the electrophysiology course for graduate students. During 2 weeks we collected the necessary equipment, formed teams of instructors, and arranged demonstration stations for the eight themes of the course. With Dr. Aquino-Cias, who worked for a year in our laboratory in Prague, we first trained two instructors for each of the following themes: electromyography and electrocardiography, normal and epileptic EEC activity, evoked responses to sensory stimuli and event-related potentials, stimulation of cortex and callosal responses, slow potentials—spreading depression, slow potentials—anoxic depolarization, unit activity in reticular formation, and hippocampal population spike elicited by perforant path stimulation. After everything was prepared, the 20 course participants were divided into 8 groups with 2 to 3 students each and rotated during 8 days through the 8 themes. This arrangement gave each student enough time to perform the whole experiment, to understand its biological and technical aspects, as well as to evaluate the results obtained. After conclusion of the experiments, the students were asked to identify the most difficult aspects of the individual methods, and various alternatives were discussed and, if necessary, demonstrated. The course showed that even with simple equipment it is possible to demonstrate almost all basic methods of contemporary electrophysiology to a relatively large audience. I have used this experience when participating in similar courses in Yugoslavia (1969), Chile (1971), and Poland (1984).

The busy contacts with the United States continued also in 1967 and in 1968, when I was invited by Jim McGaugh to attend one of his first Irvine conferences. Everything looked optimistic. In the introduction of my talk entitled "The Reunified Split Brain" (Bures and Buresova, 1970a) about communication between the two halves of the vertebrate brain, I compared the world divided by political, economical, and ideological barriers to a split brain preparation and expressed the hope that the reversible split brain technique, which can be used to restore coordinated activity between the two temporarily separated halves of the brain, will inspire politicians, economists, and philosophers to seek an analogous solution for our planet. Unfortunately, my incurable optimism proved to be wrong. Shortly after my return from the United States, in the first hours of August 21, we received a phone call from a co-worker of our Institute informing us that the Soviet army had begun the invasion of Czechoslovakia. We turned on the television and radio, trying to understand what had happened and how we could cope with the situation. Our 19-year-old daughter Olga, a student of mathematics, was an au pair girl and safe in London and thus was far from any local dangers. We had two foreign guests with small children in the laboratory: Lynn Nadel with Melissa (4 years) and Kenny (3 years) and Takanori Ookawa with his wife and 1-year-old Makiko. We advised them to leave the country as soon as possible and to wait in Western Europe until the situation clarified. While Lynn packed his family in a big van and drove to the German border over highways crowded by Soviet tanks, two days later Takanori joined a transport to Germany organized by the American Embassy for the many foreigners stranded in Prague. The streets were full of protesting people and Russian soldiers, tanks, and armored cars. Fighting started around some strategic buildings, and the Soviet army showed its resolve to use all force available to suppress the protests. The leaders of the Czechoslovak Communist Party were arrested by the Russian army and imprisoned in the Soviet Union. The Czechoslovak parliament was in session, passing resolutions protesting against the Soviet occupation, but could contact the population only through illegal radio transmission because it had no access to the official media. The situation in the Institute was desperate. Many scientists contemplated the possibility of leaving the country and staying abroad. I was, as was Olga, a member of the Communist Party since the first months after the war. We were not happy with all that had happened in our country under the communist regime, but we hoped that a more liberal policy would finally bring our part of the world the so much expected freedom we craved for during the war. The development in the 1960s that culminated in the Prague spring of 1968 seemed to indicate that such a process was underway, but the intervention of the Soviet Union showed us clearly that the liberal intellectuals had no hope to realize their dreams. However, going abroad did not appear to be correct. After the war, we wanted to do something positive for our country. To leave it now, in its time of need, seemed to be treason. We decided to stay as long as we had an opportunity to continue our research. This was a naive decision, because we did not take into account that the possibility of leaving the country, which would have been very easy in 1968, would become very difficult a year later. But in the long run, we feel that it was the correct decision. It gave us the opportunity to see life from a different point of view and to test the assumption that our position in science does not depend on political mafias and on our servile attitude toward them, but only on the output of our brains and hands.

Of course, the consequences of the Soviet invasion for our science did not develop abruptly. Foreign travel was free in 1968 and almost free in 1969. During this time I could still visit Cuba; lecture in Switzerland, Netherlands, Belgium, and Germany; teach together with Olga in an IBRO course in

Kotor, Yugoslavia; give a talk (Bures and Buresova, 1970b) at the symposium "Short-Term Processes in Neural Activity and Behavior," organized by Gabriel Horn in Cambridge; and attend the XIXth Psychological Congress in London where I organized with Olga the symposium "Split-Brain Function." However, the latter Congress marked for us the last opportunity to give an invited talk in the West for a period of 18 years, i.e., up to 1987. I was still allowed to visit Great Britain in 1970 on a commercial trip, the purpose of which was to demonstrate an invention (apparatus for early identification of fertilized eggs) and to accept an invitation from the University of Valparaiso, Chile, to organize a course of electrophysiology for graduate students in 1971. After this trip, the door to the West was completely locked. We were ousted from the Communist Party, because we did not agree with the Soviet occupation of our country. We were considered hostile elements who could perhaps be allowed to do some research provided that we were carefully watched by loyal superiors. This was clearly demonstrated in the case of Olga, who was at the time Associate Professor of Physiological Psychology at the Philosophical Faculty of the Charles University. She was removed from all teaching activities at the University, but was allowed to continue her research in the Academy.

Strategy of Isolated Scientists

We anticipated the reduction of foreign travel from the moment of the Soviet invasion and considered various strategies for maintaining our output in spite of the marked reduction in our contacts with international research. The classical defense plan was to maintain the flow of publications coming from the laboratory and to replace our visits abroad by maintaining a stable flux of visitors coming to work in Prague. Fortunately, we were not fired. I even remained head of the laboratory until 1981, when the pressure on the non-loyal scientists paradoxically increased and this position was given to a younger member of our group, our good friend Gustav Brozek. Worse was the situation of Olga, who in 1982 reached the retirement age of 58 years. Although scientists could postpone retirement until 65, the new director of the Institute insisted on her immediate retirement and formal appeals to the President of the Academy, Academician Riman, pointing out the discriminative nature of this decision, were ignored. Olga continued to work as before, but was paid only for a part-time job, although she remained one of the most productive scientists in the Institute.

Aside from the above demonstrations of administrative arrogance, there were no attempts to change the orientation of our research, the funding of which remained stable. This was advantageous for us, because in the yearly reviews of the productivity of individual departments we could report the low cost of a primary publication. The Academy started to explore the possibility of quantitative evaluation of the output of different laboratories and individual scientists using Garfield's scientometric criteria. Each published paper was multiplied by the impact factor (IF) of the journal, expressing the expected citation rate of the article in the future. The IF values were about 0.5 for *Physiologia Bohemoslovaca*, 3.0 for *Brain Research*, and 15.0 for *Nature*. The sum of the IF weighted values of papers published in different laboratories was proportional not only to the number of articles, but mainly to their IF ranking. This increased considerably the rating of laboratories publishing their results in good foreign journals. Finally, we could retain foreign funding obtained from Western countries in support of specific projects. This was quite important in this period, because in 1969 we obtained from Foundations' Fund for Research in Psychiatry a grant of $28,000 for a laboratory computer LINC 8 which made us independent from the classical LINC owned by the Institute.

Visiting Scientists

It was less clear how the Soviet invasion would influence the number of visiting scientists who formed the main work force of the laboratory. We could only extrapolate from the experience we had so far. While the first paper resulting from collaboration with a visiting scientist was published in 1955 (Bures and Koshtoyants, 1955), next collaborative studies appearing in 1961 were produced by scientists coming from the Soviet Union who were joined in 1962 by visitors from East Germany and later from other East Block countries in Central Europe. Some of them were coming for long-term stays equivalent to Ph.D. training or to a comparable university degree in their countries. Dr. W. Ruediger from the Humboldt University in East Berlin spent 2 years in Prague to prepare his Habilitation based on analysis of the effect of cortical SD in conscious rats on unit activity, excitability, and functional state of the hypothalamic and mesencephalic motivation centers. Visitors from other socialist countries were coming for shorter stays (usually two to three months), depending on the funds reserved for exchange fellowships to Czechoslovakia in their home countries. During their stay in Prague, they concentrated on the experiments that were eventually finished by other members of the team after their departure. In some cases, they could come the following year to prolong a continuing project. In this way, we gradually established tight working contacts with a group in Rusinov's laboratory in the Institute of Higher Nervous Activity and Neurophysiology in Moscow, working on SD (G.D. Kuznetsova and V.I. Koroleva). This collaboration generated almost 20 papers over the years. Similar close contacts with Konorski's group in Warsaw (I. Lukaszewska, A. Markowska, and M. Wesierska) led to experiments using SD-induced functional decortication and other forms of reversible ablation in behavioral research.

Another opportunity for financial support of visiting scientists opened in the UNESCO-sponsored fellowships for potential applicants from developing countries. The Biological institutes of the Academy offered 10 such fellowships each year and our laboratory was among those advertised. We got one applicant from Japan in 1962/1963 (I. Shima), one from Mexico in 1963/1964 (E. Roldan), and another from Cuba in 1965/1966 (J. Aquino-Cias). Shima studied SD in pigeons—the boundaries of spread and effects on unit activity (the affected parts of the striatum and remote brain structures, behavioral consequences of striatal SD). Roldan examined electrophysiology of sleep in rats (sleep cycle, neocortical and hipocampal EEG, REM sleep manifestations). Aquino-Cias explored the effects of thalamic spreading depression on the spread of epileptic afterdischarge, on caudate spindles, and on other integrative phenomena.

Visitors from developed Western countries (United States, Canada, and Australia) started to come in late 1960s, some for regular postdoctoral stays with fellowships paid for by the NIH and others for the shorter periods covered by various foundations. The first was Chuck Woody from W.H. Marshall's laboratory' who came to Prague in 1967/1968 to study the effect of SD on the conditioned eye blink elicited in cats by the glabella tap and introduced us to the use of computers for processing the electrophysiological data. At the same time, Lynn Nadel arrived with his family. He worked on interocular and interhemispheric transfer in rats and published a series of papers on the subject.

As expected, the number of papers co-authored annually by visitors from the Soviet Union and from other East Block countries dropped from 6.1 in the preinvasion period (1963–1967) to 0.25 in 1968–1971, it rose to 1.25 in 1972–1975 and to 3.25 in 1976–1979, and attained the preinvasion level by reaching the value 6.5 in 1980–1983. On the other hand, papers co-authored annually by visiting scientists from other parts of the world rose from 3.1 in the preinvasion period to 11.0 in 1968–1971, decreased to 5.25 in 1972–1975, and stabilized at the level of 3–4 in the 1980s. It was obvious that the reduced number of visitors from Eastern Block countries was due to administrative restrictions limiting travel to the dissident country in order to limit the possible spread of the dissent. It took the Soviet authorities almost 10 years to abandon this inadequate strategy and to start a kind of reform. Gorbachev's "perestroika" came too late, however, to prevent the avalanche collapse of the Eastern Block and of the Soviet Union. From the point of view of our laboratory, the Soviet decision not to allow their scientists to work in Prague was regrettable, but did not interfere with our work. The total number of visitors was not reduced, but the output was substantially increased. Among the guests were first-class researchers (Chuck Woody, Lynn Nadel, Joe Huston, Dave Megirian, Joel Davis, Ian Steele Russell, Bert Siegfried, Hans Welzl, Masaaki Shibata, Takashi Amemori, Nelson Freedman, Bruno de Luca, S. J. Dimond, Andy Greenshaw, George Gerstein, Mitchell Glickstein, Walter Freeman, and many others) who accelerated the progress of our work and continued to collaborate with us afterwards. However, the most important result was the moral boost given to us by the international neuroscience community whose delegates came to be with us in a difficult time. The fact that all the foreign guests from the United States, Canada, Great Britain, Australia, Japan, Switzerland, Italy, and other countries got visas indicates that the government tried to avoid the impression that it blocked international collaboration in science. The practical result was that those of us who could not travel to the West were not completely cut off from contacts with Western science whose delegates were permanently present in Prague.

While the above considerations indicated that our work could go on as earlier, we decided to concentrate our effort on behavior. The name of the laboratory was changed to the Laboratory of Neurophysiology of Memory. SD research continued as a prototype of the functional ablation technique, but was supplemented by other reversible inactivations induced by pharmacological and physical factors. We decided to add conditioned taste aversion (CTA), motor learning, and spatial memory to the behavioral models studied. We finished the search for the role of potassium ions in the mechanisms of SD and anoxic depolarization by demonstrating with potassium-selective microelectrodes an increase of extracellular potassium to 70–90 mM. In 1989, this paper (Vyskocil, Kriz, and Bures, 1972), made possible by our colleague Pavel Hnik, who brought from Salt Lake City to Prague the first specimens of the potassium electrodes based on the Corning ion exchanger, was identified by Current Contents as a citation classic. My visit to the laboratory of Aristides Leao in Rio de Janeiro on my return from Chile gave me the opportunity to see SD in the *in vitro* preparation of the chicken retina (H. Martins-Ferreira) and to use it for the visualization of the circulating SD demonstrated earlier in the cerebral cortex of rats (Shibata and Bures, 1972). The circling retinal SD (Gorelova and Bures, 1983) entered SD into the list of synergetic phenomena.

During the IBRO course in Kotor, Olga and I met Professor John Garcia, the discoverer of CTA. After hearing his lecture, we were immediately impressed by the exceptional properties of the phenomenon: separation of the gustatory CS and of the visceral US by an interval of up to several hours did not disrupt CTA learning, although standard CS–US associations do not survive CS–US delays exceeding a few seconds. Still more puzzling was the fact that CTA was acquired even when the US (administration of the toxin), but not the CS, was applied under deep anesthesia. It seemed that the above CTA properties were ideally suited for examination with the functional ablation methods. We started with the CTA experiments in 1971, and soon found out that CTA learning is prevented by bilateral cortical SD elicited before the CS but not before the US administration. This suggested participation of neocortex in CS processing, but not in CS storage or in the formation of the CS–US association (Buresova and Bures, 1973, 1974). Further analysis indicated the parabrachial nucleus (PBN) of the brain stem as the locus of the CS trace–US association (Ivanova and Bures, 1990). Combination of unilateral functional decortication and unilateral TTX blockade of PBN prevents CTA learning when applied to different halves of the brain, but not when applied to the same side of the brain (Gallo and Bures, 1991). This result suggests that CTA acquisition requires interaction of the cerebral cortex with PBN through ipsilateral pathways. Our CTA research was summarized in a review chapter (Bures and Buresova, 1977) and in two books (Bures, Buresova and Krivanek, 1988; Bures, Bermudez-Rattoni, and Yamamoto, 1998).

Another field we wanted to extend was motor learning. Our behavioral experiments were mostly based on active or passive avoidance tasks and on aversively or appetitively motivated discrimination learning. We hoped that training rats to master motor skills controlled by specific motor centers might simplify electrophysiological and morphological analysis of the neural networks supporting this behavior. We started by forcing the rat to reach deep into a narrow horizontal tube at the end of which was a small food pellet or by releasing the pellet only when the photoelectrically recorded forelimb extension exceeded the preset criterion time (Zhuravin and Bures, 1986). Later, we were attracted by licking, another small movement that occurs during the consumption of liquids and that is generated by rats at a very constant frequency of about 6 Hz. We attempted to slow it down to about 4 Hz using a retractable spout that was removed after each lick beyond the reach of the animal's tongue and returned back only at an interval corresponding to the 4 Hz frequency of licking (Hernandez-Mesa et al., 1985). Rats eventually learned to lick slower, but it took several weeks of training and tedious elimination of various faked solutions (e.g., 3-Hz licking produced by alternation of large amplitude licks detected by the photoelectric lick sensor and short licks that remained unrecognized). Finally, we trained rats more complex skilled movements requiring development of a new synergy between functionally unrelated effectors, e.g., between the tongue and forepaw (Brozek and Bures, 1991). After each lick, the retractable spout was removed by the computer and was returned to the accessible position when the rat pressed and released a bar located under the spout. After several weeks of training, the rats learned to produce this complex movement in a way supporting uninterrupted licking, i.e., with a phase shift of about 180 dg between licking and bar pressing. This indicated that the generator of licking in the reticular formation triggers not only the movements of the tongue, but that training connected it also to the centers controlling the bar pressing forepaw.

In the late 1970s we were deeply influenced by the renaissance of animal cognition, both at the theoretical level (O'Keefe and Nadel, 1978) and at the experimental level (radial maze—Olton and Samuelson, 1976; water maze—Morris, 1981). We were excited by the new experimental possibilities and started immediately experimenting with the homemade versions of the devices. Our first paper on the radial maze technique (Magni, Krekule, and

Bures, 1979) used a two-level apparatus in which an animal exiting from the visited arm had to descend to the floor, return below the 5-cm-elevated central platform, and climb through a central hole to start a new choice. The obligatory return to the same starting point precluded response chaining. Our first paper on the Morris water maze (Buresova et al., 1985) already used an interactive computer tracking system that raised the submerged escape platform only after the rat had spent a continuous criterion interval (1–5 sec) in the goal area. Use of this "on demand platform" eliminated the possibility of accidental detection of the hidden goal during randomly oriented swims. Later experiments concentrated on the capacity and persistence of working memory and on the physiological and pharmacological interventions disrupting the navigation performance.

Some of the above behavioral tasks were used for electrophysiological analysis. Particularly well suited for this purpose were the handedness experiments when the almost immobile rat reaching into the feeder allowed recording of units from motor cortex, basal ganglia, and cerebellum and off-line analysis of the records. Periresponse histograms of unit activity, in the motor cortex and cerebellar dentate nucleus ipsilateral to the reaching forepaw, showed clear peaks starting 100–150 msec before reach detection, but culminating in the dentate nucleus about 60 msec earlier than in the motor cortex. Perireach histograms in the contralateral caudate nucleus were characterized by an earlier and more prolonged excitation (Dolbakyan et al., 1977; Hernandez-Mesa and Bures, 1978; Moroz and Bures, 1982). A similar approach used in the analysis of unit responses of CTA-trained rats to presentation of the drinking spout containing the aversive taste stimulus revealed inhibition starting 100–150 msec after stimulus onset in the gustatory cortex, amygdala, and ventromedial hypothalamus and an excitatory response appearing about 100 msec later in the lateral hypothalamus (Buresova et al., 1979).

Finally, one activity that could be expected to be possible even under the most difficult conditions was writing books. We had hoped to write manuals for behavioral research and for the use of computers in neuroscience similar to the successful "Electrophysiological Methods." At the same time, we wanted to write a monograph about SD and another one about our approach to the neural mechanisms of behavior. The book *The Mechanism and Applications of Leao's Spreading Depression of EEG Activity* by J. Bures, O. Buresova, and J. Krivanek was almost prepared already in 1972, but its publication was delayed by the fact that one of the potential co-authors, Eva Fifkova, stayed illegally in the United States and we were not allowed to have her name among the authors. It was published by Academia in coedition with Academic Press in 1974. The manual *Techniques and Basic Experiments for the Study of Brain and Behavior* by J. Bures, O. Buresova, and J. P. Huston was published in 1976 by Elsevier. It was rapidly sold out, and the second revised and enlarged edition appeared in 1983. Its Russian translation, published in 1991 by the publishing house Vysshaya shkola, had 13,000 copies. The second manual, *Practical Guide to Computer Applications in Neuroscience*, was published in 1982 by Academia in co-edition with Wiley. It was based on a two-week workshop organized by our Institute in 1973 for researchers interested in biomedical applications of computers. The workshop included 40 hr of programming at the computer console, and the participants appreciated the opportunity to learn basic programming skills and to understand simple programs. This book was also translated into Russian and published in 1984 by the publishing house Nauka. The last book appearing in this period was *Brain and Behavior: Paradigms for Research in Neural Mechanisms* by J. Bures, O. Buresova, and J. Krivanek, published again by Academia in co-edition with Wiley. It was an attempt to describe our experience in several areas of experimental research in the context of contemporary science and to call attention to potentially significant solutions of new problems. This book did not cover our spatial memory research.

Back to Freedom

Fifteen years after the Soviet occupation of Czechoslovakia, the situation started to change. Foreign travel became easier even for the unreliable elements; a number of known dissidents were asked to leave the country or were allowed to go abroad with the hope that they would not return or that it would be possible to refuse them a reentry permit. Because I reached retirement age in 1986, restrictions on my exit permits were considerably alleviated. It was believed that a retired citizen who decides to stay illegally abroad will do a positive service to the country, because he will draw no pension.

In 1987 my eligibility for foreign travel was tested by Jim McGaugh's invitation to his "Third Conference on the Neurobiology of Learning and Memory" held in UCI Irvine on October 14–17, 1987. I obtained a permit to leave Czechoslovakia and stay for a month in the United States. I opened the meeting with a keynote address entitled "Neurobiology of Memory: Significance of Anomalous Findings." When Lynn Nadel, who was introducing me to the audience, asked how many people present in the room had been in our laboratory in Prague, more than a dozen hands went up. I was deeply moved by the feeling of being at home with people whom I knew and who knew me. I was reassured that the worst part of the postwar troubles was over for our science and that we would be able to continue from the point where our development was interrupted in 1968. Other invitations followed: in 1987 from Joe Huston to Duesseldorf; in 1988 from Mitchell Glickstein to University College London, from Richard Morris to Edinburgh, from Hans Welzl to Zurich and to the Neuropharmacological Congress in Athens, and from Professor Gispen to Rotterdam; in 1989 from Steve Rose to the European Science Foundation meeting in Sicily, and from Professor Cioffi for teaching at the University of Naples and lecturing at the Italian Congress of Physiology in Firenze. Note that all these trips took place before the Prague Velvet Revolution in November 1989. In 1990, the first free year, I was invited to a short conference in London, to an SD symposium in Brazil, and for a two-month stay in the laboratory of Professor Taketoshi Ono in Toyama University, Toyama, Japan. The frequency of invitations remained stable in the following years. The particularly memorable ones were to the University of Lethbridge, where I received an honorary doctorate in 1992; to the National Academy of Sciences (NAS) annual meeting in 1996 for inauguration as a foreign associate; participation in several meetings of the governing council of the IBRO to which I had been reelected by postal ballot in 1992; meetings of the Central Council of the European Neuroscience Association (ENA), which I was a member of in the years 1992–1999; and a meeting of the Brazilian Academy of Sciences, where I delivered a speech in honor of A. A. P. Leao, commemorating a year since his death.

There were other memorable moments that I remember well. One of them was a completely unexpected wire received on April 25, 1995, from the members of the NAS section 52 congratulating me on my election to NAS. I could not believe it, and only a phone call from Jim McGaugh (chairman of section 52) convinced me that this really happened. I felt deeply honored, but also embarrassed by knowing many colleagues who I believed deserved this distinction more than myself.

The political changes in our country did not influence my position in the Institute. I was 64 years old during the Velvet Revolution and thus too old for an administrative position. Jiri Krivanek became the head of the department, and I continued to work as a research scientist and principal investigator on several grant projects. The Institute agreed to employ me as long as I could get adequate funding and demonstrate corresponding productivity. The present head of the Department of Neurophysiology of Memory is my former student, Andre Fenton, who came as a B.Sc. from McGill University in 1991 to our laboratory to gain some experience in behavioral research. He joined our spatial memory research program and in two years completed four experimental studies dealing with the problem of interhemispheric transfer of lateralized place navigation in rats. He went from Prague to SUNY Brooklyn to become a graduate student of Bob Muller and to learn how to examine place cells. In 1998 he joined our laboratory as a postdoctoral fellow, took full responsibility for the technical and computational development of our place cell research, and significantly extended our behavioral experiments. Two years later, he was appointed head of the Laboratory of Neurophysiology of Memory and in this position became principal investigator of the European Community grant "Network Analysis of Hippocampal Memory Processing" and of a grant of the Grant Agency of the Czech Republic (GACR) "Development of Spatial Memory Tests Suitable for Early Detection of Mnestic Disorders in Neurological and

Psychiatric Disorders." Andre has a unique ability to clearly formulate ideas, rapidly establish personal contacts with colleagues, openly discuss controversial points, and find acceptable solutions. His excellent organizational talent, enabling him to simultaneously supervise a number of independent projects, is best demonstrated by his capacity to head at the same time not only the laboratory in Prague, but also a new laboratory in the Department of Physiology and Pharmacology of the SUNY Downstate Medical Center in Brooklyn. I believe that Andre's example shows that the Czech Academy of Sciences is prepared to open its facilities to foreign scientists who want to continue their research in Prague. Low salaries do not make a scientific career in the Czech Republic financially attractive, but this can be compensated by research traditions, equipped laboratories, trained personnel, and a creative environment. With more foreign scientists working in our institutes, it will be possible to change the somewhat provincial Czech science, pursued almost exclusively by Czechs, into Prague science, represented by the multinational community of scientists working in this part of Europe. I hope that this form of "reversed brain drain" may contribute to the rapid growth of strong international research in Central Europe.

In Conclusion

This chapter should probably help young people and their teachers better understand how to become scientists. I am afraid that my contribution is not much helpful in this respect. In fact, I do not believe that scientists can be educated. Somebody who is not curious, who does not feel the challenge of an interesting problem, who is not excited by the possibility of finding ways to solve it, will not become a scientist even when taught by the best teachers. The problem is not to educate scientists, but to find them and to recruit them for research. I considered each of the 100 graduate students and postdoctoral fellows I have supervised during 50 years of research not pupils but co-workers, who are fully entitled to influence the project with their ideas, technical innovations, and unorthodox interpretations. I hate the deprecatory comments that refuse the opinions of young, inexperienced people because they are "immature." This probably reflects long-term memories of my youth, when an entire generation of young scientists in Prague was clearly immature but nevertheless had entered science quite successfully. Perhaps the reason was the absence of authorities and the lack of hierarchical organization in the ruins of science that survived the war. The fact that the immature people were nevertheless able to build the new Czech science and that many of them who emigrated to West Europe and North America attained professorial positions in the Western academic system suggests that immaturity may be not a drawback but an advantage—open-minded views, less stereotyped thinking, imaginative plans. An excellent teacher, who always knows the best answer to any question, may exert an inhibitory influence on the creativity of his or her students.

Although I had few formal teachers who influenced the development of my scientific views, there were probably hundreds of scientists who helped me understand science. The anonymous reviewers of my first papers written in terrible English who deciphered the content of the message and found it suitable for publication, the unknown poster presenters eager to explain to me the critical tricks of their techniques, the authors of articles who addressed problems of interest to our group in a way that opened new perspectives for our research—these people were and are my teachers to whom I feel greatly indebted. I am trying to pay my debt back by doing the same services for other people who expect them: I am reviewing about 50 papers per year, visitors of our lab can see any technical details they are interested in, and I speak and write openly about all plans and ideas currently used in our research.

Of course there are people who are directly responsible for some important features of my personality—my mother who introduced me to the magic world of books; my brother, Charles, who supported me during my high school studies; my wife Olga who has been for more than 50 years my spouse and my closest partner in science; our daughter Olga who realized my mathematical ambitions by becoming a professor of technical cybernetics in the Czech Technical University in Prague; and our granddaughters Catherine, a neurologist, and Barbara, a lawyer. A bad case of autoimmune polymyositis prevented Olga from continuing experimental research, but she follows closely the activities of the laboratory, translates Dana Foundation documents for the Brain Awareness Week lectures, and firmly directs the activities of our household. We believe that a couple sharing one intact immune and motor system (mine) and one system with superb organizational capacities (her) can live an interesting and happy life, and we are doing our best to demonstrate it.

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