

## Obituary

### Jiří Křeček



11. 4. 1923 – 30. 1. 2014

Prof. Jiří Křeček, MD, DSc, a foremost Czech developmental physiologist, has died on January 30, 2014 at the age of 90 years. He became famous for his concept of critical developmental periods, suggesting that some abnormalities seen in adulthood might be the late consequences of early interventions applied in particular critical developmental periods.

The primary focus of his research was the regulation of water and electrolyte metabolism in developing organism with a special focus to the role of vasopressin in the control of sodium and water excretion in the weaning period. These early studies were later extended to the sex differences in salt intake that could be modified by the presence of androgens in the neonatal period. The neonatal modification of hypothalamic pattern is not manifested prior to sexual maturation when female rats begin to prefer higher saline consumption compared to males. Further late effects of certain early interventions (such as premature weaning or high salt intake) were also found in reproduction, behavior, hypertension etc.

Prof. Křeček, who was one of the cofounders of the Institute of Physiology (Czechoslovak Academy of Sciences, Prague), was deeply involved in the promotion of Czechoslovak school of developmental physiology. In a close cooperation with his coworkers (P. Hahn, J. Martínek, O. Koldovský and others), he succeeded in organizing several interesting symposia. The international

symposium on “*The Development of the Postnatal Phenotype*” was probably the most important one. However, the promising progression of Czechoslovak developmental physiology was interrupted after August 1968 when several leading scientists emigrated and the international cooperation was strongly curtailed. Prof. Křeček continued his scientific work (concerning renal physiology and salt hypertension) in the Institute of Physiology until his depart for Kuwait University (1980-1985).

After the retirement he started to work on his fundamental book “*The Individual: Gene – Environment – Ontogenesis*” (Academia, Prague 2007, E-book 2013) in which he summarized his research experience concerning developmental physiology and critical developmental periods. In the recent years he has also written an article on the necessity to study the living organism in its complexity, including all its regulations which undergo profound changes in the course of its ontogenesis (Křeček J: Holism and life manifestations: molecular and space-time biology. *Physiol Res* **59**: 157-163, 2010). Indeed, developmental physiology requires not only new detailed findings but also their conceptual synthesis. Prof. Křeček was a prominent exponent of such a scientific approach. Below you will find a part of his last unfinished manuscript about weaning.

Josef Zicha

## About the Weaning

J. KŘEČEK

Jinočany near Prague, November 11, 2013

There is a small village Konárovice nearby Kolín. The coworkers from the Department of Developmental Physiology (Institute of Physiology, Czechoslovak Academy of Sciences, Prague) appeared in Konárovice in the late fifties of the last century. They wanted to know whether the premature weaning of laboratory rats might influence their later development. In Konárovice rodent breeding facility there was a chance to perform the necessary experiments which might provide such information. How it is possible that somebody has got the idea to visit this small village in order to examine the consequences of premature weaning?

In the early fifties the academician Ivan Málek invited me, an early postgraduate student, to participate in the newly established neurophysiological department of the Central Institute of Biology in Prague. At that time there were three young men in the Institute of Physiology of Charles University (Albertov) who wanted to work in science but they had no firm basis for such a work. Thus, Petr Hahn, Jiří Martínek and me have joined this new scientific institution. The established third working group of the neurophysiological department has decided not to engage in the obligatory neurophysiology based upon a Soviet design. To succeed in this situation we have chosen another, less safe, Soviet topic – developmental physiology. Within a short time Ivan Málek has understood our focus. Thereafter, the Institute of Physiology (Czechoslovak Academy of Sciences) has been founded and our working group has become its Third Department.

The rediscovery of almost forgotten Edward Babák, one of the most important Czech physiologists, was a great support for our developmental (ontogenetic) program. In the early twenties of the last century he became famous for his study of the development of pulmonary system and his papers on animal ontogenesis were also highly important (Laufberger V: Ontogenetic functional development in Babák's studies. *Biol listy* **12**: 183-188, 1926; Křeček J: Babák's studies on the

physiology of developing organism. *Čs fysiolo* **4**: 253-259, 1955). When Babák's pupil Vilém Laufberger became our scientific supervisor, a new generation of Babák's school has been established.

The department was expanding, its coworkers were working hard and publishing diligently so that in 1956 we could summarize our results into a monograph published at the occasion of Babák's anniversary (Čapek K, Hahn P, Křeček J, Martínek J: Studies on the physiology of newborns. *Rozpravy ČSAV* **66**: 12, 1956). There were two most important findings demonstrating the abrupt onset of important functions in rat pups. In the period, when rat pups open their eyes, their thermoregulation is substantially improving and their urinary bladder evacuation begins to be controlled by the interoreceptory micturition reflex. Until then micturition of immature rat pups must be facilitated by rat mothers' licking of their reflexogenic perianal zone. Thus, the presence of rat mother in the first two weeks after the birth is the only guarantee for the survival of pups. The ability to survive the absence of rat mother appears at the beginning of the third postnatal week. We have therefore concluded that a gradual weaning process begins in rat pups at this age. Of course, there was a natural question whether the weaning period is terminated so abruptly as it begins.

It could be expected that the transient change of nutrition and water supply will be accompanied also by the behavioral changes in rat pups. A long time ago, when I was searching for methods to test adrenocortical hormones, I was fascinated by a paper how a free choice between water and saline to drink could prolong the life of adrenalectomized rats (Richter CP: Increased salt appetite in adrenalectomized rats. *Am J Physiol* **115**: 155-161, 1936). We have tried to determine the preference between drinking water and milk in rat pups whose mother has been removed at the stage when they were able to survive her absence (Křeček J, Křečková J, Dlouhá H: On problems of the regulation of water intake in newborn mammals. *Physiol Bohemoslov* **5** (Suppl):

33-37, 1956). It was evident that the pups always preferred milk but the time course of water drinking was highly interesting. Water consumption was negligible in the third and fourth postnatal week but it rose suddenly by the end of the fourth week. Again a sudden functional change! In the same paper we have demonstrated that these changes in water and milk intake have a relationship to osmoregulation. Rat pups in which osmotic balance was altered by the administration of hypertonic saline, drank predominantly milk until the end of the fourth postnatal week but thereafter they preferred water. From that time we were convinced that the weaning of rat pups is terminated by the end of the fourth postnatal week. This was confirmed by Pařízek and coworkers several years later (Babický A, Ošťádalová I, Pařízek J, Kolář J, Bíbr B: Use of radioisotope techniques for determining the weaning period in experimental animals. *Physiol Bohemoslov* **19**: 457-467, 1970), who demonstrated using radioisotope technique that rat pups cease to suckle maternal milk by the end of the fourth week of life.

We have performed a large series of experiments in which renal functions and their regulation were examined during weaning period. I have summarized them in a monograph (Křeček J: *Weaning Period and Water Metabolism*, Babák's Collection, Vol. 28, SzdN Prague, 1962). It was demonstrated that renal functions undergo dramatic changes in the suckling and weaning periods, including the important modifications of vasopressin secretion from the neurohypophysis. The most important finding was that the relationship between

vasopressin and renal function is transformed by the end of weaning period. This relationship was documented later by the experiments performed in Brattleboro rats with hereditary diabetes insipidus (Dlouhá H, Křeček J, Zicha J: The renal concentrating ability of newly born Brattleboro rats (hereditary diabetes insipidus). *Experientia* **32**: 59-60, 1976). Diabetes insipidus appeared in these rats just in the weaning period so that the maturation of neurohypophysis seemed to be causally related to the weaning period. However, this cause of weaning was excluded by further experiments in which maternal milk consumption was measured in Brattleboro rats using radioisotope technique (Babický A, Křeček J, Dlouhá H, Zicha J: Endogenous vasopressin and the weaning period in Brattleboro rats. *Physiol Behav* **36**: 631-635, 1986).

At that time we have discussed intensively a new branch of developmental physiology, i.e. critical developmental periods occurring in the early postnatal life. The intervention(s) in these critical developmental periods might permanently modify the later development of the organism. For example, the administration of sex hormones to newborn modifies the development of hypothalamic functions, a transient separation of pups from their mother can alter the later development of their behavior. Premature weaning is considered to be a severe intervention. A question arose whether premature weaning could have similar important consequences as the above mentioned interventions.

### Some related papers to be mentioned:

- KŘEČEK J, DLOUHÁ H, JELÍNEK J, KŘEČKOVÁ J, VACEK Z: The effect of hormones of the pituitary and adrenal glands on the elimination of sodium, potassium and water load in infant rats during the weaning period. *CIBA Foundation Colloquia on Ageing* **4**: 165-179, 1958.
- KŘEČEK J, HELLER J: Neurohypophysis and the regulation of water and electrolyte metabolism in infant mammals. 22nd International Congress of Physiological Sciences, Leiden 1962 (*Excerpta Medica International Congress Series* **47**: 53-69, 1962).
- HAHN P, KOLDOVSKÝ O, KŘEČEK J, MARTÍNEK J, VACEK Z: Temperature adaptation during postnatal development. *Fed Proc* **22**: 824-827, 1963.
- KRAUS M, ANDĚL J, DLOUHÁ H, FLANDERA V, KŘEČEK J, KŘEČKOVÁ J, ROKOS J: The development and the length of life of rats weaned normally and prematurely and living on a free choice of electrolyte solutions. In: *The Development of Homeostasis*. ADOLPH EF (ed), Publishing House of Czechoslovak Academy of Sciences, Prague, 1961, pp 117-121.
- KŘEČEK J, PALATÝ V: The effect of premature weaning on the development of androgenic activity in male rats. *Physiol Bohemoslov* **16**: 501-507, 1967.
- KŘEČEK J: The weaning period as a critical period of development. In: *The Postnatal Development of Phenotype*. DENENBERG V, KAZDA S (eds), Butterworth, London, Academia, Prague, 1970, pp 33-44.

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- KŘEČEK J: The theory of critical developmental periods and postnatal development of endocrine functions. In: *The Biopsychology of Development*. TOBACH E, ARONSON LR, SHAW E (eds), Academic Press, New York, 1971, pp 233-248.
- KŘEČEK J, NOVÁKOVÁ V, STIBRAL K: Sex differences in the taste preference for a salt solution in the rat. *Physiol Behav* **8**: 183-188, 1972.
- KŘEČEK J: Sex differences in salt taste: the effect of testosterone. *Physiol Behav* **10**: 683-688, 1973.
- KŘEČEK J: Effect of ovariectomy of females and oestrogen administration to males during the neonatal critical period on salt intake in adulthood in rats. *Physiol Bohemoslov* **27**: 1-5, 1978.
- DLOUHÁ H, KŘEČEK J, ZICHA J: Effect of age on hypertensive stimuli and the development of hypertension in Brattleboro rats. *Clin Sci (Lond)* **57**: 273-275, 1979.
- KŘEČEK J, DLOUHÁ H, ZICHA J: Salt supply in early life and possible consequences for hypertension in adult life. *Bibl Nutr Dieta* **31**: 121-130, 1982.
- KŘEČEK J, KOLDOVSKÝ O: Traditions of Czech and Slovak developmental physiology. *Physiol Res* **44**: 339-340, 1995.
- KOLDOVSKÝ O, HAHN P, HROMADOVÁ M, KŘEČEK J, MACHO L: Late effects of early nutritional manipulations. *Physiol Res* **44**: 357-360, 1995.
- KŘEČEK J: Holism and life manifestations: molecular and space-time biology. *Physiol Res* **59**: 157-163, 2010.
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