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The key role of gut microbiota and the enteroendocrine system in A. M. Ugolev's theory of adequate nutrition

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On the 100th anniversary of the birth of Academician A. M. Ugolev

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Abstract. Recent advancement of biological sciences has been empowered by numerous data supporting an important role played by gut microbiota in health and disease. Nutritional science has particularly benefited from the surge of this knowledge through the development of approaches that directly influence the function and composition of gut microbiota. This paper recalls that the importance of the functional links between gut microbiota and nutrition was anticipated by earlier works of Alexander M. Ugolev's laboratory in the 1960s–1980s. His discovery of membrane digestion and studies implicating intestinal microorganisms in digestive process as well as analysis of hormonal effects of the gut in feeding behavior, among other experimental data, helped Ugolev to conceptualize the nutritional connections between cells and organisms as the universal trophic elements underlying his theory of adequate nutrition. We show here that the core idea of Ugolev's theory includes the maintenance of three main flows of nutrients originating from: 1) ingested food; 2) gut microbiota and 3) enteroendocrine system. Developed about 40 years ago, the theory is still relevant to modern nutritional science. Therefore, revision of Ugolev's work deserves attention not only from historical perspective but also due to the current appreciation of his theory, which is instrumental in integrating the knowledge from nutritional disciplines and developing practical applications.

Keywords: A. M. Ugolev, adequate nutrition, trophology, gut microbiota, membrane digestion, appetite, intestinal hormones, peptides

Ключевая роль кишечной микробиоты и энтероэндокринной системы в теории адекватного питания А. М. Уголева

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Аннотация. Последние достижения в области биологических наук стали возможны благодаря многочисленным данным, подтверждающим важную роль кишечной микробиоты в здоровье и развитии заболеваний. Наука о питании особенно выиграла от резкого роста этих знаний вследствие разработки подходов, оказывающих непосредственное воздействие на функцию и состав кишечной микробиоты. В этой статье мы напоминаем, что важность функциональных связей между микробиотой кишечника и питанием была предсказана еще в ранних работах лаборатории Александра Михайловича Уголева в 1960–1980-х гг. Открытие мембранного переваривания и исследования, указывающие на участие кишечных микроорганизмов в процессе пищеварения, а также анализ гормонального воздействия кишечника на пищевое поведение, наряду с другими экспериментальными данными, помогли А. М. Уголеву концептуализировать пищевые связи между клетками и организмами как универсальные трофические элементы, лежащие в основе его теории адекватного питания. В данной работе мы показываем, что центральная идея теории А. М. Уголева включает в себя поддержание трех основных потоков питательных веществ, исходящих из: 1) потребляемой пищи; 2) кишечной микробиоты и 3) энтероэндокринной системы. Оригинальность теории, сформулированной около 40 лет назад, остается актуальной и в современной науке о питании. Поэтому переосмысление работ А. М. Уголева представляется интересным не только в историческом аспекте, но и с точки зрения современной оценки его теории, способствующей интеграции знаний из различных дисциплин в области питания и разработке практических рекомендаций.

Ключевые слова: А. М. Уголев, адекватное питание, трофология, кишечная микробиота, мембранное пищеварение, аппетит, кишечные гормоны, пептиды

Introduction

The past decade has witnessed an explosive growth of experimental and clinical data revealing functional links between gut microbiota and the host, including virtually all body systems and involved in both health protection and mechanisms of many chronic pathological conditions such as diabetes, obesity as well as cardiovascular, gastroenterological and neuropsychiatric diseases (Clemente et al. 2012; Schneider et al. 2024). Nu-

tritional science has particularly benefited from the surge of this knowledge through the development of approaches with a direct impact on gut microbiota function and composition (Bear et al. 2020; Zhang et al. 2018). While the surge of such data was made possible by recent technological advancement of the tools allowing metagenomic characterization of gut microbiota composition (Bäckhed et al. 2005), the role played by gut bacteria in host physiology and nutrition has attracted attention since the discovery of food-associated microorganisms by Louis

Pasteur. One can also cite the works of Ilya Metchnikov, who was awarded the Nobel Prize for discovering intracellular digestion by macrophages. At the beginning of the last century, he promoted the health-protective effects of *Lactobacilli* but also believed in an overall negative effect of lower gut bacteria (Metchnikoff 1910). The advent of germ-free animal technology in the 1950s offered a powerful experimental tool for the study of the role played by gut bacteria in host physiology (Gustafsson 1948, Reyniers et al. 1946). However, as subtle differences were found between germ-free and conventional animals, including data on negative effects of gut bacteria (Wostmann 1981), and antibiotics came to be used on a massive scale, the interest in the research of gut microbiota diminished. On the other hand, digestive physiology was transformed since the molecular structure of peptide hormones, such as insulin, cholecystokinin (CCK) etc., was identified, contributing to the definition of the gut enteroendocrine system (Mutt 1988). Moreover, after the spectacular effects of selective brain lesions on feeding behavior and body weight were demonstrated around the same time, the hypothalamus was made the key feeding regulatory center, and the research of the brain control of energy metabolism was triggered (Anand, Brobeck 1951).

The Russian school of physiology was greatly shaped by Ivan Pavlov's work on the digestive system, and many of his followers were trained to perform complex experimental surgery on the gastrointestinal tract (GIT) in dogs, cats and rats. Such experimental approaches, combined with recent advancements in nutritional biochemistry and microbiology, inspired young scientists in the post-war period to address the burning questions of the molecular mechanisms of nutrient digestions and appetite regulation. It is hence remarkable that a theory of adequate nutrition assigning a major role to gut microbiota was born in Russia in the 1980s. It has thus anticipated a wide-scale recognition of this phenomenon by about 30 years. In this brief historical review, we would like to give credit to Alexander M. Ugolev, who put forward the theory of adequate nutrition. In the light of current knowledge, we have critically revisited some of his pioneering works, which led him to set forth the theory of adequate nutrition — still a work of fundamental significance.

Biographical overview and discovery of membrane digestion

Alexander Mikhailovich Ugolev (1926–1991) was a prominent scientist in the field of nutri-

tional physiology, who co-authored more than 400 papers and wrote 15 books. He had a full-fledged, typically professional career which still requires a deeper biographical investigation that goes beyond the scope of this paper. Here, we would like to highlight only few details. Starting off as a student in the Naval Military Medical Academy, from which he did not graduate due to health problems, he completed his medical education in his native city of Dnepropetrovsk in 1948. At the age of 32, he finally obtained the second doctorate degree, to become a corresponding and thereafter full member of the USSR Academy of Sciences eight years later. As a young scientist, he worked in Leningrad and Moscow, massively performing experimental surgery on the digestive system together with his mentor V. N. Chernigovsky at the Institute of Normal and Pathological Physiology. Soon after membrane digestion was discovered in 1958, he moved back to Leningrad to join the Pavlov Institute of Physiology, where he set up a laboratory of nutrition physiology, leading it until the rest of his life (Fig. 1).

Alexander Ugolev is well known in Russia — and regrettably, much less abroad — for the discovery of 'membrane digestion', a natural phenomenon of nutrient digestion which occurs on the surface of intestinal mucosa complementing luminal digestion (Ugolev 1960a). Before this discovery, the nutrient digestion process was considered to occur only due to enzymes excreted into the gut lumen from digestive glands. His pioneering work was later confirmed, and several brush border enzymes participating in oligosaccharide hydrolysis identified (for review see: Gray 1992). Some of Ugolev's original drawings illustrate different types of digestion (Fig. 2).

The discovery of membrane digestion was followed by a series of studies contributing to a better understanding of the mechanisms behind hydrolysis of disaccharides and peptides in the small intestine (Jesuitova et al. 1964; Ugolev, Kooshuck 1966; Ugolev et al. 1964a; 1964b; 1979a; 1979b). Ugolev produced several in-depth reviews on the mechanisms of membrane digestion and food assimilation (Ugolev 1965; Ugolev, Iezuitova 1982). Using the inverted intestinal segment technique, Ugolev's laboratory also revealed that different nutritional substrates (amino acids and sugars) competitively interact for hydrolytic enzymes in various species, suggesting a coordinated mechanism of the digestion process, including symbiotic digestion (Ugolev et al. 1975).



Fig. 1. Members of the Laboratory of Nutrition Physiology of the Pavlov Institute of Physiology of the USSR Academy of Sciences in Leningrad in 1983. Alexander M. Ugolev is in the middle of the first row. From left to right, first row: V. V. Egorova, A. V. Leiman, N. M. Mityushova, N. N. Iesuitova, A. M. Ugolev, V. F. Varlamov, V. G. Kassil; second row: L. F. Smirnova, V. M. Vorontsova, N. B. Skvortsova, B. Z. Zaripov (postdoc), N. M. Timofeeva, A. P. Petrova, L. N. Myina, M. Yu. Punin; third row: G. V. Lasareva, D. A. Shinder (PhD student), L. V. Gromova, I. S. Rybin (PhD student), I. S. Podorozhnyak, L. O. Stepanova, I. I. Shtykova, V. M. Nabokova, M. A. Vasheva, V. A. Tsvetkova, A. A. Nikitina, L. G. Ekkert (postdoc), V. G. Gredin (PhD student). (Photo from the archive of the Laboratory of Nutrition Physiology)

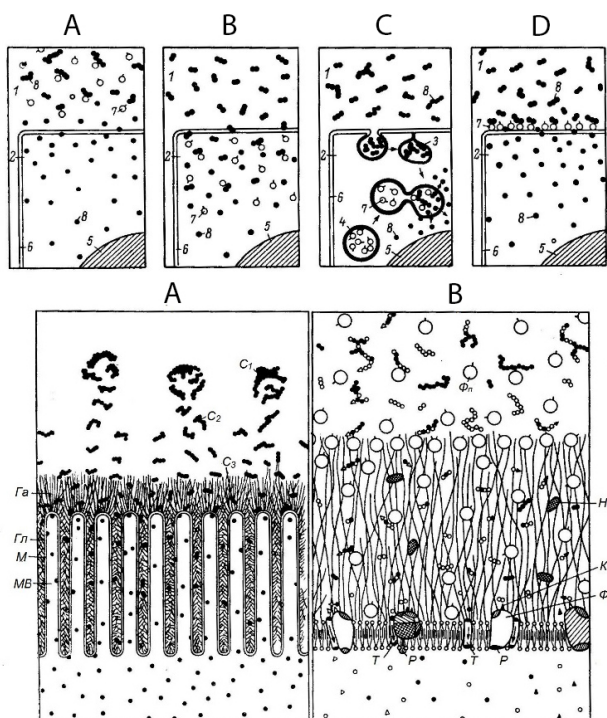


Fig. 2. I (upper panel) — main types of digestion:
A — extracellular distant digestion;
B — intracellular cytoplasmic digestion;
C — intracellular endocytose-based vesicular digestion; D — membrane digestion/
1 — extracellular medium; 2 — intracellular medium; 3 — intracellular digestive vacuole;
4 — lysosome; 5 — nucleus; 6 — membrane;
7 — enzymes; 8 — substrates and their hydrolysis products. II (lower panel) — interactions between luminal and membrane digestion. A — gradual depolymerization of food substrates in the lumen and on the membrane in the small intestine;
B — fragment of the lipoprotein membrane with adsorbed and transmembrane intestinal enzymes;
M — membrane; MB — microvilli; Γ_a & Γ_λ — apical and lateral glycocalyxes; C_1 — C_3 — substrates; Φ_Π & Φ_M — pancreatic and membrane enzymes; T — transport membrane system;
P — regulatory centers of enzymes, HЭ — non-enzymatic factors (Ugolev 1991)

Theory of adequate nutrition

The discovery of membrane digestion and the work that followed inspired Ugolev to put forward 'trophology' as a term for a new nutritional discipline (Ugolev 1980) that explains the existence of universal trophic links between cells in a multicellular organism as well as between simple and complex organisms based on the common mechanisms of nutrient digestion, including both structural and functional trophic units (Fig. 3).

Analysis of the nutrient flow through trophic chains led Ugolev to the idea of the three main nutrient flows from the gastro-intestinal tract to the rest of the organism, which underpinned his theory of adequate nutrition (Ugolev 1986). The theory was then presented as a scientific improvement of the

current balanced nutrition theory, which is premised on the idea of quantitatively feeding the organism with nutrients and qualitatively matching their body needs. Indeed, as compared to this well-accepted balanced theory of nutrition, beside food-derived primary nutrients, the new theory assigns an important nutritional role to gut-bacteria-derived metabolites as well as to hormones which are produced in abundance by the gut enteroendocrine system. Therefore, the purpose and practical implementation of *adequate nutrition* in the frame of the identically named theory would be to adequately feed all these three nutrient flows (Fig. 4). Below, we present in more detail why the support of the nutrient flow from gut bacteria and the maintenance of the hormonal flow from the gut enteroendocrine system became integral parts of Ugolev's theory of adequate nutrition.

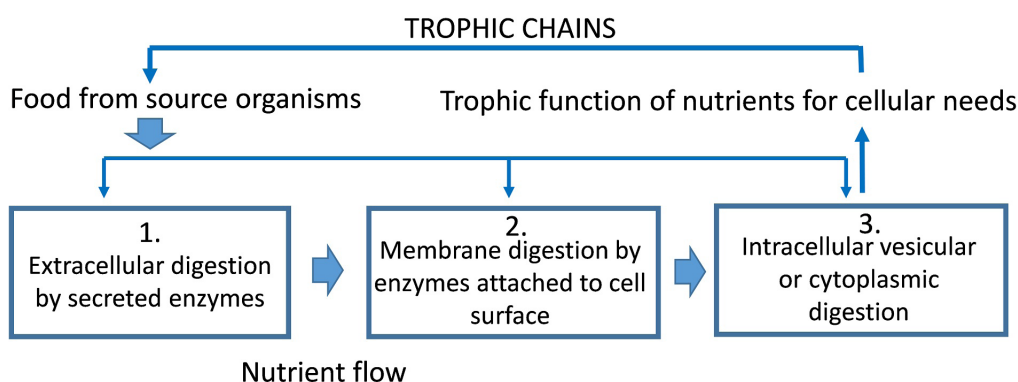


Fig. 3. Ugolev's view of the key role of the nutrient flow ('trophology') in connecting all living organisms in the biosphere through trophic chains. Three main types of digestions represent the universal, both structural and functional, trophic units shared among the organisms. The various trophic chains are not of the closed but of the open system types, forming trophic networks together with other trophic chains and the solar source of energy (adapted from: Ugolev 1985)

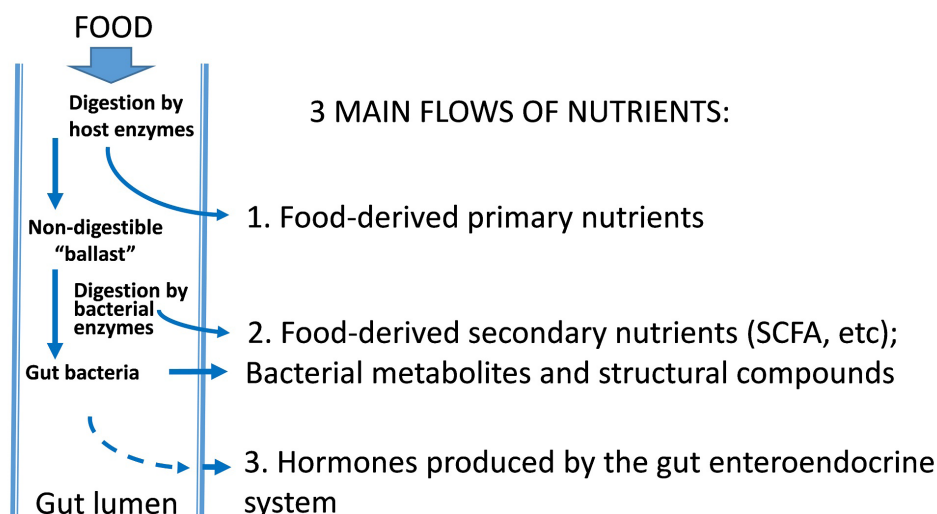


Fig. 4. Three main flows of nutrients from the gut as a result of food digestion by both host and bacterial enzymes as well as from feeding-induced secretion of gut hormones. SCFA, short-chain fatty acids (adapted from: Ugolev 1991)

The role of gut microbiota

As follows from the title of this paper, Ugolev has assigned a key trophic role to gut microbiota in his new theory of adequate nutrition. For him, symbiotic digestion by gut microorganisms provides the host with food-derived secondary nutrients, bacterial metabolites as well as bacterial structural compounds altogether constituting a major flow of nutrients from the gut to the body. He argued that when the host is starved, e. g. when food is scarce and the animal is forced to search for new food sources, gut bacteria may represent an important trophic source for the body, whereas its initial composition will play a major role in the capacity of the organism to adapt to the new feeding environment, i. e. determining the organism survival. According to Ugolev, such fundamental role of gut microbiota should be then considered homeostatic, or more specifically 'trophostatic', and should therefore form an integral part of the concept of the body homeostasis.

A key difference between the adequate and the balanced nutrition theories was changing the view on the role of the so-called 'ballast' component of the food, i. e. non-digestible fibers. The beneficial role of dietary fibers was also promoted in the 1970s by Denis Burkitt, an Irish surgeon known for Burkitt's lymphoma, who also identified the low incidence of colorectal cancer in native African population, which he attributed to high fiber consumption (Burkitt et al. 1974). Thus, while balanced nutrition theory was aimed at purifying nutrients to get rid of the 'ballast', the theory of adequate nutrition keeps this 'ballast' as an essential substrate for bacterial metabolism, resulting in the synthesis of 'secondary' nutrients. Therefore, he criticized elementary diets and stressed a particular role of gut bacteria in the synthesis of short-chain fatty acids (SCFA).

Other 'digestive' functions of gut bacteria included the process of decarboxylation of amino acids such as histidine, a precursor of histamine, or that of tyrosine, a precursor of tyramine, a trace amine. Some of Ugolev's interesting practical suggestions included the infection of new-born infants with a polyculture of beneficial microbes or creating banks of commensal bacteria to replenish the impoverished gut microbiota when needed, e. g. during space travel. It is clear that today many of Ugolev's predictions came true. In fact, the role of gut bacteria in the production of SCFA by metabolizing non-digestible fibers has been well established, forming an integral part of healthy nutrition (Alexander et al. 2019). The consumption of ultra-processed food was associated with chronic metabolic diseases (Martinez Leo, Segura Campos

2020). Recent data also show that histamine production by some *Lactobacillus* species may justify their use as anti-inflammatory probiotics, while the role of bacterial production of trace amines has become a topic of active research (Hall et al. 2019; Gainetdinov et al. 2018).

A breakthrough technology for rearing germ-free animals was developed in the 1940s–1950s by James Reyniers in the USA and Bengt Gustafsson in Sweden, allowing the study of the influence of gut bacteria on host physiology (Gustafsson 1948; Reyniers et al. 1946). An impressive number of studies by Bernard Wostmann, Reyniers' colleague, exhibited an impact of germ-free life on nutrition, in particular revealing an important role of gut bacteria in the production of some essential amino acids and vitamins (Wostmann 1981). We admit that although many 'nutritional' properties of gut microbiota were not directly investigated in Ugolev's laboratory, such experimental data, including those from gnotobiotic animals, also have fed Ugolev's mind, helping him to create and promote the theory of adequate nutrition.

Nevertheless, his laboratory has also contributed to this research topic with several original investigations. In the 1970s, for instance, based on the differences between luminal and membrane digestions, he was testing a hypothesis on the difference in symbiotic contribution of gut bacteria between these two gut compartments. He and his colleagues found that bacteria with caseinolytic and hemolytic activities were less represented in the mucosal fraction, implying different roles of luminal and mucosal bacteria in digestion (Mitiushova et al. 1972). Besides, changing the diet produced a differential effect on mucosal and luminal populations; e. g. the use of amino acid mixture vs. the native casein diet in rats was followed by an increased number of bacteria mainly in the mucosal fraction of the rostral part of the small intestine (Mityushova et al. 1975). Furthermore, using the biopsies from patients with several gastrointestinal disorders and a method of consecutive washes of the intestinal sample (each reflecting distribution of bacteria from the lumen to the mucosa), they found different densities of several cultured bacteria: e. g. in patients with duodenal ulcer, *Escherichia coli* was detected in the luminal but not mucosal fraction, while *Enterococcus* was elevated in both fractions (Misautova et al. 1975). In another study, Ugolev tested if the natural phenomenon of coprophagia could influence the enzymatic function of the small intestine in rats submitted to diet changes. He found that excluding coprophagia resulted in a greater modification of the enzymatic intestinal function, which was interpreted as a missing buffering effect

of ingested bacteria helping the gut to adapt to new diets (Ugolev et al. 1981).

Although functional significance of these and other similar studies needed further validation, the obtained results allowed Ugolev to conclude on the importance of gut microorganisms in symbiotic digestion together with the macroorganism which is dominant in extracting nutrients from food. It is hence essential to preserve microbiota, e. g. when it was suppressed by antibiotics, and to feed it with nutrients such as non-digestible fibers which should not *a priori* compete with the host (Ugolev 1991). However, Ugolev's view of membrane digestion as mainly a 'sterile' process, i. e. unavailable to gut bacteria, can be now challenged in light of the data showing that mucus-feeding commensal bacteria with health-positive effects such as *Akkermansia muciniphila* adhere to the epithelial gut surface and enhance the gut barrier function (Reunanen et al. 2015). While assigning a major trophic role to gut bacteria, however, he did not discuss their possible regulatory role in feeding behavior, a phenomenon which has recently received experimental backing (Fetissov 2017). Yet, he presumed that gut flora may produce some regulatory chemical messengers which can be supplied to the internal milieu together with gut hormones.

The role of gut hormones

A. M. Ugolev stressed that the activation of the gut enteroendocrine system during digestion is an essential part of the theory of adequate nutrition. In fact, by the 1980s, about 30 such hormones of both peptide and amine chemical structure have been identified in both the gut and the brain, giving birth to the gut-brain axis concept (Mayer 2011). Recently, this concept has been enriched by including the gut microbiota (Hooks et al. 2018). A potential role of symbiotic digestion is also currently explored in the pathogenesis of neurodevelopmental disorders such as autism (Kushak et al. 2017). Ugolev proposed the collective name of 'enterines' to GIT hormones, but the term was not widely adopted, although sometime reappearing in Russian literature (Ugolev 1975; 1978). Quite importantly, Ugolev contributed to the research field of gut hormonal regulation of feeding behavior by showing that a protein extract of the rat duodenal mucosa displayed hormone-like satietogenic effects which were independent from the *n. vagus* (Ugolev 1960c). This effect was duodenum-specific since the mucosal extracts from the stomach or some other tissues did not show any anorexigenic effects.

This work was complemented by numerous studies on the effect of duodenectomy on feeding

behavior in cats. In fact, this challenging experimental surgery, developed by Ugolev and colleagues, revealed that following the operation, animals start to lose weight but two months later become hyperphagic and obese. Importantly, it was shown that such effects of duodenectomy were endocrine-like because they were observed only in animals with surgically removed yet not isolated duodenum (Ugolev 1960b). The experimental duodenectomy approach showed that the duodenal functional deficit affects many tissues and organs, such as hypothalamic neurosecretory neurons (Skvortsova et al. 1973), allowing Ugolev to functionally compare the duodenum with the hypothalamo-pituitary system.

Unfortunately, despite the significant effort undertaken by Ugolev together with his colleagues from the Shemyakin Institute of Bioorganic Chemistry in Moscow, the molecular structure of the anorexigenic protein purified from the pig's duodenal mucosa, which they called arenterin, for appetite-regulating enterin, has not been identified (Skvortsova et al. 1975). Nevertheless, it is remarkable that the initial findings of the satietogenic hormone-like effects of the duodenal mucosa were made more than 10 years before the satietogenic effect of CCK was reported by Gibbs, Young and Smith in 1973 (Gibbs et al. 1973). Ugolev was convinced that arenterin should be distinct from the CCK protein because of its more prolonged anorexigenic effect vs. CCK after their intraperitoneal administrations in rats (Ugolev 1991). This riddle still remains unresolved, but we can speculate that arenterin preparations contained anorexigenic enterobacterial protein ClpB (Thomas et al. 2026).

Another experimental surgical approach developed by Ugolev and his colleagues was avascular perfusion of the isolated 'abdominal complex' in rats which included the GIT from the lower part of the esophagus down to the colon including the pancreas and received the blood supply from the abdominal aorta (Ugolev et al. 1985). This approach helped to distinguish the production of structurally identical hormones between the GIT and the brain and the pituitary. For instance, it was shown that after adrenalectomy, the levels of immunoreactive adrenocorticotrophic hormone (ACTH) were dramatically increased in the perfusate, pointing to the local, gut-localized production of this hormone (Bulgakov et al. 1982). Although ACTH-like immunoreactive cells were indeed detected in the pyloric region of the stomach and the duodenum (Larsson 1981), the functional significance of the possible gastrointestinal ACTH production is still unknown. Alternatively, an increase in ACTH-like

bacterial protein production in this preparation can be a possible source for ACTH-like immunoreactivity.

According to the theory of adequate nutrition, the flow of hormones massively produced in the gut during nutrient digestion should be preserved for accurate metabolic regulation at both local and systemic levels. Nevertheless, although called 'eutrophic', i. e. necessary for a normal trophic function, the main meaning of this hormonal flow was assumed only as regulatory. One may ask why a direct trophic function of peptide hormones was not mentioned by Ugolev. In fact, beside their signaling role, regulatory peptides may serve as nutrients after their intracellular digestion by target cells. A direct practical consequence of the idea to preserve feeding-induced hormonal flow, among other factors, is now implemented in the guidelines on parenteral nutrition where enteral nutrition should be always the first choice when the total parenteral nutrition is considered, e. g. in elderly or cancer patients (Laviano, Meguid 1996; Sobotka et al. 2009).

Conclusion

Although Ugolev's theory of adequate nutrition was poorly-known to the international community, most likely due to its publication in Russian scientific literature, it was nevertheless successful as it has been integrated in both medical education and at least partly in medical practice in Russia and some other post-soviet states. In fact, it has clearly shaped the minds and activity of medical practitioners educated in the USSR and Russia during the last 40 years by including the paradigm of dysbiosis, sometime called dysbacteriosis, as a diagnostic term directing the strategies for treatment and prevention of some chronic diseases (Tkachenko 2014). This, in turn, initiated a large number of works for the search of new approaches for the treatment and prevention of intestinal dysbiosis. Ugolev's students and co-workers from the Laboratory of Nutritional Physiology (Pavlov Institute of Physiology RAS, Saint Petersburg) have also contributed to this research — in particular, by showing together with their colleagues from the Institute of Experimental Medicine that certain probiotic bacteria (e. g. *Enterococcus*) may efficiently restore digestive function

during experimental dysbiosis in rats (Ermolenko et al. 2013). The present article has aimed to briefly present Ugolev's theory, making it available for a wide international audience. Although some papers by Ugolev, his colleagues and followers, as referenced here, have been published in Russian, the language translators available nowadays can be conveniently used to read them anywhere across the world.

As concluded by Ugolev in his book *Theory of Adequate Nutrition and Trophology*: '...the theory of adequate nutrition has just started to be built, it still has many lacunas which will be filled by future studies opening new horizons' (Ugolev 1991). We also conclude this paper by saying that Ugolev's work looks interesting not only from the historical perspective. In fact, given recent advancement of nutritional science revealing important trophic roles of gut microbiota and the enteroendocrine system, Ugolev's theory of adequate nutrition appears as a yet viable contemporary approach to nutrition, which provides an insight into complex molecular processes of energy exchange and drives the development of practical nutritional applications.

Conflict of Interest

The authors declare that there is no conflict of interest, either existing or potential.

Конфликт интересов

Авторы заявляют об отсутствии потенциального или явного конфликта интересов.

Author Contributions

- a. Sergueï O. Fetissov — concept, writing and editing the article;
- b. Lyudmila V. Gromova — selection of figures, formatting the bibliography.

Вклад авторов

- а. Фетисов Сергей Олегович — концепция, написание и редактирование статьи;
- б. Громова Людмила Викторовна — подбор рисунков, оформление библиографии.

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