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Chapter 2

ROLE OF ISOTOPES IN THE BIOSPHERE

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ABSTRACT

This chapter consists of two main parts. The first deals with the phenomenon of biological fractionation of stable isotopes as a contribution to isotopic fractionation in geological processes. The second deals with biological roles of natural radioisotopes.

We briefly address kinetic, thermodynamic, and magnetic isotope effects. Fractionation of stable isotopes of some biogenic elements (H, C, O, N, Mg, S, K, Ca, Fe, Cu, and Zn) in the human body is discussed. In particular, we consider (a) the natural isotopic composition of human tissues, fluids, and gases including the temporal dynamics of those isotopic compositions; (b) impacts of diet and geographical peculiarities on human isotopic composition; and (c) dependence of human isotope ratios on the state of health and age. We suppose that each living organism and each of its systems can be characterized by a typical isotopic composition, "an isotopic signature", which is related to the environment. In the signature, typical isotope ratios may fluctuate supporting the state of isotopic homeostasis, a part of the general homeostasis of the organism. There are also sharp changes in typical isotope ratios exceeding the ranges of such fluctuations. Sharp isotope shifts may be used as natural internal markers of pathological processes.

Finally, we address biological effects of natural radioisotopes and their role in speciation and biological evolution. Experimental studies testify that natural background radiation is an important factor for the vital activity of organisms. Paleontological data suggest that dramatic periods of speciation and diversification have regularly occurred in periods of high natural radioactivity of the environment associated with the deposition of uranium-rich sediments. Within the East African Rift, a combined impact of regional geological processes has formed a zone of increased natural radiation that is suggested to have played a principal role in the origin of *Homo sapiens*. Possible mutagenic effects of the cosmic radiation increased during geomagnetic reversals and excursions are also discussed. We suggest that natural low dose ionizing radiation may be deleterious to individuals but beneficial for the population being one of the key factors generating variations that are acted upon by natural selection.

Keywords: isotopic fractionation; isotope effects; isotopic shift; biogenic element; natural radiation; radon; speciation.

2.1. INTRODUCTION

The biosphere is integrated into the course of all geological processes (Vernadsky, 1929b, 2001). Biological fractionation of isotopes – preferential use of one stable isotope over other(s) during processes in living organisms – is a contribution to isotopic fractionation in geological processes (Galimov, 1985).

A concept of the biological fractionation of isotopes of biogenic elements (Tables 2.1 and 2.2) was initially based on the fact that living organisms and abiotic compounds have dissimilar isotopic compositions. For example, the carbon of living organisms is enriched in ^{12}C as compared with abiotic sources (Degens, 1969). This has usually been explained by the kinetic isotope effect (Section 2.2).

It was later proposed that distinctions in isotopic fractionation in different biosystems may be explained by peculiarities of exchange processes (Degens, 1969). Abelson and Hoering (1961) proved an influence of a medium on the isotopic composition of an organism. Studies of the impact of heavy water on biological processes suggested that a biological system responds to both the isotopic composition of a medium and its divergence from the isotopic composition of the biosystem (Roginskii and Shnol', 1965).

Adaptation to unfavorable conditions, accompanied by resource mobilization, may modulate biological isotopic fractionation. It was proposed that (a) such changes may be used as an integral parameter characterizing the state of biochemical processes in the organism, and (b) the intramolecular distribution of isotopes may be sensitive to any deviations of biosynthesis from the norm. However, *in vivo*, such deviations cannot be explained by isotopic effects only: their influences are modulated by interferences of the metabolic conditions (Roginskii and Shnol', 1965; Schmidt, 2003).

Galimov (1985) suggested that a consistent distribution of isotopes between and within biomolecules is an intrinsic property of all biochemical reactions in living organisms. He proposed that biological isotopic fractionation is characterized by differences in the isotopic composition between an organism and a medium, between biochemical fractions, between individual compounds in such fractions, and between biomolecules. This author also suggested that biological isotopic fractionation takes place at a cellular level, while substance transport and intercellular exchange play a lesser role in this process.

The influence of environmental media on the isotopic composition of living organisms can be generalized in geographical terms. There is spatial variability in isotopic ratios typical of particular tissues of plants, animals, and humans (Nakamura et al., 1982; Rubenstein and Hobson, 2004; Bai et al., 2008; Ehleringer et al., 2008; West et al., 2008). The variability depends on climatic conditions, the isotopic composition of meteoric water, chemical properties of bedrocks, soils, and groundwater, topographic position as a control on insolation and the gravity-driven redistribution of water and nutrients in the landscape, proportion of C_3 and C_4 vegetation, and geographically dependent chemical characteristics of food (Figure 2.1).

Table 2.1. Biogenic classification of chemical elements (Bgatov, 1999)

Type	Group	Elements	Description
Biogenic	Protoelements	H, C, O, N	Basic elements of organic molecules originated in the Precambrian. Components of most of amino acids.
		P, S	Obligatory components of protein molecules, DNA, and RNA. Creators of proto-life, precellular life.
	Macroelements	K, Na, Ca, Mg, Cl, Si	The elements of buffer system of first unicellular organisms and cell potential. First elements of skeletal system of protists.
	Essential microelements	Fe, Cu, Zn, Mn, Cr, Se, Mo, I, Co, F	The elements integrated in metabolism with the advent of the blood system. Participants of redox reactions. Components of coenzymes.
	Conventionally essential microelements	As, Br, Li, Ni, V, Cd, Pb	Narrow-specialized elements "used" by some species only. Sometimes, components of coenzymes.
	Brain elements	Au, Sn, Tl, Te, Ge, Ga	Probably, the elements take part in brain signaling in mammals. They were possible integrated in metabolism in the Quaternary Period.
Abiogenic	Neutral	Al, Ti, Rb	Despite of a wide abundance in the lithosphere, the elements were not integrated in metabolism of animals due to weak reactive ability.
	Competitors	B, Sr, Cs	The elements were integrated in metabolism of marine species. This resulted in their further competition with other elements (e.g., Ca) in metabolism of land species leading to pathologies.
	Aggressive	Hg, Be, Os, Bi	The elements of late volcanic activity. Thus, they were not integrated in metabolism. Dangerous in low doses.

Lysenko and Sobotovich (2006) proposed a concept of isotopic zonality, that is, well-ordered spatial distribution of stable isotopes in the biosphere. Isotopic zonality, controlled by the geological environment, generates background conditions for biological isotopic fractionation.

The phenomenon of biological isotopic fractionation has been much studied for hydrogen (Thomson, 1963), carbon (Ivlev, 2001), oxygen (Barbour, 2007), nitrogen (Handley and Raven, 1992), magnesium (Black et al., 2008), silicon (Street-Perrott and Barker, 2008), sulfur (Johnston et al., 2005), calcium (DePaolo, 2004), iron (Beard et al., 2003), copper (Zhu et al., 2002), zinc (Cloquet et al., 2008), and selenium (Johnson, 2004). Results of numerous studies (see bibliographies in reviews cited) strongly supported a hypothesis by Vernadsky (1929a) that living organisms selectively utilize specific isotopes. However, a number of problems remain to be solved.

Table 2.2. Abundance and some nuclear characteristics of selected elements and their isotopes discussed in this chapter and section 3.3

Element	Abundance, weight % (Vernadsky, 2001)		Isotope	Isotope-abundance variation, % (De Laeter et al., 2003)	Nuclear characteristics* (Stone, 2005)		
	Crust	Biota, fresh weight			Spin, ħ	Magnetic dipole moment, nm	Electric quadrupole moment, b
$_{1}$H	1.00	70.00	^{1}H ^{2}H	99.99 0.01	1/2 1	+2.79284734 +0.857438228	 +0.0028
$_{3}$Li	0.005	10^{-5}	^{6}Li ^{7}Li	7.59 92.41	1 3/2	+0.8220473 +3.256427	-0.00082 -0.0406
$_{6}$C	0.35	18.00	^{12}C ^{13}C	98.93 1.07	0 1/2	 +0.7024118	
$_{7}$N	0.04	0.30	^{14}N ^{15}N	99.64 0.36	1 1/2	 -0.28318884	
$_{8}$O	49.13	10.50	^{16}O ^{17}O ^{18}O	99.76 0.04 0.20	0 5/2 0	 -1.89379	 -0.02578
$_{9}$F	0.08	$5\cdot10^{-4}$	^{19}F	100	1/2	+2.628868	
$_{12}$Mg	2.35	0.04	^{24}Mg ^{25}Mg ^{26}Mg	78.99 10.00 11.01	0 5/2 0	 -0.85545	 +0.199
$_{14}$Si	26.00	0.20	^{28}Si ^{29}Si ^{30}Si	92.22 4.69 3.09	0 1/2 0	 -0.55529	
$_{16}$S	0.10	0.05	^{32}S ^{33}S ^{34}S ^{35}S	94.99 0.75 4.25 0.01	0 3/2 0 3/2	 +0.6438212 +1.07	 -0.678 +0.0471
$_{19}$K	2.35	0.30	^{39}K ^{40}K ^{41}K	93.26 0.01 6.73	3/2 4 3/2	+0.39147 -1.298100 +0.2148701	+0.585 -0.073 +0.0711
$_{20}$Ca	3.25	0.50	^{40}Ca ^{42}Ca ^{43}Ca ^{44}Ca ^{46}Ca ^{48}Ca	96.94 0.65 0.14 2.09 0.004 0.19	0 0 7/2 0 0 0	 -1.3173 	 -0.055
$_{26}$Fe	4.20	0.01	^{54}Fe ^{56}Fe ^{57}Fe ^{58}Fe	5.85 91.75 2.12 0.28	0 0 1/2 0	 +0.09062300	 0.11
$_{27}$Co	0.002	$2\cdot10^{-5}$	^{59}Co	100	7/2	+4.627	+0.35
$_{29}$Cu	0.01	$2\cdot10^{-4}$	^{63}Cu ^{65}Cu	69.15 30.85	3/2 3/2	2.227206 2.3816	-0.211 -0.195

Element	Abundance, weight % (Vernadsky, 2001)		Isotope	Isotope-abundance variation, % (De Laeter et al., 2003)	Nuclear characteristics* (Stone, 2005)		
	Crust	Biota, fresh weight			Spin, ħ	Magnetic dipole moment, nm	Electric quadrupole moment, b
$_{30}$Zn	0.02	$5 \cdot 10^{-4}$	^{64}Zn ^{66}Zn ^{67}Zn ^{68}Zn ^{70}Zn	48.27 27.98 4.10 19.02 0.63	0 0 5/2 0 0	+0.8752049	+0.150
$_{33}$As	$5 \cdot 10^{-4}$	$3 \cdot 10^{-5}$	^{75}As	100	3/2	+1.43948	0.314
$_{34}$Se	$8 \cdot 10^{-5}$	10^{-6}	^{74}Se ^{76}Se ^{77}Se ^{78}Se ^{80}Se ^{82}Se	0.89 9.37 7.63 23.77 49.61 8.73	0 0 1/2 0 0 0	+0.5350422	1.1
$_{38}$Sr	0.04	$2 \cdot 10^{-3}$	^{84}Sr ^{86}Sr ^{87}Sr ^{88}Sr	0.56 9.86 7.00 82.58	0 0 9/2 0	-1.0928	+0.33
$_{53}$I	10^{-4}	10^{-5}	^{127}I	100	5/2	+2.81327	
$_{82}$Pb	0.002	$5 \cdot 10^{-5}$	^{204}Pb ^{206}Pb ^{207}Pb ^{208}Pb	1.40 24.10 22.10 52.40	0 0 1/2 0	+0.592583	0.51
$_{92}$U	$4 \cdot 10^{-4}$	10^{-6}	^{234}U ^{235}U ^{238}U	0.005 0.72 99.27	0 7/2 0	-0.38	4.936

* Related to the ground state.

In particular, Vernadsky (1931) proposed that distinct isotopes of an element may differently influence biota. As far as we know, this issue has been much studied in two contexts only: unnatural conditions (e.g., cultivation of organisms in heavy water – Katz and Crespi, 1966) (Section 2.3.4) and effects of radionuclides (UNSCEAR, 2001, 2008). Although the impact of diet on the isotopic composition of an organism has been generally characterized (Section 2.3.2), a poorly understood issue is the response of biological isotopic fractionation to aging and stress factors (e.g., physical load and disease – Section 2.3.3). This issue has been mainly studied in the context of nutritional stressors (McCue and Pollock, 2008).

This chapter consists of two main parts. The first deals with the phenomenon of biological fractionation of stable isotopes. We discuss fractionation of stable isotopes of some biogenic elements (H, C, O, N, Mg, S, K, Ca, Fe, Cu, and Zn) in humans. We consider (a) the isotopic composition of human tissues, fluids, and gases including the temporal dynamics of those isotopic compositions; (b) impacts of diet and geographical peculiarities on the isotopic composition of humans; and (c) dependence of human isotopic fractionation on both state of health and age. In the second part, we address biological effects of natural radioisotopes and their role in speciation and biological evolution.

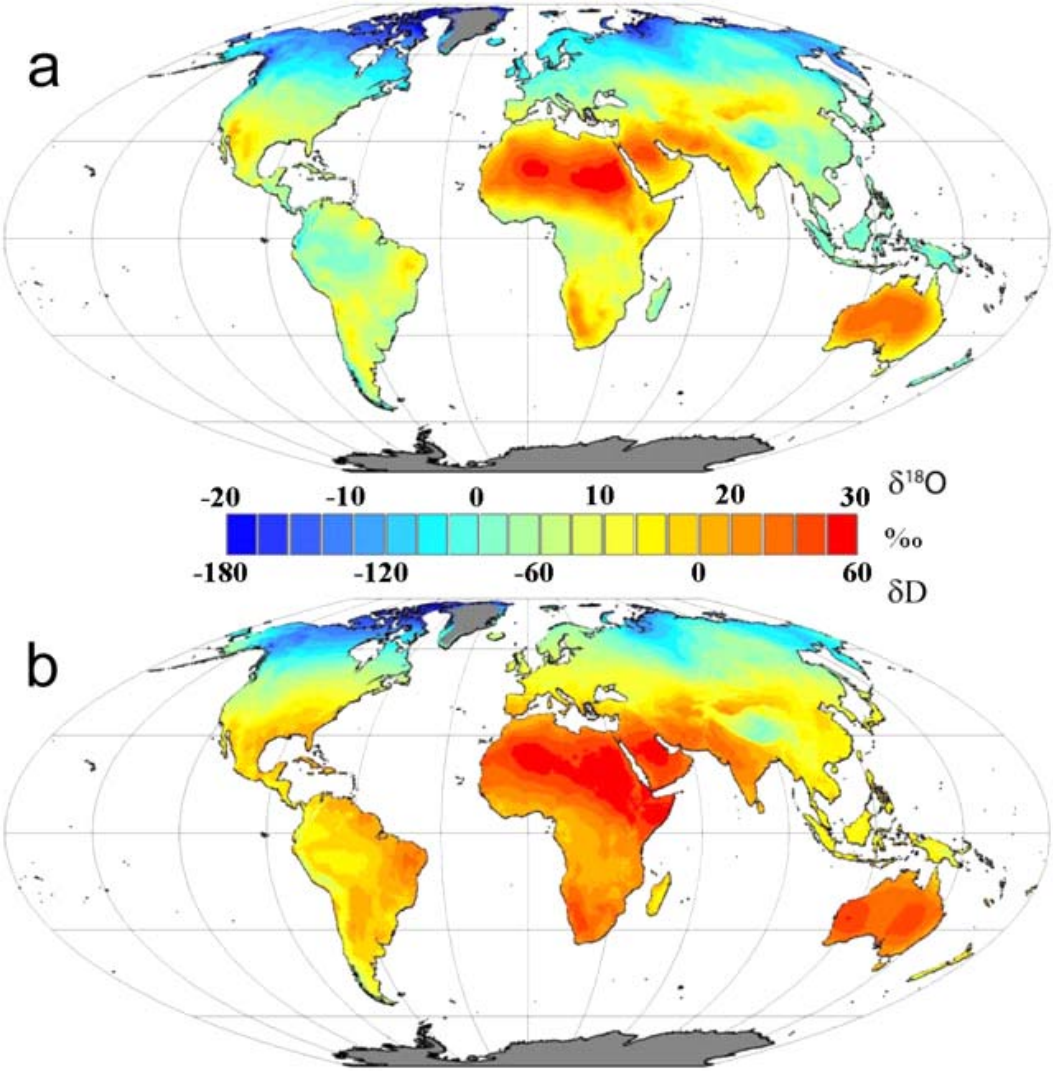

Figure 2.1. Global distribution of modeled values of mean annual values of leaf water $\delta^{18}O$ and δD. Means were derived from monthly model predictions that utilized input grids of annual average precipitation isotope ratios as plant source water, elevation (for barometric pressure), and modified monthly climate grids for temperature and humidity. Grid cells where monthly temperature averages were never above freezing resulted in blank cells shown as gray (after West et al., 2008; © West et al., 2008, courtesy of PloS ONE).

2.2. ISOTOPE EFFECTS

Isotopic fractionation, leading to differences between the isotopic composition of a reaction product and that of the initial compound, is a result of the physico-chemical nonequivalence of isotopes. Below we outline three types of isotopic effects: kinetic, thermodynamic (equilibrium), and magnetic.

A kinetic isotope effect (Melander, 1960; Collins and Bowman, 1971; Roginskii and Shnol', 1965) is caused by distinct rates of chemical reactions for different isotopic forms –

compounds having similar composition and structure, but including dissimilar isotopes of an element in one or several positions. In a system of interactive particles, lighter particles possess higher velocities. Thus, molecules containing a lighter isotope are more mobile than those containing a heavier one. Chemical bonds formed by a heavy isotope are more durable than those formed by a light isotope. The activation energy of a reaction involving an isotopically heavy form is higher than that involving an isotopically light form. The kinetic isotope effect of a chemical reaction is quantitatively estimated as the ratio of reaction rate constants for the two isotopic forms. It depends on the difference in activation energies, but does not depend on the absolute value of the activation energy. Reaction products are usually enriched in a light isotope if the ratio of reaction rate constants is >1. In this case, a heavy isotope is accumulated in an unreacted residue.

An isotopically heavy form possesses less free energy than an isotopically light form. In the general case, the minimal free energy of a system can be achieved with different isotopic compositions of its components. A thermodynamic isotope effect corresponds to the resultant distinction in isotopic compositions of the components. Redistribution of an isotope between system components can be expressed as an isotopic exchange reaction. The equilibrium constant of the reaction can be determined using concentrations of initial reagents and products, or by the change of free energy in the reaction. Thermodynamic isotope effects determine an overall tendency for isotopic fractionation in biosystems, but there are also variations associated with peculiarities of biosynthesis, metabolism, and organism evolution (Galimov, 1985; Schmidt, 2003).

Some chemical and biochemical processes are associated with a change of the total electronic spin of the reactive system (e.g., triplet–singlet transformation). The probability of such a transformation differs for nuclei possessing different spin values. The magnetic isotope effect results in fractionation of odd, magnetic isotopes and even, nonmagnetic isotopes in chemical and biochemical processes (Buchachenko, 2000, 2009) according to their nuclear spin values and magnetic moments (Table 2.2). Unlike kinetic isotope effects, magnetic isotope effect depends on the intensity of the external magnetic field (Salikhov, 1996; Buchachenko, 2000). Currently, the magnetic isotope effect is established for H, C, O, Mg, Si, S, Ge, Sn, Hg, and U (Buchachenko, 2009).

From a biological point of view, it is important that a synthesis rate of adenosine triphosphate (ATP) – a source of chemical energy within cells – depends on the nuclear spin and magnetic moment of Mg^{2+} in creatine kinase and ATPase. The higher the portion of the magnetic isotope ^{25}Mg in the magnesium isotopic composition of the enzymes, the higher the ATP synthesis rate (Buchachenko et al., 2006; Buchachenko and Kouznetsov, 2008).

Isotopes of a heavy element have relatively small differences in masses (Firestone et al., 1996). The magnetic isotope effect can be effective in this case, changing the theoretical ranges of variations in the isotopic ratios of heavy elements. The ranges may be broader than those estimated for fractionation based solely on differences in the atomic mass. It is important to note that the main rock-forming elements (O, Si, Mg, Ca, and Fe) have isotopes with different spins (Table 2.2). In the context of the magnetic isotope effect, studies of isotopic ratios of heavy elements can open a way to better understand both biogeochemical mechanisms of ore formation and biochemical reactions in living organisms.

2.3. ISOTOPIC FRACTIONATION OF BIOGENIC ELEMENTS IN THE HUMAN BODY

Compared with investigations of plants and animals, processes of isotopic fractionation in the human body are still little understood. In this context, H, C, O, and N are the most extensively studied biogenic elements. Some limited data are available on the isotopic fractionation of S, Fe, Mg, Zn, K, Ca, and Cu in the human body. In this respect, other biogenic elements (Table 2.1) having stable isotopes have not been studied.

Investigations has been conducted in the following areas:

1. Isotopic composition of tissues, fluids, and gases including the temporal dynamics of isotopic ratios;
2. Relations between the isotopic composition of human tissues, diets, and geographical peculiarities;
3. Dependence of human isotopic fractionation on the state of health and age;
4. Influence of stable isotopes on the human organism.

See Appendix 2.A for a description of the δ isotope ratio notation for elements discussed below.

2.3.1. Isotopic Composition of the Human Body

It seems likely that Lasnitzki and Brewer (1942) pioneered the description of the isotopic composition of human tissues. They found an enrichment of bone including marrow in ^{41}K ($\delta^{41}K$ = 10.28–21.91‰). Some tissues were enriched in ^{39}K: liver $\delta^{41}K$ ranged from 0‰ to -3.19‰, brain $\delta^{41}K$ was -1.79‰, kidney $\delta^{41}K$ ranged from 0‰ to -5.98‰, and heart $\delta^{41}K$ was -5.28‰. The potassium isotopic composition of lung, spleen, and skeletal muscle did not vary from that of a standard material (KCl). However, Mullins and Zerahn (1948) have argued that all these findings were erroneous, because of inaccuracies and artifacts in the method used by Lasnitzki and Brewer (1941). As far as we know, since then nobody has tried to estimate potassium isotope ratios in the human body. We should stress that the main argument of Mullins and Zerahn (1948) – that potassium isotopes are not fractionated in biota due to their large atomic mass – cannot be accepted, since it has been established that isotopes of heavier elements (e.g., Fe, Zn, and Se) fractionate in living organisms (Beard et al., 2003; Johnson, 2004; Cloquet et al., 2008).

Lyon and Baxter (1978) presented the first comprehensive data set on the carbon isotopic composition of various tissues of the human body (Table 2.3). One can see that different human tissues are characterized by dissimilar carbon isotope ratios: blood is the most enriched in ^{13}C, whereas the thymus is the most depleted (the difference is about 7‰). Bone carbonate is enriched in ^{13}C by about 10‰ relative to soft tissues.

It should be realized that the isotopic ratio in a particular tissue is not a constant value. There is temporal variability of such ratios manifested at various temporal scales. This variability can be associated with biorhythms, endo- and exogenous processes in the organism (some of them being governed by dietary peculiarities, inter-regional movement, aging, and

disease – Sections 2.3.2 and 2.3.3). Different tissues are characterized by distinct dynamics of isotopic ratios because of different rates of metabolism, regeneration, and remodeling typical of those tissues.

Table 2.3. $\delta^{13}C$ variation in human tissues from a single individual (Lyon and Baxter, 1978)

Organs and tissues	$\delta^{13}C$, ‰
Pancreas	-25.3
Thyroid	-22.7
Thymus	-25.6
Kidney	-24.0
Heart	-22.8
Muscle	-23.6
Spleen	-22.2
Liver	-22.7
Brain	-21.1
Lung	-22.4
Testes	-22.3
Blood	-18.2
Blood plasma	-18.7

For example, Ivlev et al. (1992) observed slow oscillations with a period of 20–30 days and variable amplitude in the carbon isotopic composition of humans hairs. The maximum deviation from a mean level was 6‰. Different individuals had dissimilar oscillation patterns. They were associated with biorhythms accompanied by oscillations in the energetic and biosynthetic demands of epidermic cells that determined the degree of pyruvate pool depletion associated with ATP and keratin syntheses.

Later, Ivlev et al. (1994) found relationships between daily rhythms in the human organism and variations of the carbon isotopic composition of expired CO_2. There are two phases in the daily variation of $\delta^{13}C$ corresponding to day- and nighttime types of metabolism. The daytime phase consists of altering maxima and minima of $\delta^{13}C$ in expired CO_2 associated with periodicity in feeding and movement activity. The nighttime phase is marked by continuous enrichment of expired CO_2 in ^{12}C. More detailed examination of diurnal variations in the carbon isotopic composition of expired CO_2 allowed Ivlev et al. (1996b) to detect short-term oscillations with periods of 2–3 h. The period is little dependent on the functional state of the organism. This phenomenon can be connected with the periodic filling/depletion of the cytoplasmic pool of CO_2 (Ivlev, 2001) in the cells of organs that are most active in a particular functional state of the organism.

Metges and Petzke (1997) presented data on $\delta^{15}N$ of thirteen plasma-free amino acids in humans (Table 2.4). Phenylalanine and threonine were the most depleted in ^{15}N. There were small differences in the nitrogen isotopic composition of alanine, leucine, proline, and ornithine: their $\delta^{15}N$ values ranged from 10 to 15‰. The metabolically related phenylalanine and tyrosine differed in their nitrogen isotopic composition by ~15‰. Later, Petzke et al. (2005) measured $\delta^{15}N$ and $\delta^{13}C$ in fourteen amino acids of human hair (Table 2.4). The difference between the lowest and highest $\delta^{13}C$ values of the individual amino acids (leucine

and glycine) was ~30‰, whereas the difference between the lowest and highest $\delta^{15}N$ values (for threonine and proline) was ~25‰. Fuller et al. (2005) proved that $\delta^{15}N$ values in human tissues are influenced by deviations in nitrogen homeostasis: a catabolic state leads to an increase in $\delta^{15}N$, whereas an anabolic state results in a decrease in $\delta^{15}N$ of the body.

Demikhov (2005) studied the hydrogen isotopic composition of human tissues and fluids. The water of human blood, saliva, sweat, and urine is characterized by a similar hydrogen isotopic composition within limits of the measurement accuracy (Table 2.5). These fluids are deuterium enriched by ~30‰ relative to local drinking water (its δD was -74‰). The increase of δD in human blood, saliva, sweat, and urine relatively to local drinking water should be compensated by secretion of hydrogen with low δD from the human organism in other ways. A probable way is sebaceous gland activities: human cerumen has a very light hydrogen isotopic composition (Table 2.5).

Table 2.4. Average values of $\delta^{15}N$ and $\delta^{13}C$ (‰) in amino acids of human blood plasma and hair (Metges and Petzke, 1997; Petzke et al., 2005)

Amino acids	Blood plasma	Hair	
	$\delta^{15}N$	$\delta^{15}N$	$\delta^{13}C$
Histidine	1.64	3.7	-20.1
Isoleucine	no data	9.8	-25.6
Leucine	11.4	10.5	-30.4
Lysine	2.94	2.5	-27.0
Phenylalanine	-10.89	2.0	-27.5
Threonine	-5.43	-9.7	-26.2
Valine	8.34	13.3	-25.3
Alanine	9.86	9.2	-16.5
Aspartic acid	no data	9.0	-15.6
Glutamic acid	8.41	14.4	-17.7
Glycine	6.08	6.4	-0.1
Proline	13.87	15.7	-20.7
Serine	7.12	8.7	-22.2
Tyrosine	6.08	4.1	-16.5
Ornithine	10.1	no data	

Table 2.5. δD variation in human fluids and tissues (Demikhov, 2005)

Fluid and tissue	δD, ‰
Breathed-out moisture	-83
Saliva	-49
Blood	-48
Sweat	-45
Urine	-44.5
Hairs	-78
Nails	-82
Earwax (cerumen)	-161

Analyzing δD, $\delta^{13}C$, $\delta^{15}N$, and $\delta^{18}O$ of scalp hair and fingernail samples every two weeks for eight months, Fraser et al. (2006) found relatively small fluctuations in $\delta^{13}C$ and $\delta^{15}N$ of hair (-20.59 ± 0.59‰ and 9.90 ± 0.71‰, respectively) and nails (-21.14 ± 0.56‰ and 10.06 ± 1.04‰, respectively). Larger fluctuations were found for δD and $\delta^{18}O$ values of hair (-66.2 ± 4.1‰ and 14.7 ± 1.7‰, respectively) and nails (-60.7 ± 7.6‰ and 13.1 ± 1.5‰, respectively). O'Connell et al. (2001) found that (a) bone collagen is enriched relative to hair keratin by 1.4‰ in $\delta^{13}C$ and 0.86‰ in $\delta^{15}N$; (b) no significant difference exists between hair and nail keratin in $\delta^{13}C$; and (c) nail keratin is enriched relative to hair keratin by 0.65‰ in $\delta^{15}N$. It was proposed that the $\delta^{13}C$ differences may be caused by differences in amino acid composition between hair keratin and bone collagen.

Walczyk and von Blanckenburg (2002, 2005) demonstrated that the human intestines preferentially absorb the lightest iron isotope. They found that human blood and muscle tissue have similar iron isotopic compositions (mean $\delta^{56}Fe$ are -2.74‰ and -2.58‰, respectively); hair is enriched in ^{54}Fe ($\delta^{56}Fe$ = -3.8‰), whereas the liver is enriched in ^{56}Fe (mean $\delta^{56}Fe$ is -1.37‰). The mean $\delta^{57}Fe$ of human blood was estimated as -3.8‰ (Walczyk and von Blanckenburg, 2002). Ohno et al. (2004) determined $\delta^{56}Fe$ and $\delta^{57}Fe$ of human erythrocytes as about -3‰ and -4.5‰, respectively. There were no seasonal changes in these ratios over a period of one year, probably due to the slow turnover of body iron. The trend of enrichment of the human blood in ^{54}Fe and depletion in ^{56}Fe and ^{57}Fe was supported by observations of Stenberg et al. (2005).

Maréchal et al. (1999) pioneered estimation of copper fractionation in humans: $\delta^{65}Cu$ = 0.30‰ for the human blood. There is also evidence for zinc fractionation in the human body. Maréchal et al. (1999) reported the $\delta^{66}Zn$ value of the human blood as 0.41‰. Stenberg et al. (2004) measured $\delta^{66}Zn$ values of human hair and whole blood as -0.60‰ and 0.56‰, respectively. Ohno et al. (2005) estimated $\delta^{66}Zn$ and $\delta^{68}Zn$ of human hair as -0.16‰ and -0.31‰, respectively, whereas $\delta^{66}Zn$ and $\delta^{68}Zn$ of human erythrocytes were 0.43‰ and 0.83‰, respectively. These authors found no seasonal fluctuations in these values.

Among vertebrates, bone $\delta^{44}Ca$ is ~1.3‰ lower than dietary $\delta^{44}Ca$ and dissolved soft tissue $\delta^{44}Ca$. This difference is associated with fractionation during bone formation, whereas bone resorption does not fractionate Ca isotopes. Thus, if dietary $\delta^{44}Ca$ is constant and the rates of bone formation and resorption are equal, the difference in $\delta^{44}Ca$ between bone and soft tissue should be constant. It was found that urinary $\delta^{44}Ca$ responds to changes in bone mineral balance in less than a month (Skulan et al., 2007).

There is limited evidence on gender differences in stable isotope fractionation. For example, the blood $\delta^{56}Fe$ and $\delta^{57}Fe$ of males is lower by ~0.3‰ than that of females (Walczyk and von Blanckenburg, 2002, 2005). Ohno et al. (2004) also reported that female erythrocytes are more enriched in ^{56}Fe and ^{57}Fe than male ones: $\delta^{56}Fe$ values were -2.55‰ for females and -3‰ for males; $\delta^{57}Fe$ values were -3.77‰ for females and -4.4‰ for males. Prowse et al. (2005) demonstrated that bone collagen of females is more depleted in ^{13}C than that of males ($\delta^{13}C$ values were -19‰ and -18.7‰, respectively), and bone collagen $\delta^{15}N$ values are consistently lower among females than males. Although these effects are still poorly known, one can presume that they are associated with gender differences in metabolism.

2.3.2. Dependence of Isotopic Composition of the Body on Diet and Geography

Plants from different climatic zones have different carbon isotopic compositions due to distinct rates of metabolism (Craig, 1954). DeNiro and Epstein (1978, 1981) were the first to study a dependence of isotopic composition of animal bodies on diet. Later, it was established that isotopic ratios of C, N, O, H, and S in human tissues can retain information on the dietary and environmental conditions that prevailed during tissue formation. Since different tissues have dissimilar rates of regeneration or remodeling (some tissues are not remodeled after formation, such as tooth enamel), isotopic ratios of a particular set of tissues may reflect the life circumstances of a person during distinct periods of his or her life.

The influence of diets and geographical peculiarities on the isotopic composition of human hair, fingernails, teeth, and bones is the best-understood issue of the isotopic composition of the human body. Most of these studies are connected with research in archaeology (Ambrose and DeNiro, 1986; Dupras and Schwarcz, 2001; Wilson et al., 2007) and forensics (Bol et al., 2007; Meier-Augenstein and Fraser, 2008; Mützel Rauch et al., 2009). In archaeology, intrinsic isotope ratios in human tissues are analyzed to reconstruct paleodiets and migration routes. In forensics, such isotope analyses may be used to identify mutilated bodies, to reconstruct the life circumstances of a person, and to verify the origin of migrants.

C_4 plants (e.g., maize), using the Hatch–Slack photosynthetic cycle, fractionate carbon differently from C_3 plants (most grasses, trees, roots, and tubers), using the Calvin cycle (Hatch and Slack, 1970). Variations in $\delta^{13}C$ of human tissues may distinguish C_3 from C_4 food diets including grass- or corn-fed animal products (Nakamura et al., 1982). In particular, North Americans usually have higher $\delta^{13}C$ values in human tissues as compared with Europeans. For example, hemoglobin $\delta^{13}C$ values are -24.4‰ and -18.7‰ (Apostol et al., 2001), and hair $\delta^{13}C$ values are -20.5‰ and -18.2‰ (Bol et al., 2007), respectively. These differences reflect a higher proportion of C_4 food in North American diets.

$\delta^{15}N$ values in human tissues may be used to distinguish plant from animal protein diets. Higher $\delta^{15}N$ values of human hair relate to omnivorous and ovo-lacto-vegetarian diets, whereas lower $\delta^{15}N$ values relate to more vegetarian diets (O'Connell and Hedges, 1999). However, there are significant differences in $\delta^{15}N$ values of fingernails sampled from vegetarians living in different regions (Nardoto et al., 2006). High $\delta^{15}N$ values are typical for persons with a marine diet (Schoeninger et al., 1983; Prowse et al., 2005; Buchardt et al., 2007).

Meteoric water is marked by spatial variability of $\delta^{18}O$ and δD values due to Rayleigh distillation in the global rainfall cycle (Bowen, 1991). In particular, precipitation at higher latitudes is $\delta^{18}O$ and δD depleted compared with lower latitudes (Figure 2.1). Thus, $\delta^{18}O$ and δD values of human tissues may provide information on the geographical location where a person consumed food and water (Sharp et al., 2003; O'Brien and Wooler, 2007; Daux et al., 2008; Ehleringer et al., 2008).

$\delta^{34}S$ values in human tissues can be used to discriminate between terrestrial and marine diets (Richards et al., 2001; Bol et al., 2007; Buchardt et al., 2007).

In general, the ^{13}C and ^{15}N enrichment of tissues increases along food chains (Minagawa and Wada, 1984; Bump et al. 2007). For animals, DeNiro and Epstein (1978, 1981) established that tissues are usually enriched in ^{13}C by ~1‰ and in ^{15}N by ~3‰ relative to the

diet. For humans, Ivlev et al. (1996a) found ^{12}C enrichment of the expired CO_2 by 3–6‰ relative to diet. The isotopic balance is maintained by ^{13}C enrichment of urine urea by 3–5‰. Human blood and tissues are enriched in ^{54}Fe as compared with the diet: the blood $\delta^{56}Fe$ value is lower by ~2.6‰ than the dietary $\delta^{56}Fe$ (Walczyk and von Blanckenburg, 2002, 2005).

Human breast milk is enriched in ^{18}O relative to the water imbibed by a lactating mother, due to the preferential expiration of $H_2{}^{16}O$ (Wright and Schwarcz, 1998). Roberts et al. (1988) showed that urine $\delta^{18}O$ values of breastfed infants are higher than those of bottle-fed infants by 1.85‰, whereas the urine $\delta^{18}O$ values of bottle-fed infants are higher than those of local meteoric water by 2.6‰. Fuller et al. (2006) found that fingernails and hair of breastfed infants are enriched in ^{13}C (~1‰) and ^{15}N (2–3‰) compared with those of mothers during the lactation period, whereas bottle-fed infants have no increase in $\delta^{13}C$ or $\delta^{15}N$ values.

Aside from the spatial (geographical) variability in the dietary control of human isotopic composition, there is temporal variability in these dependences, which are manifested at various temporal scales. For example, Lacroix et al. (1973) demonstrated that oral administration of glucose naturally enriched in ^{13}C resulted in a marked rise in $\delta^{13}C$ in the expired CO_2. $\delta^{13}C$ reached its maximum at 4 h and then declined. Urine δD and $\delta^{18}O$ quickly respond to a travel-related change in drinking water (Horvitz and Schoeller, 2001; O'Brien and Wooler, 2007). Hair δD and $\delta^{18}O$ are more stable: changes were observed about 4 weeks after moving (Nakamura et al., 1982; Ehleringer et al., 2008).

Slatkin et al. (1985) demonstrated that a difference in $\delta^{13}C$ of cerebellar neuronal deoxyribonucleic acid (DNA) and cerebellar white matter is ontogenetically controlled. $\delta^{13}C$ of the cerebellar neuronal DNA is stable corresponding to the maternal diet during fetal development, because nearly all neurons are formed during maturation of the fetal brain and do not remodel thereafter. $\delta^{13}C$ of the cerebellar white matter is changeable, reflecting the predominant diet of a person, because white matter tissue turns over rapidly.

Human tissues can provide records of dietary history. For example, enamel of teeth developed at older ages is more enriched in ^{13}C and more depleted in ^{18}O than that developed at younger ages. Such an isotopic shift can be caused by the shift to solid foods from lipid-rich milk (Wright and Schwarcz, 1998). Long hairs can include an "isotopic memory" of seasonal dietary variations as fluctuations of δD, $\delta^{15}N$, and $\delta^{13}C$ values along a hair (Sharp et al., 2003).

In this context, it is appropriate to mention two abiogenic elements, lead and strontium. $^{206}Pb/^{204}Pb$, $^{207}Pb/^{204}Pb$, $^{208}Pb/^{204}Pb$, and $^{87}Sr/^{86}Sr$ ratios are usually considered as "signatures" of the local geological situation. It is commonly assumed that both lead and strontium are hardly fractionated in biological processes due to very small differences in isotopic masses (Capo et al., 1998; Blum and Erel, 2003). These assumptions allow one to use the Pb and Sr isotope ratios in human teeth and bones to reconstruct migration patterns: the ratios in tooth enamel reflecting the geographical origin of food and water consumed in childhood may be used as a birthplace marker, whereas the ratios in bone tissues formed in different periods of life can reflect migration routes (Price et al., 2002; Bower et al., 2005; Montgomery et al., 2005). However, we note that actual $^{87}Sr/^{86}Sr$ ratios in plant and human tissues slightly differ from those of local bedrocks (Price et al., 2002). This is in conflict with the theoretical assumption that biota does not fractionate strontium. Although ^{86}Sr and ^{87}Sr have very small differences in masses, they have different spin values (Table 2.2). Therefore, biological

fractionation of these isotopes may be possible due to the magnetic isotope effect (Section 2.2).

2.3.3. Shifts in Human Isotope Ratios Depending on the State of Health and Age

Lasnitzki and Brewer (1942) found that tumor tissues (primary carcinomas of liver, lung, stomach, rectum, kidney, and colon, as well as liver metastasis) are enriched in ^{39}K ($\delta^{41}K$ ranged from -12.2‰ to -7.37‰) as compared with normal tissues (Section 2.3.1). Although Lyon and Baxter (1978) did not observe clear shifts in carbon isotopic composition of healthy and cancerous tissues, there was a methodical drawback in that study: the authors compared the $\delta^{13}C$ range of all available healthy tissues (i.e., adrenals, brain, bone collagen, gall-bladder, heart, kidney, liver, lungs, muscle, pancreas, prostate, skin, spleen, testes, and thyroid) with the $\delta^{13}C$ range of all available cancerous tissues (i.e., breast, colon, prostate, stomach, and rectal muscle). A close look at the only paired data, which were for prostate, shows that cancerous prostate tissue is enriched in ^{13}C by 2.5‰.

Kaznacheev et al. (1987) found that normal aortic walls and eye lens are gradually depleted in ^{13}C with age. $\delta^{13}C$ values of normal tissues decreased from -21.3 to -23.9‰ as the age increased from 1 month to 70 years. They observed that atherosclerotic aortic walls and cataract lens are depleted in ^{13}C relative to normal tissues. The more severe were the atherosclerotic manifestations (adipose strip, fibrous plaques, and atheromatous plaques with ulceration), the higher the ^{13}C depletion found: $\delta^{13}C$ decreased by ~1‰, 1.5‰, and 3‰, respectively, relative to the normal aorta. Such shifts in $\delta^{13}C$ were observed for all age groups. For cataract lenses, $\delta^{13}C$ values decreased by 0.8–1.7‰ depending on age.

Katzenberg and Lovell (1999) found that collagen of some pathological bones is enriched in ^{13}C as compared to norm ($\delta^{13}C$ = -19.6 – -20.5‰): $\delta^{13}C$ values ranged from -13.8‰ to -14.4‰ for post-paralytic atrophy and from -17‰ to -17.9‰ for osteomyelitis, whereas a healing fracture was slightly depleted in ^{13}C by 0.4‰. Compared with $\delta^{15}N$ values of normal collagen (8.9–11.4‰), there was depletion in ^{15}N by ~2‰ for post-paralytic atrophy and enrichment in ^{15}N by ~1.5‰ for osteomyelitis, whereas a healing fracture was marked by a similar nitrogen isotopic composition to normal tissue. Prowse et al. (2005) demonstrated that there is a trend of enrichment of bone collagen in ^{15}N and ^{13}C with age. On the other hand, there is a trend of depletion of bone apatite in ^{13}C with age.

Studying the dynamics of hair carbon isotopic composition, Ivlev (1992) recorded a temporal substantial enrichment of hair in ^{13}C by 20‰ relative to a mean $\delta^{13}C$ level for a person experiencing a temporal acute worsening of his state of health. The sharp increase in $\delta^{13}C$ began one day before a crisis peak; the highest $\delta^{13}C$ was estimated as 0.4‰ on the day after the peak; then a gradual decrease in $\delta^{13}C$ values to their mean level was observed over a period of three days.

Ivlev and Goncharov (1993) studied the carbon isotopic composition of the blood plasma of patients suffering from diabetes mellitus, obesity, hyper- and hypothyreosis, and Cushing's disease. Blood plasma carbon of the diabetics was depleted in ^{13}C ($\delta^{13}C$ varied from -23‰ to -24.5‰) relative to that of obese patients ($\delta^{13}C$ varied from -20.5‰ to -21.99‰). Patients with hypo- and hyperthyreosis and Cushing's disease had a wider range of $\delta^{13}C$ values, probably associated with biorhythms and heterogeneity of Cushing's disease. There were

clear isotopic differences in the blood sera of adults and children for all diseases. This may testify to changes in cellular metabolism in the ontogenesis.

Ivlev et al. (1994) studied daily variations in $\delta^{13}C$ values of expired CO_2 in insulin-dependent diabetes and obesity. Unlike healthy persons (Section 2.3.1) and obesity patients, diabetic patients have a stable level of $\delta^{13}C$ during the night. Obese patients had daily $\delta^{13}C$ variability similar to that of healthy persons, but more smoothly varying. Studying daily average $\delta^{13}C$ values of expired CO_2 and urine urea sampled from patients in different hormonal metabolic states (i.e., nanism, thyroiditis, hypothyreosis, diabetes mellitus, and obesity), Ivlev et al. (1996a) found well-marked variations in these characteristics relative to those of healthy persons. However, daily average $\delta^{13}C$ values of expired CO_2 or urine urea cannot be considered as a specific index of a particular pathology or functional state of the organism, because these values change in any situation when a new functional state influences the energetic exchange in cells.

Demikhov (2005) studied the influence of age on the hydrogen isotopic composition of human urine. The urine δD of 60 year old humans differed significantly from that of 16 year old humans (-39‰ and -48‰, respectively). The increase of urine δD with age can be explained by the change of urine chemical composition, for example, due to an increase of the protein content.

To test a relation between bone mineral balance and soft tissue $\delta^{44}Ca$, Skulan et al. (2007) measured $\delta^{44}Ca$ of urine from participants in a study in which extended bed rest (17 weeks) was used to induce bone loss. They found a depletion of urine calcium in ^{44}Ca for the experimental group: the urine $\delta^{44}Ca$ values were -0.48‰ and 0.12‰ for the experimental and control groups, respectively.

Krayenbuehl et al. (2005) studied iron fractionation under hemochromatosis conditions, a disorder characterized by progressive iron overload of tissues due to ineffective control of intestinal iron absorption associated with mutations in the HFE gene. Blood of hemochromatosic patients is marked by a higher $\delta^{56}Fe$ values (-2.11‰) than blood of healthy persons (from -2.72‰ to -2.58‰). Blood $\delta^{56}Fe$ values of hemochromatosic patients correlate with severity of the disease (e.g., prevalence of liver disease, arthropathy of metacarpophalangeal joints). These conclusions were in general agreement with results by Stenberg et al. (2005). They found that the blood of hemochromatosic patients is enriched in ^{56}Fe and ^{57}Fe by ~0.40‰, but depleted in ^{66}Zn, ^{67}Zn, and ^{68}Zn by ~0.10‰.

Sobotovich et al. (2007) examined $\delta^{13}C$ values of blood erythrocytes in 72 persons of various ages in different states of health: 27 healthy persons, 30 persons suffering from diseases of different etiology (e.g., hypertension, ischemic cardiac disease, and peptic ulcer), 5 leukemia patients, and 10 radiation disease patients. We found that erythrocyte $\delta^{13}C$ values of healthy persons ranged from -23‰ to -24‰ for all age groups (Figure 2.2). On the other hand, erythrocyte $\delta^{13}C$ values of persons suffering from diseases of different etiology had age-dependent shifts relative to those of healthy persons (Figure 2.2). The clearest shift of the carbon isotope ratio was found for erythrocytes of radiation disease patients: $\delta^{13}C$ values ranged from -20‰ to -22‰ (Figure 2.2). It is clear that the erythrocyte carbon of all the types of sick persons studied was enriched in ^{13}C relative to the control group.

Data presented in this section demonstrate that changes of the state of health due to sickness and aging influence isotopic ratios of human tissues. However, there is no an unambiguous trend in such shifts (which can be temporary in cases of short-term mild disorders or acute but reversible diseases).

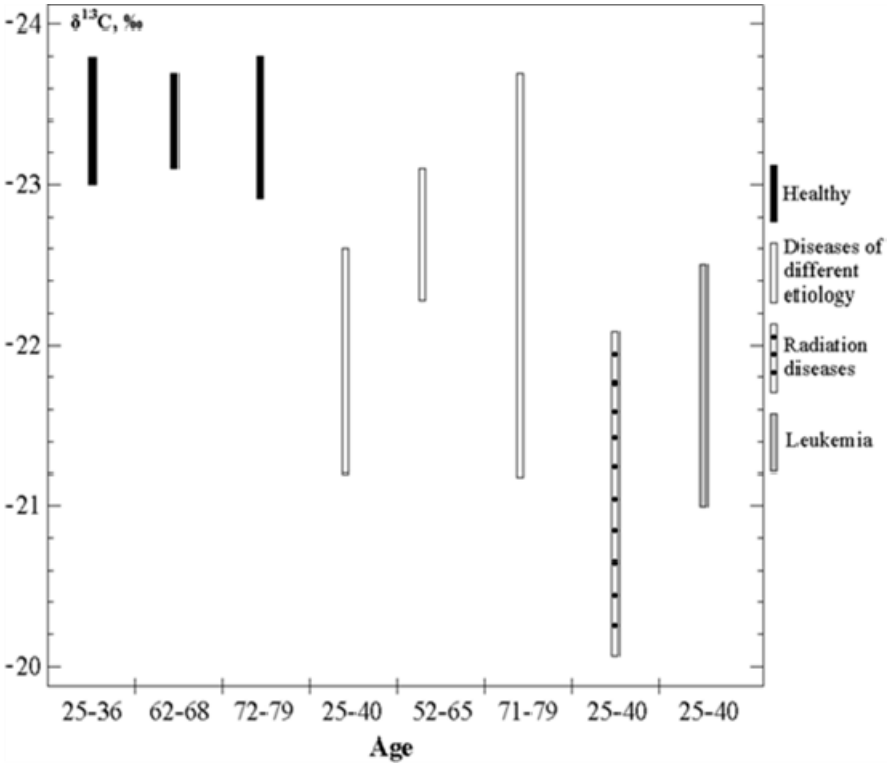

Figure 2.2. Carbon isotopic composition of blood erythrocytes for healthy and sick people.

For different tissues, one can observe enrichment of the isotopic composition in both heavier and lighter isotopes under different disease conditions or with age. Therefore, the facts are in conflict with a hypothesis by Shchepinov (2007) postulating that processes of aging are accompanied by depletion of human tissues in heavier isotopes.

2.3.4. Isotopic Composition of the Human Body as a Natural Internal Marker

Various stable isotopes are widely used as tracers *in vivo* in biochemical and pharmacological studies as well as in clinical practice for diagnostic purposes and monitoring of the state of health (Bier, 1997; Koletzko et al., 1997; Rennie, 1999; Abramson, 2001; Patterson and Veillon, 2001). Compared with radioisotope tracers, stable isotopes have many well-known advantages (Roginskii and Shnol', 1965; Bier, 1997). It is generally believed that '*the doses of stable isotope tracer substances that are used for clinical diagnostic and research purposes appear safe and without any adverse effects*' (Koletzko et al., 1997). With rare exceptions, the effects of stable isotopes of an element on the human organism are poorly known.

A distinct response of living organisms to different isotopes was first found in research on the biological effects of heavy water (Kritchevsky, 1960; Lobyshev and Kalinichenko, 1978). On the one hand, there were successful attempts to cultivate deuterated organisms

(Katz and Crespi, 1966). On the other, it was found that D_2O is toxic to many living organisms (Thomson, 1963). Replacement of ordinary water with D_2O may lead to inhibition of mitosis and other physiological processes. This effect was used in experiments to suppress human tumor cells growing using heavy water (Hartmann et al., 2005). However, deuterium-depleted water also possesses anticancer properties (Somlyai et al., 1993; Krempels et al., 2008). The similar anticancer effects of both heavy and light waters may testify that a restricted range of deuterium content in tissues is essential for the normal functioning of living organisms.

Distinct responses of living organisms to different isotopes were also observed in the context of bipolar disorder treatment. Studying the membrane transport of ^{6}Li and ^{7}Li by human erythrocytes, Lieberman et al. (1979) found that ^{6}Li is taken up in preference to ^{7}Li. Stoll et al. (2001) demonstrated that effects of ^{6}Li on polyuria and polydipsia were greater than those of ^{7}Li. Kidneys from ^{6}LiCl-treated rats were marked by more frequent severe lesions in renal tubules than those from ^{7}LiCl-treated rats.

Medical side effects apart, what is the level of scientific rigor of stable-isotope-tracer methods? Roginskii and Shnol' (1965) emphasized that an "ideal tracer" for biochemical research should not influence a process under study; it must be an indicator rather than a reagent. Conventional stable isotope tracers, injected into an organism or separated tissue, cannot be considered as ideal tracers because mass and spin variation of isotopes of an element can cause isotopic effects, which may lead to artifacts.

On the other hand, the human organism can be characterized by an intrinsic complex of isotopic ratios of its tissues, fluids, and gases varying between normal and pathological states (Section 2.3.3). Shifts in intrinsic isotope ratios of human tissues can serve as a natural internal marker for medical diagnostics and monitoring of the state of health (Ivlev, 1992; Sobotovich and Lysenko, 2001). Shifts in intrinsic isotope ratios of tissues may probably be used for early diagnostics because the isotopic composition of a living organism is more sensitive to some stressors than other biochemical systems (Shaw-Allen et al., 2005).

At an intramolecular level, the isotopic composition may retain aspects of the physiological history of the organism (Brenna, 2001): each stereochemically unique position in each molecule has an isotopic ratio reflecting processes of synthesis and degradation. If this hypothesis is valid, an analysis of the intramolecular isotopic composition will be appropriate to detect the origins of chronic diseases.

Hatch et al. (2006) analyzed intrinsic shifts in hair δ^{15}N and δ^{13}C values to develop diagnostic criteria for two nutritional disorders, anorexia and bulimia. Results of the study demonstrated that isotopic ratios of the two elements are not sufficiently informative to achieve a correct discrimination between these disorders. We believe that to develop criteria for monitoring of the state of health and medical diagnostics based on isotopic ratios of the human organism, there is a need to analyze isotopic ratios of a *representative set* of biogenic elements possessing multiple stable isotopes, such as H, B, C, O, N, Mg, Si, S, Cl, K, Ca, V, Fe, Ni, Cu, Zn, and Mo. Materials presented in this chapter testify that fractionation of Mg, S, K, Ca, Fe, Cu, and Zn isotopes in the human body is scantily known, whereas the isotopic fractionation of other biogenic elements (Table 2.1) has not been studied. Therefore, apart the development of methods for intrinsic-isotope-ratio diagnostics, further investigations should include two lines: (a) comprehensive research into fractionation of all biogenic elements in the human body; and (b) development of precise instrumental methods to analyze isotopic fractionation in biological samples.

2.4. NATURAL RADIOISOTOPES AND LIVING MATTER

There are over 60 naturally occurring radionuclides (Firestone et al., 1996) classified under two groups:

1. Primordial radionuclides and their decay products contained in materials of the planet since its creation (e.g., isotopes of U and Th families, ^{40}K, ^{48}Ca, and ^{87}Rb).
2. Cosmogenic radionuclides forming by interactions of cosmic rays with atoms of some elements (e.g., ^{14}C and ^{3}H).

All biotic and abiotic components of the environment are radioactive, since they contain natural radioactive elements (Grodzinsky, 1965; Pertsov, 1967; Eisenbud and Gesell, 1997; UNSCEAR, 2000b). The natural terrestrial radiation is generally associated with rocks containing K, U, Th, and members of their families. Together with secondary cosmic rays, these are the main source of external irradiation of biota. Each living creature contains some amount of radioisotopes of biogenic elements (e.g., ^{14}C and ^{40}K) incorporated into cells. These radioisotopes are the main source of internal irradiation of living organisms. Additional sources of internal irradiation are radioisotopes of Pb, Pu, Ra, Th, and U. In particular, they are easily incorporated into bone crystals (Tandon et al., 1998).

These environmentally distributed radionuclides cause permanent exposure of all living beings to ionizing radiation. In most cases, the dose rate is very low because the natural radioactivity content is low. In the biosphere, the average dose rate is ~10 cGy/yr, varying over a broad range depending on local concentrations of radionuclides in the environment. Specifically, the rate can be higher in terrains with an increased concentration of natural radionuclides in soil and rocks. This content, as a rule, reflects peculiarities of ancient biogeochemical processes.

In the 1920s, two seminal ideas were generated. First, a concept of radiation hormesis was proposed: results of physiological experiments allowed Zwaardemaker (1924, p. 349) to state that '*energy of bio-radioactivity may have a decisive influence on the living system… Applied in heavy doses radium destroys the tissues, but applied… in microdoses radioactivity may cause a revival*'. Second, it was hypothesized that the natural terrestrial radiation is one of the possible reasons for speciation and biological evolution (Olson and Lewis, 1928; Babcock and Collins, 1929).

2.4.1. Radiation Hormesis

Experimental attempts to find an impact of the natural background radiation on biological systems encounter large difficulties. This is because experiments of this sort should be designed considering two factors. First, studies should be carried out in deep mines to isolate experimental organisms from the action of cosmic rays (Babcock and Collins, 1929). Besides, mines should be excavated in rocks with a very low intrinsic radionuclide content. Second, the diet should contain potassium without the ^{40}K radioisotope. These difficult design requirements led to conflicting experimental results.

For example, Vinogradov (1957) did not observe any influence of the replacement of potassium of natural isotopic composition with ^{40}K-free potassium on the growth and development of *Aspergillus niger*. Moore and Sastry (1982) proposed that low-energy Auger and Coster-Kronig electrons, emitted after the electron capture decay of ^{40}K, may have highly localized radiochemical effects on the genetic material dependent on the intercellular location of ^{40}K. However, the expected number of electron capture disintegrations was estimated as 3×10^{-10} per cell per day, a value below the observed spontaneous mutation rate (Gevertz et al., 1985). These authors did not find clear effects of ^{40}K in media on the spontaneous mutation rate in several strains of *Escherichia coli*.

On the other hand, numerous physiological experiments by Zwaardemaker (1920, 1924) demonstrated that isolated hearts of *Petromyzon*, eel, and frog can beat if one replaces K in the Ringer solution with Ra, Th, U, or Rb. Moreover, revival of the isolated frog heart occurred using external irradiation if the radiation level due to such radioactive source was close to the natural radioactivity of ^{40}K contained in the blood. These results have later been reproduced by Verkhovskaya and Arutyunova (1953) and Hoitink and Westhoff (1956). They have used ^{32}P, ^{238}U, and ^{24}Na as external radioactive sources. Roginskii and Shnol' (1965) proposed that such extremely low doses of radiation serve as a trigger for the rhythmic activity of heart.

Planel et al. (1969) demonstrated an influence of decreasing intensity of background radiation on *Protozoa*. Chambers with lead walls were located at a depth of 200 m in a salt mine. Although total inactivation of the cell population was not observed, a negative impact of decreasing background radiation on the vitality of paramecium was found. Experiments with various cultures and organisms showed that an artificially depleted natural radiation environment may cause general suppression of vital functions, whereas low doses of γ radiation may trigger enzyme activity and culture growth (Croute et al., 1982; Conter et al., 1983, 1986; Planel et al., 1987).

Epidemiological research testified that various territories with an enhanced level of the natural terrestrial radiation are marked by decreased rates of cancer morbidity (Nambi and Soman, 1987; Haynes, 1988; Mifune et al., 1992; Cohen, 1995).

As results of such laboratory and epidemiological studies (for bibliography see Luckey, 1991), the concept of radiation hormesis was developed (Luckey, 1991; Macklis and Beresford, 1991; Calabrese, 1994; Vaiserman, 2008). The concept states that (a) only relatively high doses of radiation (more than five times higher than natural background radiation) can cause a damage in biological systems; and (b) low doses of natural ionizing radiation are necessary for living organisms, since they stimulate certain vital functions of an organism, in particular, the immune system (Safwat, 2008).

To explain the health beneficial effects of low dose radiation, several mechanisms have been proposed, such as changes in gene expression, stimulation of DNA repair, detoxication of free radicals, production of stress proteins, activation of membrane receptors and release of growth factors, and compensatory cell proliferation (Macklis and Beresford, 1991; Feinendegen, 2005). Kuzin (1997) proposed that absorption of a quantum of radiation by a biopolymer molecule within a cell leads to forming a polariton, a persistent exciton. Degradation of polaritons is accompanied by the emission of low-intensity light (this is reminiscent of a concept of mitogenic rays – Gurwitsch, 1932). These rays stimulate cell division and growth of the cell population in prokaryotic and eukaryotic organisms. However, the energy absorbed by cells from the natural background radiation is very low. Thus, it is

unlikely that effects of the background radiation on the vital activity have an energetic nature. Rather it is suggested that they are mediated through information transfer processes.

We should stress that there is no consensus among researchers as to low dose effects (Mossman, 2001; Cohen, 2002; Bonner, 2003; Brenner et al., 2003; Kadhim et al., 2004). Numerous data suggest that low-dose ionizing radiation adversely affect human health (UNSCEAR, 2000a, 2001, 2008). The contradiction between these observations and the concept of radiation hormesis can naturally be exemplified by well-known cancerogenic effects of radon gas exposure (Cothern and Smith, 1987) and therapeutic effects of radon bath treatment (Erickson, 2007) (Section 3.3.10).

2.4.2. Speciation and Natural Ionizing Radiation

There are two adaptive strategies to stress impacts in living organisms: ontogenetic and phylogenetic adaptations (Grodzinsky, 2006). In the case of ionizing radiation, the first strategy is expressed as radioadaptation and results in an augmentation of radioresistance after irradiation at low doses. The mechanism of ontogenetic adaptation consists in induction of the synthesis of enzymes concerned with DNA repair. Most likely the ontogenetic adaptive strategy operates as a basis for ensuring the sustainability of organisms in modified environmental conditions marked by an increase in genotoxicity. Widening the diversification of organisms over generations is achieved by means of the genomic instability induced in response to irradiation at low doses. It is reasonably safe to suggest that many responses of organisms to low-level chronic irradiation may be considered as consequences of the active reactions of living organisms associated with realization of such adaptive strategies. The second – phylogenetic – adaptive strategy increases the frequency of genetic diversification, which enlarges the possibilities for active natural selection.

2.4.2.1. Effects of the Terrestrial Radiation

During precellular biochemical evolution (Chapter 1), the level of natural radioactivity was higher than it is now. Ionizing radiation was no doubt a powerful factor in the early steps in the origin of organic substances. In the continental crust, one of the most important radioactive sources was the production and accumulation of Rn within the crust porosity (Garzón and Garzón, 2001). Synthesis of low molecular weight organic compounds in gases of the primary atmosphere, polymerization of monomers leading to formation of protein-like molecules, and other radiation chemistry processes formed a basis for the precellular evolution of life. Later, the presence of an eternal field of ionizing radiation due to the natural radioactivity in the environment could be a precondition for spontaneous mutagenesis in populations of any species.

Neruchev (1976) argued that there were periods in the geological past of the Earth when the level of the natural radioactivity in local regions of the Earth's crust increased manifold because of the geochemical transport and accumulation of uranium. Durations of these radioactive periods varied from one to several million years. Paleontological studies carried out in various stratigraphic groups disclosed direct relations between the level of radioactivity in the environment and speciation processes (Figure 2.3).

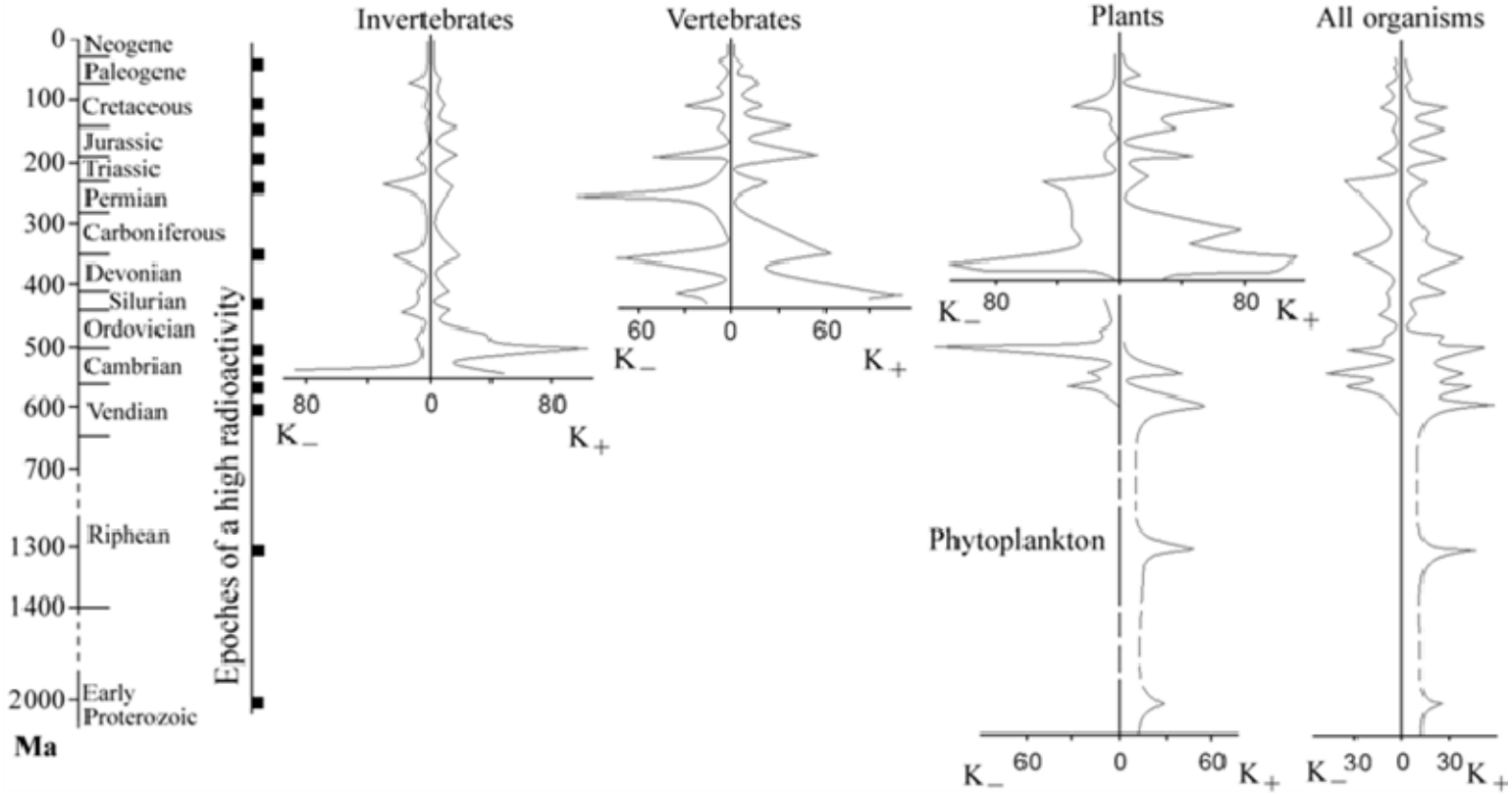

Figure 2.3. Relationships between epochs of high natural radioactivity and changes in rates of species extinction and origination. K_- is the extinction coefficient, K_+ is the origination coefficient; $K_- = \frac{\sum n_m}{\sum n_t} \cdot 100$, $K_+ = \frac{\sum n_n}{\sum n_t} \cdot 100$, where n_m is a number of extinct species, n_n is a number of new species, and n_t is a number of surviving species for a particular stratigraphic level (after Neruchev, 1976, figure 3, © Allerton Press, 1976; reproduced with kind permission of Allerton Press, Inc.).`

Neruchev (1976, 2007) presented examples of drastic modifications in flora and fauna during periods of high natural radioactivity in the environment. For instance, a rapid transformation of algae occurred in the radioactive epoch between the Lower and Middle Cambrian. Many new taxons of sponges and bryozoans appeared in the Late Jurassic when the terrestrial radioactivity was very high. The first vertebrates (*Ostracodermi*) appeared in the radioactive period of the Early Ordovician. The first terrestrial tetrapods (*Ichthyostega*) came into being in the radioactive epoch between the Late Devonian and Carboniferous. The first reptiles have emerged in the Pennsylvanian, during an intensive sedimentation of uranium-enriched deposits. Rather similar mutations of front limbs of different animal groups, which allowed them to fly, were developed during radioactive epochs: The first flying animals, *Pterosaurs*, emerged in the radioactive epoch between the Late Permian and Triassic. The first birds emerged in the other radioactive epoch between the Late Jurassic and Cretaceous. The first flying mammals, microbats, originated in the Eocene radioactive epoch.

Matyushin (1974, 1982) proposed a hypothesis for the origin of *Homo sapiens* in the context of geological peculiarities of the East African Rift, "the homeland of humanity" (Section 10.3.2.1). He demonstrated that biological changes of local anthropoids, resulting in the origin of the human species, occurred due to ancient activization of regional geological processes connected with riftogenesis. In particular, high tectonic activity led to the exposure of uranium deposits and formation of Oklo natural reactors (Gauthier-Lafaye et al., 1996). An increase of volcanic activity caused effusion of radioactive magma. The combined impact of these geological factors, forming zones of increased natural radiation in East Africa, played a key role in numerous mutations of the local anthropoids and, as a result, in the origin of *Homo sapiens* (Matyushin, 1974, 1982).

Lenz (1979) proposed a closely related hypothesis. It is well-known that there is an increased release of Rn through active faults prior to earthquakes (Osika, 1981; King et al., 1996, 2006). Lenz (1979) suggested that Rn and its decay products (Section 3.3.10), dissolved in groundwater, could act as a mutagenic agent for hominid groups in East Africa and other seismically active regions in India, China, and Java. Persistent ingestion of radon-enriched water could lead to the increase in the frequency of mutations in the populations. These mutations could affect the rate genes resulting in a rapid morphological and physiological changes of hominids, such as increase in brain size, reduction in body hair, changes of glands, loss of estrus, an increase of the pregnancy term, a decrease in the maturity of the infant at birth, an increase of a period of infant dependency, etc.

2.4.2.2. Possible Effects of the Cosmic Radiation during Geomagnetic Reversals and Excursions

Thomas (1936) suggested that the large variety of species and high number of endemics often found in high mountains may be results of mutations due to irradiation by cosmic rays. In the 1960s, it has been observed that there were correlations between species extinction and geomagnetic reversals (Watkins and Goodell, 1967; Hays, 1971). It was proposed that during geomagnetic reversals, when the intensity of the geomagnetic field is drastically reduced (Vogt et al., 2009), living organisms were bombarded by increased cosmic radiation causing enhanced mutation rates and mass extinctions (Uffen, 1963; Simpson, 1966). However, it was shown that the cosmic radiation-induced increase in the mutation rate would be too small to cause mass extinctions (Waddington, 1967; Harrison and Prospero, 1974).

Several hypotheses were proposed to explain correlated periodicities of mass extinctions and geomagnetic reversals. In particular, it was suggested that extinctions were caused by the strong decrease of the geomagnetic field *per se* during reversals (Crain, 1971; Kopper and Papamarinopoulos, 1978) (see biotropic effects of the depleted geomagnetic field elsewhere – Kopanev and Shakula, 1985). Valkovic (1977) hypothesized that the decline of geomagnetic intensity could disturb intake and metabolism of essential trace elements in living organisms. Kopper and Papamarinopoulos (1978) suggested that geomagnetic reversals could drastically increase the mutagenic potential of the ultraviolet-B radiation (Section 10.3.2.3). Loper et al. (1988) proposed that geomagnetic reversals, being connected with cycles of the endogenous activity in the core and mantle, are just indicators of its intensification (cf. Milanovskii, 1996). The rise of the endogenous activity increases volcanic activity leading to the release of large amounts of CO_2 and sulfates, which have a pronounced effect on biota. We can add that the intensification of the endogenous activity can also enhance the deep hydrogen degassing and seismicity, which are powerful biotropic factors (Section 10.3.2.3).

An interest in the possible biological effects of geomagnetic reversals was rejuvenated by Kuznetsov and Kuznetsova (2004). They argued that several turning points of human evolution that happened in Africa correlate with geomagnetic reversals and excursions in the Late Cenozoic (see a geomagnetic polarity time scale elsewhere – Mankinen and Wentworth, 2003). For example, the human brain expansion and origin of *Homo erectus* (Hawks et al., 2000) were preceded by two key mutations during the Gauss-Matuyama reversal (~2.58 Ma ago): the genes encoding CMP-*N*-acetylneuraminic acid hydroxylase and the predominant myosin heavy chain were inactivated ~2.7 Ma (Chou et al., 2002) and ~2.4 Ma ago (Stedman et al., 2004), respectively. The most recent common ancestors of modern human mitochondrial DNA and Y chromosome are ~230 ka and ~100 ka old, respectively (Cavalli-Sforza and Feldman, 2003). These dates correlate with the Jamaica and Blake excursions, respectively. One of the variants of Microcephalin gene, regulating brain size, that arose in modern humans ~37 ka ago (Evans et al., 2005) correlates with the Mungo excursion (Kopper and Papamarinopoulos, 1978).

Kuznetsov and Kuznetsova (2004) explained such a correlation by a drastically enhanced cosmic radiation over Africa (and Europe) during the reversals. The geomagnetic field was presumably 10 times weaker in Africa than in other regions in those periods due to two features: (a) a specific trajectory of the virtual geomagnetic pole motion (Kuznetsov, 1999); and (b) the absence of large magnetic anomalies in Africa, like Brazilian, Canadian, and Siberian ones, which have maintained a remanent field in the Americas and Asia. Regardless of which agent caused the mutations during the reversal – an enhanced cosmic radiation or other geogenic factors mentioned above – this issue calls for further investigations. The Kuznetsovs' study may be complimentary to the Matyushin hypothesis described in the previous section.

2.5. CONCLUSION

In dynamic equilibrium, energy, information, and properties of a natural system are interconnected so closely that miniscule changes of one of these parameters can cause some nonlinear functional and structural, quantitative and qualitative changes of the entire system.

We suppose that isotopes, being subsystems of the element, provide it with an additional adaptive feasibility. “Isotopic adaptation”, governed by a set of physical and chemical properties of isotopes, allows the element (a) to retain its status as a building block of nature; (b) to exhibit nuances in its properties; and (c) to extend its capacity in creation of abiotic and biotic systems reflecting the finest features of biochemical processes in living organisms.

Each living organism and biosystem can be characterized by a typical isotopic composition, “an isotopic signature”, which closely related to the environment including the geosphere. In the signature, typical isotope ratios may fluctuate to a limited degree supporting the state of isotopic homeostasis, an integral part of the general homeostasis of the organism. There are also sharp changes in typical isotope ratios exceeding the ranges of such fluctuations. Sharp isotope shifts may be used as internal markers of pathological processes.

Future studies should be focused on (1) development of precise instrumental methods to analyze isotopic fractionation in biological samples; (2) comprehensive research on isotopic fractionation of all biogenic elements possessing multiple stable isotopes and present in the human body; and (3) development of methods for intrinsic-isotope-ratio diagnostics. Attention should be centered on (a) the possibility of occurrence of not only mass-dependent (kinetic and thermodynamic) isotope effects, but also spin-dependent (magnetic) isotope effects (especially for elements heavier than S), and (b) metabolic mechanisms of such isotope effects.

Paleontological, anthropological, and geological data suggest that natural radiation was of primary importance in micro- and macroevolution. This coincides with thoughts of Timoféeff-Ressovsky et al. (1935) on the role of gene mutations in evolution. The main mechanisms of speciation due to radiation effects may be related to an increase in the frequency of recombination in genetic structures, augmentation of the intensity of error-prone DNA repair, and induction of genomic instability. Thus, natural ionizing radiation may be deleterious for individuals, but have a beneficial effect for entire populations being one of the key factors in natural selection.

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APPENDIX 2.A. THE δ NOTATION

Sample isotopic composition is commonly described relative to a standard in parts per thousand (‰) using the δ notation:

$$\delta = \left(R_{sample} / R_{standard} - 1\right) \times 1000 , \qquad (2.A.1)$$

where R is the ratio abundance of a heavier to the lightest isotope of a particular element in a sample or in a standard reference material.

As a standard reference material, the standard mean ocean water (SMOW) is used for D and ^{18}O determination; Pee Dee Belemnite (PDB) limestone standard is used for ^{13}C determination; atmospheric nitrogen gas is used for ^{15}N determination; calcium carbonate reference material NIST-SRM 915a is used for Ca isotope determination; Canyon Diablo troilite (CDT), a meteoritic sulfide is used for S isotope determination; Fe isotopes are reported relative to the reference material IRMM-014; Cu isotopes can be reported relative to the reference material NIST SRM 976 (De Laeter et al., 2003). An internationally certified Zn isotope standard reference material does not exist. Data are reported relative to a material from the Lyon-CNRS laboratory, a Johnson Matthey (JMC) Zn standard solution (Cloquet et al., 2008).

Negative and positive δ values indicate depletion and enrichment of a heavy isotope, respectively.

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