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Heterochromatin: The Visible with Many Invisible Effects

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Abstract

Heterochromatin represents a large fraction of eukaryotic genomes and is characterized by a high density of sequence repeats that remain condensed through the cell cycle. Based on our limited knowledge, we still suspect that chromosomal heterochromatin regions (HRs) in the genome of higher eukaryotes probably have no functions in the traditional in biology sense, and are possibly maintained by natural selection in the genome only owing to a number of important effects they have on the organism. But unlike other known forms of variability (biochemical, immunological, anthropogenetic, morpho-physiological, etc.), chromosomal HRs have no phenotypic manifestations.By studying chromosomal HRs variability in the human populations permanently living in various climatic-andgeographic conditions of Eurasia and Africa, in norm and pathology we have obtained the data indicating possible participation of chromosomal HRs in cell thermoregulation.Here we give some examples of possible cell thermoregulation participation in some stages of evolution and development.

Index terms— heterochromatin, Q-heterochromatin, C-heterochromatin, condensed chromatin, cell thermoregulation, human body heat conductivity.

1 Introduction

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Study of a possible biological role of chromosomal HRs in genome have never stopped and accompanied with use of all newest methods of the scientific researches, applied in the modern biology. Interest to chromosomal HRs has amplified on having become clear, that the Human Genome Project has not justified hopes placed upon it. Mapping of genes has not approached us by no means to understanding of the genome functioning. The traditional approach: "genotype ? phenotype" has turned out not in full measure suitable for studying biological roles of chromosomal HRs in vital activity of the higher eukaryotes. Probably, new approaches and methods of researches will be required. The present work is devoted to description of one of such approaches.

3 II. Chromosomal Heterochromatic Regions

Before the genome mapping it was known, that a fundamental feature of chromosomes in higher eukaryotes, including man, is the presence of two evolutionally consolidated types of genetic material: euchromatin and heterochromatin. Euchromatin, the conservative portion of the genome, contains transcribed structural genes, while heterochromatin, the variable portion of the genome, is predominantly composed of non-transcribed repeated DNA sequences.

Heterochromatin is universally distributed in the chromosomes of all the eukaryotes -plants, animals and man, accounting for 10% to 60% of their genome. Heterochromatin regions (HRs) account for about 15% -20% of the human genome [1][2][3][4]. Chromosomal HRs does not change during ontogenesis and are inherited in a regular manner as discrete traits.

To-date two types of constitutive heterochromatin are recognized: Q-and Cheterochromatin [5][6][7][8]. There are several significant differences between them: C-heterochromatin is found in the chromosomes of all the

higher eukaryotes, while Q-heterochromatin -only in man (Homo sapiens), the chimpanzee (Pan troglodytes) and gorilla (Gorilla gorilla) [9,10]. C-heterochromatin regions (C-HRs) are known to be invariably present in all the chromosomes of man, varying mainly in size and location (inversion).

Despite the fact that chromosomal C-and Qheterochromatin are defined by a single term, "constitutive heterochromatin", they are undoubtedly significantly different intrachromosomal structures [Fig. 1 and 2].

4 Keywords: heterochromatin, Q-heterochromatin, Chete-rochromatin, condensed chromatin, cell thermoregulation, human body heat conductivity.

hough the chromosomal heterochromatin regions (HRs) are seen through an optical microscope already more than 80 years, their phenotypic manifestation are still not possible to be seen. Existence of genes has been guessed on their phenotypes though they cannot be seen through a microscope. A paradoxical situation has formed: it is known incomparably more about the invisible genome part activity, than about its visible one. Q-heterochromatin regions (Q-HRs) variability can be found in man only on seven autosomes **??**3, 4, 13, 14, 15, 21 and 22), as well as on chromosome Y. Chimpanzees have Q-HRs on five autosomes **??**14, 15, 17, 22 and 23), while in gorillas they are present on eight **??**3, 12, 13, 14, 15, 16, 22 and 23) and on chromosome Y [8,[10][11][12][13][14]. Individuals differ in the number, location, size, and intensity of staining (fluorescence) of these specific chromosomal regions [8,15,16].

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Chromosomal Q-HRs is subject to considerably greater variability in any population as compared to C-HRs. Erdtmann [17] emphasized that "recent analyses... show a great population and evolutionary stability of Cband homeomorphisms... From interpopulation comparisons, C-band means show a tendency to maintain a constant amount of constitutive heterochromatin".

III.

5 Hypotheses of Possible Chromosomal HRs Role

Despite the over 80-year history of studying the heterochromatin part of the genome of higher eukaryotes, its biological role remains unclear. According to most hypotheses heterochromatin is a reservoir of "excess" DNA, and some investigators call DNA in the genome of eukaryotes useless and even "selfish" because these DNA consist of non-coding, short and highly repeated sequences. Our ignorance of the true role of heterochromatin has left the field open for a variety of hypotheses ranging from the idea that it is "selfish DNA" simply perpetuating itself to ascribing to it an important function in development and evolution.

Before considering the existing hypotheses on possible role of chromosomal HRs it is necessary to keep in mind, that "Heterochromatin is a 'macroscopic' structure, and there is no need to use data on the structure of satellite DNA to explain its function. No hypothesis as to functions of heterochromatin requires it to contain satellite like DNA. With the formation of constitutive heterochromatin some new properties are acquired, which is not characteristic of either satellite DNA or proteins that separately form a part of constitutive heterochromatin, i.e., the properties of constitutive heterochromatin are not a sum of properties of its components". "...at the moment, the question as to heterochromatin functions rather represents a cytogenetic problem than a molecular-biological one" [18].

Basic features of chromosomal HRs upon which all hypotheses about their role are based, are the following: they consist, basically, of highly repeated sequences of DNA; HRs occupy quite certain loci of chromosomes having rather great values, namely: areas of centromeres and telomeres, and areas of nucleolar organizers, bearing rRNA genes; replication lability; wide intraspecific variability and, on the other hand, evolutionary fixedness of chromosomal HRs in higher eukaryote genome.

A number of authors [16,20,21] assume, that chromosomal HRs can "not to have any function", that is they have something in common with known point of view of Brown [22], that for HRs "importance of doing nothing". Such view was reasoned in particular by wide quantitative variability of HRs chromosomes in the genome of populations without any phenotype manifestations, and their extraordinary heterogeneity revealed at molecular level.

The idea that constitutive heterochromatin may not have any function is not new. In reviewing the biology of heterochromatin in general, John [23] suggested that "there is then a very real possibility that heterochromatin per se has no function in either development or evolution" and "the inertness of constitutive heterochromatin in terms of its transcriptional inability, is a consequence of its distinctive DNA structure and not of its condensed nature, which may itself be a secondary consequence of its peculiar DNA sequence organization".

Regarding the attempts to establish the biological role of chromosomal HRs based on their molecular characteristics, Miklo? [24] stated that the analysis of sequences does not bring us closer to understanding of any biological regularity.

There are some hypotheses related to the potential function of chromosomal HRs in the interphase nucleus. In particular, their possible participation was considered in the formation of the interphase nuclei specific pattern being important in its functioning by maintaining of a certain spatial position of chromosomes relatively

to each other and the nuclear membrane [25][26][27][28][29][30][31]. According to Bostock [19], constitutive heterochromatin influences the genetic constitution of the genome and is subject to selection. Selection does not involve a certain satellite DNA sequence, but simply involves the structure of DNA promoting the formation of condensed heterochromatin state. Variability of the amount of satellite DNA (and hence of heterochromatin) can ensure more rapid changes in the genome that those that could be only achieved by mutations of structural genes.

As well the "bodyguard hypothesis" [32] has been proposed, assuming that heterochromatin is used by a cell as a protective body to guard euchromatin by forming a layer "shield", distributed on the outer surface of the nucleus . Mutagens, clastogenes or even viruses attacking the nucleus, firstly contact with the constitutive heterochromatin, which absorbs the attack, thereby protecting genes in euchromatin areas of chromosomes.

Some authors suggest that the function of chromosomal HRs is attached to the processes of cell division. Thus, the ability of chromosomal HRs by nonhomologous conjugation can determine behavior of chromosomes prior to their pairing and formation of synaptonemal complex [33,34]. This hypothesis is known as the hypothesis of "recognition". However, it is theoretically controversial [35], as it is unclear how the non-homologous conjugation can provide "recognition" of homologous chromosomes, and, in addition, this property of HR is rather impedes, than facilitates proper synapsis of chromosomes in meiosis.

Comings [36] considered the chromosomal HRs as the material for creation of new genes. **??**ershenson [37] first showed that near chromosomal HRs the crossing-over usually not occurs. On the basis of the comparison of these data with the usual localization of HR, it was suggested that pericentromeric HR, due to such mechanism, prevents the crossing-over in the centromere area and thereby holds it in a certain position. The same mechanism can ensure the unity of all blocks of ribosomal genes and prevent the crossing-over in sex chromosome [34,35,38], since HR does not form synaptonemal complex, which is necessary condition for crossingover.

Darlington [39] first attributed to heterochromatin the important role in the evolution, namely, the speciation through formation of viable translocations. There are data that species are not indifferent to increase or decrease in quantity of heterochromatin. The main result of these studies is that changes of HR in different species have apparently adaptive nature, providing them with quick adaptation to changing environmental conditions [40][41][42].

Gruzdev [43] proposed a hypothesis explaining some features of heterochromatin -tight packaging, inactivity in transcription, tendency to aggregation ("stickiness") and the effect of the position effect of variegation (PEV) -the fact that DNA molecules in chromosomal HRs are topologically open and contain single-stranded breaks in DNA. However, this hypothesis, as well as the others, does not explain the biological meaning of the existence of a wide intra -and interpopulation heterogeneity in content of chromosomal HRs.

Thus, the diversity of roles attributed to chromosomal HRs, expresses only our ignorance of its true biological significance, as neither of the above hypotheses has no experimental confirmation. However, we note again that everything that has hitherto been said about the possible biological role, function, effects, etc. of chromosomal HRs in eukaryotes in general and man in particular only concerned C-heterochromatin.

6 IV. Chromosomal Q-heterochromatin Regions

Chromosomal Q-heterochromatin regions (Q-HRs) were for the first time found in human chromosomes [5]. It is known that man inherited chromosomal Q-HRs from the same ancestor as that of the chimpanzee and gorilla [9,13]. Over 40 years have passed since then, and over these years data have accumulated, beginning from methods of their detection in the nucleus till investigation of their distribution at the level of human populations. It can now be considered well established that Q-HRs are present in the genome of only three higher primates. The greatest number of Q-HRs is observed in the gorilla genome, then in the chimpanzee and in man [11][12][13]. However, there is one basic difference between them: wide quantitative variability of chromosomal Q-HRs in the genome only exists in human populations [14]. Therefore, subsequent systematic studies were mainly carried out in man.

Q-HRs variability in populations is usually described in the form of five main quantitative characteristics. (1) The distribution of Q-HRs in the population, i.e. distribution of individuals having different numbers of Q-HRs in the karyotype regardless of their location (distribution of Q-HRs), which also reflected the range of Q-HRs variability in the population genome. (2) The derivative of this distribution, an important population characteristic, is the mean number of Q-HRs per individual. (3) The frequency of Q-HRs in twelve loci of seven Q-polymorphic autosomes in the population. (4) The distribution of Q-HRs on autosomes according to their size and intensity of fluorescence (types of Q-HRs), estimated as described by the Paris Conference [8]; and (5) the size of the Y chromosome, being (a) large (Y ? F), (b) medium (F>Y>G), and (c) small (Y ? G) [44].

1) Q-HRs is detected on certain loci of only seven autosomes **??**3, 4, 13, 14, 15, 21 and 22) in both sexes, as well as on the Y chromosome of males.

On the seven autosomes and the Y chromosome there are only 13 loci where Q-HRs can be detected (Paris Conference, 1971; Suppl., 1975); 2) despite the fact that in the human karyotype there are 13 loci in which Q-HRs can be detected (3cen, 4cen, 13p11, 13p13, 14p11, 14p13, 15p11, 15p13, 21p11, 21p13, 22p11, 22p13, Yq12), i.e., there could theoretically exist individuals with 25 Qvariants in their genome, but such cases have not as yet been reported. In individuals of a population the number of Q-HRs usually ranges from 0 to 10 [44][45][46]. Both complete absence and the maximum number of Q-HRs in the genome have no visible phenotypic manifestations

[38]. 3) distribution of the number of Q-HRs in individuals of a population is almost normal [47][48][49][50][51][52] (Table 1);) at the population level the distribution of Q-HRs on the seven Q-polymorphic autosomes is uneven, the greatest number of Q-HRs is found on chromosomes 3 and 13 (over 50%), the rest of them are distributed more or less evenly on the other autosomes (Table **??**) [54];

Table **??** : Chromosomal Q-HRs frequencies in seven Q-polymorphic autosomes in native populations of Eurasia and Africa [55]. 10) changes in the amount of Q-HRs in the population genome tend to decrease from southern geographical latitudes to northern ones, and from low-altitude to high-altitude ones [47][48][49][50][51][52]59] (see Fig. 3); 12) males in the population differ from each other in the size of the Q-heterochromatin segment of the Y chromosome [8,44,118]; 13) the Q-HR on the Y chromosome is the largest in the human karyotype, and its average size is twice greater than all the Q-HRs on autosomes taken together, so the overall amount of Q-HRs in females is as rule lower than in males [14,44,63]; 14) at the population level the amount of Q-HR on the Y chromosome influences the m value, for example in males with large blocks of Q-heterochromatin on the Y chromosome, the number of Q-HRs on their autosomes is lower and vice versa ((D D D D) C**16**

) in the first days, weeks, months and years of life, ceteris paribus, among healthy children the infants often die with the greatest number of Q-HR in genome (Table **??**) [66].

Distribution of the numbers and mean number of chromosomal Q-HRs in newborns and deceased babies [66] 17) individuals capable of successfully adapting themselves to the extreme high-altitude climate (e.g. mountaineers) (Table 6) and of the Far North (e.g. oil industry workers of the Jamal peninsula of polar Eastern Siberia) (Table **??**) are characterized by extremely low amounts of Q-HRs in their genome [47][48][49]; 18) individuals with a lower amount of Q-HR in their genome proved to be prone to alcoholism and obesity, while those with a greater amount of Q-HR -to drug addiction (Table 8 and 9); Besides the aforementioned data, there is a number of fundamental features that human Q-HRs share with C-HRs: 1) as a rule, Q-HRs are part of secondary constrictions in nucleolar organizers; 2) the nucleolar organizers, which consist of ribosomal RNA genes, of which in man amount to about 200, are situated at the satellite stalks of the D and G chromosomes; 3) as a rule chromosomal Q-HRs variants are constant from one generation to the next and show normal Mendelian inheritances; 4) with the exception of the long arm of the Y chromosome, Q-HRs are situated at the centromere regions; 5) they situated in a high condensed state on the periphery of the nucleus and are closely bound to the nuclear membrane and nucleolus.

No data are available on the mean number and distribution of Q-variants in natural chimpanzee and gorilla populations. However, the bulk of data in literature suggests that the genome of the gorilla and chimpanzee contains the greatest number of Q-variants, while that of man -the smallest. The chimpanzee has larger brilliantly fluorescing autosomal regions than those in human autosomes. Certain regions, such as those on autosomes of gorillas, may be as large as those on the human chromosome Y. It must be noted that such brilliantly fluorescing chromosomal segments are absent in the orangutang [13]. A particular type of Q-heterochromatin located on the distal ends of certain chromosomes (7,11,20,23 in gorillas; 20, 21, 22, 23 in chimpanzees) was found in these species, but not in man. The nature of distal bright Q-bands found only in chimpanzees and gorillas is not clear, yet they are stained by quinacrine mustard and fluoresce intensively, suggesting that this is also Qheterochromatin [67].

In a small sample of chimpanzees' five to seven acrocentric chromosomes had intensely fluorescent regions. It seems that the frequency of Q-HRs in these polymorphic chromosomal regions stabilizes at higher values in the chimpanzee than in man [9]. Based on these studies, Pearson [10] came to the conclusion that these species "have a relatively recent origin, that man, chimpanzee, and gorilla form a natural group and that they have had a recent common ancestor".

7 V. The Cell Thermoregulation Hypothesis

In 1904 Boveri [68] defined chromatin as a substance of the cell nucleus, which is transformed in the process of mitosis into the chromosome. Heitz [69] invented the term heterochromatin to describe and denote chromosome segments, or in some cases entire chromosomes, that maintains a condensed state during the interphase of the mitotic cell cycle and therefore appears in the resting nucleus as a chromocenter [23].

At present we have extensive information concerning the features of organization and properties of chromosomal HRs. The best-known features of HRs However, the role -if any -that heterochromatin plays is still essentially unknown. This is also reflected in the variety of hypotheses, none of them backed up by solid evidence concerning the possible effects of heterochromatin. These ranges from the idea that heterochromatin has no function; consisting of 'selfish DNA', to the assumption that it has an important role in development and evolution (see above).

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We are supporters of the authors who hold the view that chromosomal HRs may play an important role in the vital activity of higher eukaryotes. We have been suggested a hypothesis of cell thermoregulation (CT), which was formulated based on studies, mainly on the distribution of chromosomal Q-HRs in human populations [70]. However, in the hypothesis of the CT we do not separate chromosomal HRs on C -and Q -heterochromatin,

and consider them together as a single intracellular structure under the general title of the condensed chromatin (CC).

We suggest that CC of higher eukaryotes is likely to relate to the thermoregulation in a cell. CC, being the most densely packed material, apparently has the greatest heat conductivity in the interphase cell [70]. Everything that is known about chromosomal HRs, an interphase nucleus and redundant DNA does not contradict the idea of a possible heat conductivity role of CC between cytoplasm and nucleus in a cell, including the following: (1) At both light and electron microscopy, the nuclear periphery in most cell types is predominantly occupied by heterochromatin, which is closely associated with the lamina and the inner nuclear membrane, and nucleoli are surrounded by dense chromatin, which in addition connects the nuclear membrane with one of the nucleoli [6,19,25,[72][73][74][75] (Figure 4).

(2) Membranes of the nuclear envelope serve to compartmentalize the nucleus of higher eukaryotic cells. The outer nuclear membrane shares its proteins and functional properties with the endoplasmic reticulum, whose lumen is continuous with the perinuclear space. The inner nuclear membrane has unique characteristics. It contains a distinct set of membrane proteins [76]. Their functions include providing attachment sites for heterochromatin and the nuclear lamina Heterochromatin: The Visible with Many Invisible Effects nucleoli and in the human genome all rDNA loci are embedded in constitutive heterochromatin. As a result of this linear proximity along the chromosome, nucleoli are always tightly associated with heterochromatin in the interphase nucleus. (**??**) It has been demonstrated that variable segments (G-, Q-and R-bands) are absent in plants and are always present in chromosomes of higher vertebrates (reptiles, birds and mammals). In case of invertebrates, fishes and amphibians, it is difficult to reveal the variable segments. In some insects part of the segments is equivalent to C bands, and variable segments apparently are absent [38,71]. Difficulties of revealing variable segments in plants, insects, other invertebrates, fishes and amphibians are frequently explained by methodological difficulties. But we believe that it is not connected to the reproducibility of techniques of differential staining and reflects a true state of affairs. (8) A new kind of structural heterochromatin -Qheterochromatin -appeared at a later stage of evolution of the animals in the ancestors of three higher primates (Homo sapiens, Pan troglodytes, Gorilla gorilla) [8][9][10]. (9) If HRs were simple "parasitic" DNAs or "junk" DNA, the high regularity distribution of chromosomal Q-HR in human populations might not be expected. This nonrandom behavior is evident from the constraints on the number of Q-HR in human genome, from chromosomal locations (only seven autosomes and Y chromosome); (10) Unlike chromosomal C-HRs, GC-rich sequences that are less condensed in the interphase, chromosomal Q-HRs predominantly contain AT-rich sequences allowing these areas to preserve the most condensed state in all the interphase nucleus and thus a reduction in recombination [80]; Chromosomes have both internal (repair, recombination, rearrangement, modification, restriction) and external (replication, transcription, packaging, organized movement) molecular activities, which are accompanied, inter alia, by some heat output. If for any reasons the temperature in a nucleus begins to exceed that in cytoplasm there is a need for dissipation of surplus heat outside the nucleus. To do this the nucleus has two options: increasing its volume or increasing the heat conductivity of the nuclear membrane. The first option is limited for obvious reasons. The second option is the more promising one should the heat conductivity of the nuclear membrane be increased somehow. Since the nuclear envelope consists of double-membraned extension of the rough endoplasmic reticulum, the nuclear membrane cannot essentially change its structure. But it is necessary to remove the surplus heat from the nucleus somehow. Since the proposed idea is based on cell phenomena, apparently nature 'found' a very simple and effective solution: it increased its heat conductivity through compression of the internal layer of the nuclear membrane by CC.

There are much specific data suggesting that intercellular fluid or blood flow cannot effectively contribute to the loss of excess heat from the cells: a) the cell is surrounded by a thin (~8 nm) external cell membrane that regulates, in addition, the flow of substances into the cell and out of it; b) almost all of the RNA is synthesized in the nucleus and only then enters into the cytoplasm where it directly participates in the synthesis of proteins, as well as, very likely, in other yet unknown processes; c) unlike the synthesis of DNA, the synthesis of RNA occurs throughout the interphase, only stopping during mitosis. For example, in a subject weighing 70 kg about 100 g of protein are renewed every 24 hours; d) finally, the following experimental observations are indicative of the existence of thermoregulation at the cellular level: at the cellular level, organisms respond to hyperthermic stress by synthesizing highly conserved families of proteins, the heat shock proteins.

In essence the idea proposed is reduced to the evolution of the genome structure and the physiology of the whole organism in higher eukaryotes going in parallel to counteract changes of temperature in the ambient environment for more effective preservation of constancy of temperature of the internal environment. The outcomes of such a parallel evolution were: (1) the appearance of different kinds of CC (C-and Qheterochromatin, G+ and Q+ bands), at a genome level the effect of which is generally subject to the laws of physics, and (2) formation at an organism level of a complex organ-based physiological system of thermoregulation. This is why redundant DNA in the form of chromosomal HRs has no phenotypic expression and bears no specific function because HRs in CC participate in thermoregulation at the level of individual cells; an indirect display of this can be found, e.g. in the wide quantitative variability of chromosomal Q-HRs in human populations permanently living in different climatic and geographical conditions of the earth, as well as in the development of some forms of the socalled 'diseases of civilization': alimentary obesity, alcoholism and drug addiction (see Table 8 and 9).

Our hypothesis will possibly disappoint many people by its simplicity and straightforwardness. But we, like

many others, think it reasonable to consider the world as being simple until facts force us to agree that it is complex. As it can be seen from this Table, there is a statistically significant relation between the number of chromosomal Q-HRs in the human genome and the reaction of the body to the controlled thermal load. Individuals, the genome of which contain more than the average in the population chromosomal Q-HRs, the peak temperature occurs in the first five minutes of the thermal load, and vice versa.

Relationship between the amount of chromosomal Q-HRs and the temperature difference between the surfaces of the right palm and the oral cavity at rest is shown in [Table 11].

9 VI. Experimental Verification of the Cell Thermoregulation Hypothesis

It is supposed that any scientific hypothesis can be verified. But what conceivable experimental and natural system can be offered to verify the foregoing idea? It might be reassuring if someone managed to show the following: at the change of temperature in the thermostat above or below 37 °C, the speed of transfer of heat from the nucleus to the cytoplasm in a human cell culture depends, for example, on the amount of chromosomal Q-HRs in the genome of the given individual.

Certainly, cell thermoregulation (CT) hypothesis should be checked in vivo on the cell level. But we have not had such opportunity till present. Nevertheless, we have checked this hypothesis on the level of human organism assuming that CT is the basis for heat conductivity of whole cell part of body [81,82]. However, if the determining the amount of chromosomal Q-HRs in the human genome is a well-established procedure, the same cannot be said about assessing human body heat conductivity (BHC) due to the complete lack of any experience in this regard. In particular, it is still not possible to develop a method to accurately measure the BHC of human, as it is done on homogeneous nonliving objects by physicists.

Through trial and error we have identified areas of the body (right and left hand and oral cavity) and the thermal load mode (creating artificial temperature gradient between left hand and water bath), which allows to roughly estimating the level of human BHC (high, medium and low). Our experience has shown that the most informative are (in descending order): a) the time the peak temperature takes place on the surface of the right palm during a thermal load; b) temperature (T) difference between the surface of the right palm and the oral cavity before the thermal load; c) T amount of the right palm the moment the peak temperature occurs and d) T of the right palm at rest. Temperature of the left palm was used only for the preparation of 'hot' water, to create a temperature gradient between the arm and the water bath individually for each person (for more details see [84]).

Table 10 shows the relationship between the number of chromosomal Q-HRs in the human genome and the rate of reaction of the body to the controlled thermal load, which was determined by the time (in minutes) of occurrence of the peak temperature on the surface of the right palm. As we see in Table 11, the more the chromosomal Q-HRs in the human genome, the smaller the T difference between the oral cavity and the surface of the right palm, and vice versa.

Table 12 shows the relationship between the number of chromosomal Q-HRs in the genome and the amount of T of the right palm at the moment of peak temperature occurrence during the controlled thermal load. As shown in the Table 12, there is a statistically significant relation between the number of chromosomal Q-HRs and the value of T of the right palm at the moment of peak temperature occurrence, namely, in individuals with a great number of Q-HRs in the genome T of the surface of the right palm rises less, and vice versa.

Table 13 shows a different pattern: the more the number of chromosomal Q-HRs in the human genome, the higher the T of the surface of the right palm at rest, and vice versa. How do we interpret the data? We believe that the time of occurrence of the peak temperature on the right palm reflects the rate of conductivity, while the value of T of the right palm surface at that moment seems to reflect the quantity of thermal energy in the individual's body. If the peak temperature on the surface of the palm occurs in the first five minutes after the thermal load, then such an individual is considered as a person with high BHC, and vice versa. In other words, we believe that a person with high BHC conducts heat through the body quicker and eliminate its excessive quantity through body shell quicker as well to maintain a constant level of inner body temperature.

Statistically significant relation between the number of chromosomal Q-HRs in the genome and the T difference between the oral cavity and the right palm at rest may also characterize the heat conducting ability of the human body, the smaller the T difference, the higher the BHC, and vice versa. We believe that the smaller T difference between the oral cavity and the palm reflects the high heat conductivity ability of the body, in a sense that such an organism equalizes the T difference between the different parts of the body more effectively, thereby successfully avoiding overheating of the organism in hot conditions. Temperature of the right palm at rest, presumably, also reflects the level of BHC; individuals with high T of palm may have higher BHC, and vice versa.

As is known, the heat conductivity caused by transfer of energy is one of the three phenomena of transfer existing in the Nature. From the point of view of physicists, heat conductivity (HC) is a transfer of energy from more heated sites of a body to less heated ones as a result of thermal movement and interaction of micro particles. HC leads to equalization of body temperature. Virtually, there is nothing new in the idea that the body of the human should possess some heat conductivity. Nevertheless, it (heat conductivity) has not drawn the attention of nor physicists, neither physiologists for the present as the important physical characteristic of a human body.

Apparently, it is connected with known physical heterogeneity (in sense, density) of a human body. Probably that's why, we did not manage to find in the literature not only a special method, but even any attempt to estimate BHC of alive organisms in vivo [81,82]. In thermo physics, measurement of heat conductivity of solid bodies (f.e. metal) is carried out by determination of heat conductivity coefficient by a calorimetric method. Transfer of heat occurs through a metal rod, the ends of which are placed in a calorimeter with the water taken attemperatures; T1 and T2 (T1 > T2). It is necessary estimation of HC, where lowering of temperature to determine quantity of heat and time transferred through experiment to measure the heat conductivity coefficient of the given metal rod. It is obvious that direct transfer of a method of measurement of the heat conductivity, applied in thermo physics is unacceptable to a human body both for technical and ethical reasons. However we have tried to approximate to the decision of this problem indirectly, by an estimation of part of a human body. For this purpose, we had to modify the standard technique of physicists so that it was acceptable to the human [84].

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These data showed that there are differences in the BHC between individuals in population. In particular, we were able to show that individuals in a population significantly differ from each other in terms of BHC level. It was found that the level of BHC is affected by sex, age and climate and geographical features of the individual's place of origin. However, the level of BHC is not affected by weight, height, values of arterial pressure, pulse rate and respiration [81,82]. In other words, there are some parallels in the distribution of the amount of chromosomal Q-HRs and variability of BHC at the level of human populations.

Which of the existing biological phenomena could underlie of wide human BHC variability in population? First thing that comes to our mind is, of course, basal metabolic rate, which is well-known from the courses of physiology. But it is known that the core temperature of those living in the tropics is within a similar range to those dwelling in the Arctic regions. Apart from that, basal metabolic rate is influenced by such factors as height, weight, body constitution, pulse rate and environmental temperature, which contradicts our data [81,82].

As of possible genetic factors the most appropriate is the amount of chromosomal Qheterochromatin in human genome. Certainly, the thickness of peripheral layer of CC around cellular nucleus depends on total amount of chromosomal Cheterochromatin in the genome. But as we suppose, packaging density (compactization) of CC itself is basically connected with the amount of chromosomal Qheterochromatin in nucleus [70]. The point is that human populations do not differ significantly in the quantity of C-heterochromatin in their genome [17,85]. Wide quantitative variability at the level of populations is found only in the amount of Q-heterochromatin. Some quantity regularities in distribution of chromosomal Q-HRs in population depending sex, age and peculiarities of permanent place residence are determined [15,16,[44][45][46][57][58][59][60][61][62]86,89]. It is notable, that these regularities turned out to be very similar to the wide BHC variability in population [81,82]. To be exact, apparently, human BHC depends mainly on the amount of chromosomal Qheterochromatin in his genome. As the amount of chromosomal heterochromatin does not change in ontogenesis, it is possible that the level of BHC may be a constitutional character, the same as the color of skin, eye shape, body constitution, height and other innate physical human peculiarities.

11 VII. Cell Thermoregulation in Evolution and Development

Despite the impressive achievements of modern genetics is still not built comprehensive theory of heredity. Such theory must explain the phenomenon of heredity in full, including genetic basis of adaptation and selection, dominance inheritance, the inheritance of acquired characters, regeneration and many groups of facts pertaining to variation, inheritance and development.

For example, Maynard Smith and Szathmáry [88] pointed to some major transitions in biology: the origin of the first eukaryotic cells; the emergence of sex and sexual mode of reproduction; the origin of multicellular plants and animals; the emergence of warm-blooded animals and the origin of modern human, which is difficult to explain within the framework of existing theories of evolution. In this regard, we believe that some of the answers to these questions can be obtained by studying biology of chromosomal HRs in the genome of higher eukaryotes. Because, it is very difficult to explain the aforementioned and some other biological phenomena in the framework of the "genecentric" concept, that is, due to the accumulation of favorable mutations and selection of genes.

By studying variability of chromosomal Q-HRs in human populations residing permanently in different climatic and geographic conditions of Eurasia and Africa, in norm and pathology , we hoped to understand what, if anything, heterochromatin is doing and why its amounts can vary dramatically, even in organisms that have similar numbers of genes [44,[47][48][49][50][51][57][58][59]89, **??**22]. In the result, we received data evidencing of the possible participation of chromosomal HRs in intracellular thermoregulation [70,84,90]. Now the question arises whether can the phenomenon of cell thermoregulation clear the above the problem put by Maynard Smith and Szathmáry [88]? We pre-condition, we do not claim to have received satisfactory answers to these complex problems of modern biology. Here we just want to give some examples of the possible participation of cell thermoregulation (CT) in some important processes of evolution and development.

12 a) Possible role of chromosomal Q-HRs in human adaptation to various temperature conditions

Most early human evolution was in the tropics or subtropics and our fossil ancestors occupied semiarid environments, it is not surprising that modern humans are well adapted to rather hot and dry conditions. Then, about 50 000 to 100 000 years ago our ancestors left the African savannas and began to master climatic zones that differed from those of tropical and subtropical Africa. There the main obstacle met by Homo sapiens as a tropical species was cold, and nevertheless man was able to master all the dry land, including high-altitude regions of the Earth, over a very short historical period.

Therefore, for populations to cope with new and challenging habitats there must be an interaction between their genome and their physiological response to allow them to survive a variety of environmental stress. What the "genetic response" of man to the new ecological challenge was we do not know for sure. However, we have repeatedly noted that man adapted himself to cold and high-altitude hypoxia without the involvement of specific structural genes and managed to do so with the aid of a genetically inert but very mobile (in the sense of hereditary variability) portion of his genome -chromosomal Q-HRs [47][48][49][50][51]53,54,[57][58][59]87,91, **??**22].

The fact that excessive body insulation invariably results in decreased physical activity of man is evidenced by examples from the life of contemporary individuals in the Far North and at high altitudes. We find it appropriate to give here the following well-known examples. As soon as a man in heavy insulation begins to work, he is in the situation of being a tropical man in Arctic clothing. Among the many problems the Eskimo had to solve was how to keep from building up a large quantity of wet or frozen insulation. The problem is illustrated by a quotation from a member of Scott's Antarctic expedition; Cherry-Garrard (1948) wrote: '?on the most bitter days it seems that we must be sweating; and all of this sweat instead of passing away through the porous wool of our clothing and gradually drying off us, froze and accumulated. It passed just away from our flesh and became ice' (cf. [92]).

According to the principle of temperature homeostasis, heat must leave the body; otherwise, dispersing in tissues, it causes a rise in temperature that is incompatible with life. As heat cannot be used by the body as a source of energy necessary for useful biological work, removal of heat is apparently the most important task of thermoregulation, since only a few degrees are needed to prevent thermal death. If heat emission into the external environment ceases completely, dangerous events of overheating during complete muscular rest may develop in 3-4 hours in man; in mice the corresponding period takes about 40 minutes, while in small birds -only a quarter of an hour. During moderate muscular exercise these periods are several times shorter [93]. Thus, the organism is not a thermal "machine" and does not use heat to perform physiological work. Therefore, thermoregulation is mainly directed at preventing overheating of the organism, which in terms of biology is more dangerous **??**94].

Many studies have shown that prolonged adaptation to cold by increased thermo genesis is hardly possible. Therefore, homeotherms adapt themselves to cold by increasing thermal insulation, though the problem of removing excess heat arises. Even in polar animals prevention of possible body over heating in winter is the most crucial function of thermoregulation [92].

Allied animal species living under polar and hot climatic conditions do not differ significantly in the intensity of basal metabolism. Polar animals also do not show any significant differences in winter and summer, for it is known that the level of basal metabolism is not a physiologically regulated value and is established by nature. Perhaps that is why people living under different climatogeographical conditions do not differ significantly as to the level of basal metabolism.

Unlike many animal species, man is unstable to live in an extreme cold environment. He is basically a tropical homoeothermic. However, due to various reasons, human populations have to live under conditions of low or high environmental temperature where maintaining the temperature homeostasis is especially difficult. Naturally, all three effectors of thermoregulation systems mobilize: heat production, heat loss and thermoregulatory behavior. Though being important, they cannot be effective at long-term perspective. We suppose that H. sapiens, besides those inherent in all mammals possesses an additional but very fine and simple mechanism of thermoregulation. In the present case, in order to preserve temperature homeostasis under different environmental conditions, in addition to physiological, behavioral and biochemical mechanisms such as wide intra population variability by BHC was used. Possibly, for the H. sapiens, BHC diversity is necessary because no single genotype can possess a superior adaptadness in all environments.

From the point of view of the cell thermoregulation hypothesis intracell thermoregulation mechanisms of human adaptation to various temperature conditions different from climate of Eastern African savannah can be represented schematically in the following way: 1) in the North (where cold is the main limiting human life harmful physical factor of environment) an individual with fewer amount of chromosomal Q-HRs maintains temperature homeostasis in organism more effectively because of low BHC, permitting to preserve additional amount of produced metabolic heat in organism longer and slow down body cooling rate because of external cold; 2) on the North an individual with high BHC, constantly loosing by means of conduction additional amount of heat necessary to organism in conditions of cold climate and exposing to relatively fast cooling because of cold, has to produce bigger amount of heat and/or consume more high-calorie food for heat production, which is not always simple and healthy, because hunger and vice versa overweight reduce his chances to survive; 3) on the South (where environment temperature is higher than body temperature) an individual with low BHC besides his own internal

heat production receives additional heat from environment by means of conduction, which, as it is known, is not used in useful physiological work. That is why these individuals' bodies overheat faster and they have to give up heat surplus (through sweating, polypnoe, forced rest, behavioral reactions and etc.) to environment at the cost of significant decrease of physical activity that finally negatively influences on their adaptation to hot climate; 4) individual with big amount of Q-HRs in genome in the South having body with high thermal conductivity perhaps adapts better to high temperature of environment, more effectively leveling temperature differences in different parts of the body and faster directing excess heat flow from organism to environment, including directly the way of heat radiation. We in particular assert that BHC has vital importance to an organism in preserving temperature homeostasis in body influencing on rate of leveling temperature differences in its different parts at the same time taking no active part in chemical and physical heat production processes. At the base of heat conductivity of cell part of the body is cell thermoregulation, effectiveness of which is defined by packing density degree of condensed chromatin in interphase nucleus [70,90]. And physical density of condensed chromatin of a human in its turn depends on the amount of Qheterochromatin contained in it. Since individuals in population differ in terms of the amount of chromosomal Q-HRs in genome, we expected existence of wide variability in heat conductivity of their bodies and it proved to be true [81,84].

In light of the aforementioned, it is possible rationally explain why the mean number of Q-HRs is considerably lower in the genome of populations living permanently in northern latitudes and high-altitude regions, and in newcomers well adapted to the extreme conditions of high altitude (mountaineers) and the Far North (oil-industry workers-drillers at Western Siberia) as compared to populations living in temperate zones of Eurasia and in low-altitude subequatorial Africa (see Fig. 3 and Table 6 and 7).

In the same manner it is possible to explain why the amount of chromosomal Q-HRs is greater in the genome of newborns, then in senior age groups [52,57,65] and the same chromosomal material is found in greater quantity in the genomes of infants died during first weeks, months, and years of their life [66]. Prevalence of people with lesser quantity of Q-HRs in the genome in senior people groups may be connected with negative selection of individuals with greater amount of chromosomal Q-HRs during first years of their life. As it is well-known, infants' ratio of body surface to body capacity is higher than adults' ratio. When one more physical factor (high BHC) superimposes on this, then these infants are more vulnerable to colds and their consequences.

Our data on the temperature difference between the oral cavity and the palm could explain the data obtained in other research programs. Thus, the average difference between the oral and axillary temperatures of Indian children aged 6-12 was found to be only 0.1 °C (standard deviation 0.2 °C) [95] and the mean difference in Maltese children aged 4-14 between oral and axillary temperature was 0.56 °C [101]. These observations do not yet have a rational explanation. As part of our hypothesis (of a possible link between the amount of Q-HRs and level of human BHC) these data could be explained by the fact that the amount of chromosomal Q-HRs in the genome of populations of India is significantly greater than that of the inhabitants of Europe [50,61]. We have also demonstrated that the natives of India are characterized by high levels of BHC, compared with the indigenous people of Central Asia [50,82]. Indian peninsula is known for it hot climate, where the maintenance of temperature homeostasis pose serious stresses for human body. Assuming our hypothesis -the larger the amount of chromosomal Q-HRs, the higher the heat-conducting ability of the human body -the low temperature difference between the oral cavity and armpit among Indian children could be explained by the presumed selective value of the amount of Q-heterochromatin in human adaptation to hot climate (see more in [89]). This, in turn, means that the body of Indian children has higher heat conductivity than their Maltese counterparts, allowing them to better eliminate excess thermal energy to the environment and more effectively maintain the temperature difference between the different parts of the body.

While developing the idea about the possible significance of BHC in the adaptation of contemporary man to certain extreme natural factors, we have previously considered the hypothesis on the possible role of Q-heterochromatin in the origin of Homo s. sapiens [54,55]. According to our hypothesis, since individuals with different amounts of Q-HRs began to appear in the H. sapiens population (as occurs now as well), our ancestors apparently took advantage of this unique feature properly when climate in the African savanna began to change and when they tried to leave it to look for new place to live in as it became necessary to adapt themselves to the new, more inclement environment. Under these conditions advantage is gained by individuals capable of engaging in prolonged and high physical activity. In this case individuals with a lesser amount of chromosomal Q-HRs and accordingly, a lower BHC, who had a certain advantage as concerns survival, could form new populations with a small amount of Q-heterochromatin in the genome, and although the appearance of individuals burdened with a large amount of Q-HRs continued, the pressure of natural selection on such populations was on the whole lower than on the initial ones (for details see [54,55]).

It is hard to say why the ancestors of P. troglodytes and G. gorilla were unable to use the same route. However, the assumption which we feel is likely is the following one: initial Q-HRs frequencies on all the variable loci proved to be high enough to produce of individuals with significantly different numbers of chromosomal Q-HRs (see Table **??** would be able to survive under unfavorable conditions was quite improbable. In other words, the chimpanzee and the gorilla were initially unable to vary the amount of Q-HRs of their genome as much as man could. The following facts are in favor of this assumption: 1) the range of variability in the number of Q-HRs in the chimpanzee genome is from 5 to 7 [9,10], whereas in the human population it is from 0 to 10, i.e., considerably wider [44,53,96]; 2) in the gorilla and the chimpanzee, but not in man, a special type of Qheterochromatin was

found, located on the distal ends of certain chromosomes **??**7, 11, 20, and 23 in the gorilla; 20, 21, 22, 23 in the chimpanzee), and that itself makes hard to produce of individuals with different amount of Q-HRs in the karyotype less probable. The nature of these bright distal Q-bands that are only present in the chimpanzee and the gorilla is unclear, however, they are stained by quinacrine mustard and show intense fluorescence, suggesting that this is also Qheterochromatin [67].

13 b) The possible role of cell thermoregulation in development of some human diseases

The second group our specific biomedical data related to the wide quantitative variability of chromosomal Q-HRs in man concerns patients with alimentary obesity, alcohol abuse and drug addiction. We found that in patients with alimentary obesity and alcoholism the amount of chromosomal Q-HRs was considerably lower than in controls from the same population and ethnic group. At the same time, in drug addicts the mean value of Q-HRs in their genome is on the average twice greater than in subjects with alcoholism and obesity, taken from the same ethnic group (see Tables 8 and 9).

We once again feel that the reason for this difference lies in the features of cell thermoregulation. Thus, in patients with alimentary obesity and therefore with a low BHC (even assuming that they use the same amount of calories as people with normal weight), we believe that a part of the calories accumulates in the body in the form of adipose deposits due to inadequate heat loss. The point is that alimentary obesity mainly occurs in people living in temperate, more often in northern but economically developed countries. Surplus heat is not completely removed from the body due to good heat insulation (comfortable habitation and life) and body insulation in the form of modern clothes that are warm but do not adequately contribute to heat loss. If we also take into account the use of high-caloric, easily assimilable food-stuffs, hypodynamia and, possibly, the use of power consuming beverages (alcohol), ineffective heat loss in alimentary obesity become evident.

It is also difficult to explain the possible relation between the BHC and the development of alcoholism. It is appropriate to mention here that the frequency of using strong alcoholic drinks tends to increase according to latitudes (from the South to the North) and to altitudes [67,98,99]. Let us conceive the most extreme case. Actually, life and climate in the Far North or at high altitude frequently predisposes, in a certain sense, to taking strong alcoholic drinks just to get a feeling of heat comfort. But at the same time, as we suspect, one and the same dose of alcohol in subjects with different levels of BHC may lead to different consequences. Thus, subjects with a low BHC, to get a sense of thermal comfort should take a relatively large dose of alcohol than individuals with the same physical characteristics. And this is fraught with well-known consequences: overheating of the body; a stronger intoxication; a hangover syndrome etc.. The other metabolic, clinical and psychic aspects of this problem have been closely studied.

Drug addicts, i.e. subjects with a high BHC and accordingly with rapid heat loss, become accustomed to narcotics due to the intuitive wish to get a feeling of thermal comfort, but this time this "pleasure" is really due to "narcotic cooling" with ensuing emotional and other feelings, since narcotics and certain relaxants decrease sensitivity of hypothalamic thermoregulation centers to temperature rises [100].

14 c) Condenced chromatin and origin of multicellularity

The emergence of multicellular organisms from single-celled ancestors which occurred several times, independently in different branches of the eukaryotic tree is one of the most profound evolutionary transitions in the history of life. However, the genetic changes that accompanied the several origins of multicellularity remain elusive [102].

There are various mechanisms by which multicellularity could have evolved. For now, there's little evidence to support choosing one of them as the first to evolve. Examination of the DNA record of several lineages suggest that multicellular transitions are frequently characterized by increases in gene family complexity of molecules involved in one of the three key processes for multicellular growth and differentiation: cell adhesion, cell-cell signaling, and transitional regulation. Much, however, remains to be understood. What was the relative contribution of extrinsic (ecological and environmental) and intrinsic (genetic) factors in the origins of animal multicellularity [103]?

As is known, the metabolism of organisms proceeds well only within narrow ranges of internal physical and chemical conditions. With the appearance of multicellularity, one serious problem emerged, that is the elimination of surplus heat from the cells located in the deep parts of the body. The point is that the ?ells convert energy from one form to another as they carry out the business of life. None of these energy conversions is 100% efficient -some energy is always lost as heat. All of these energy conversions are often Volume XV Issue III Version IYear 2 015 (D D D D) C

accompanied by the production of heat, not all of which can be made to do work. Heat generated by the chemical reaction within cells must be dissipated for the organism to survive. However, by the mechanisms of heat loss the body and individual cells apparently differ. As is known, the external heat flow from a body is performed by way of radiation, conduction, convection and evaporation of water. Apparently, of these mechanisms, the cell can use only the heat conduction [90].

On the question of whether bacteria often have the traits of a multicellular organism, or whether this is a rare case, the answer given states that most of them, but probably all of them lead the life of multicellular organisms

[104]. There are really a lot of examples of prokaryote behavior as multicellular organisms. Concerning the issue which is being discussed here, another thing is important: (1) despite the fact that prokaryotes ruled on the Earth for about one billion years, coexisted with eukaryotes for more than 2 billion years, and there is constant contact between the cells of prokaryotes proper, neither now nor before did the prokaryotes form multicellular organisms, and (2) among the multicellular organisms the prokaryotes are not found, despite the fact that in the colonies the specialization of bacterial cells and regulation of protein synthesis are performed by means of signals, i.e. as it is performed in multicellulars. We assume that the inability of prokaryotes to form a multicellular organism with a common external cover is attributed to the absence of a mechanism providing maintenance of a relative constancy of temperature in the cells located in the deep parts of body, which is impossible without condensed chromatin [81,90].

We believe that, perhaps, a dense layer of condensed chromatin around the cell nucleus, which is the physical basis of CT, has played crucial role in appearance of multicellular organisms. As it seems to us for the emergence of macroscopic multicellular organisms, among others, it is required to exist an effective mechanism for the timely removal of excess metabolic heat from the cells located in the deeper parts of the body [90].

There are also other data, though obtained within the framework of other conceptions, which may testify to our assumption of a possible role of the CT in the origin of the multicellularity:

(1) Lability of the replication features constitutes a most important peculiarity of HRs, displayed in ontogenesis and phylogenesis. The HR contents in different tissues vary, and are controlled by their underreplication and overreplication [38]. (2) Heterochromatin is formed during early development. It is well known that at the first steps of Drosophila development, the nuclear chromatin is finely dispersed and mitotic chromosomes look like thin filaments. By the blastoderm stage chromocenters and nucleoli are already visible in the nucleus [105] and chromosomes can be differentially stained [106].

(3) In the fertilized egg, the first blastomeres (salmon, trout, mouse and field vole) and in the spermatocytes of Drosophila melanogaster the HRs are completely absent or are of a very small size.

Only beginning with stage 4-16 blastomeres, i.e. in mitosis of early embryogeny, the first large blocks of heterochromatin blocks appear [38]. (4) Formation of heterochromatin during early embryonic development in mice has been studied in more detail. It has been demonstrated that at the very beginning (2-4 blastomeres), the interphase nuclei are uniform, and the metaphase chromosomes appear as slim uniform filaments.

However, already at the blasocyst stage, G+ bands in the chromosomes are as distinct as in chromosomes of the late embryo fibroblast [107]. In females, X chromosomes are also heterochromatinized in the blastocyte stage. As the HRs in the chromosome during the embryogenesis process appears only with the appearance of 4-6 cell blastomeres, i.e. at the stage of actual multicellularity, there are reasons to assume that CT really could have a relation to the origin of the multicellular organisms.

(5) Examination of Earth's history indicates two major events immediately prior to the origin of complex multicellularity, namely predation [108] and a sharp increase of oxygen levels [109], that may have contributed to its relatively late appearance. The latter circumstance is particularly important since the amount of excess heat in the body depends on intensity of cellular metabolism, and in turn it is connected to the concentration of oxygen in the atmosphere. However, to maintain a high metabolic rate in the cell without detriment to its normal functioning of the body, in addition to ?T, must have a mechanism capable to withdraw excess heat from the body parts that are not directly contact with the external environment. Such additional mechanism contributing to the maintenance of the relative temperature homeostasis in the body is the circulatory system. In the literature, we could not find theories or hypotheses to explain the origin of the circulatory system (CS), although its role in the vital activity of multicellular organisms is well established.

We believe that the CS has arisen after the physical conditions have formed in the body of macroscopic animals that cause intercellular fluid to move from one part of the body to another. Such conditions occur when heat production and heat loss vary considerably in different parts of the body. If constant regions with different temperatures (e. types of cells, tissues or organs), appear in such organisms, whereas intercellular fluid will move from the hot to the cold parts of the body. Possibly, in due time, part of the extracellular space become the blood vessels, and the latter, in turn, acquired the ability to contraction so to increasingly push fluid from one body part to another. No matter what be, the phylogeny of evolution CS in animals suggests exactly this picture, which has ended with the formation of 4-chamber heart in mammals.

Speaking about the evolution of CS, we should mention the occurrence of warm-bloodedness. As it is known, warm-blooded animals are birds and mammals. It is generally assumed that they have become warmblooded, because of their ability to maintain a very high level of metabolic rate and presence of 4-chamber heart. However, as we see it, the level of cellular metabolism is not determined by the ability of animals to obtain high-calorie foods or its (food) availability. Here it is crucial ability of cells to timely withdraw excess metabolic heat in the intercellular space, in order to avoid the consequences of not desirable high heat effects upon such vital genetic processes as repair, recombination, replication, transcription, rearrangement, packaging and etc of DNA. And this is possible only if there is a dense layer of CC in interphase cells.

Therefore, we postulate a priori that the CC should be the densest domain in the cells of birds and mammals among higher vertebrates. This confidence is related to that the most clear-cut differential staining (C-, G-and Q-bands) provide the human mitotic chromosomes, and then the other great apes, and then other mammals. Chromosomes of reptiles and amphibians are poor or no differentiated. Apropos, only C-bands can be obtained

on the chromosomes of plants. Referring to the ability of chromosomes to give differential staining, we mean that the well-known fact that C+, G+ and Q+ bands represent the most intimate parts of the body of mitotic chromosomes, enriched with heterochromatin and other types of non-coding high repetitive DNAs, which make up the physical basis of the CC. Our confidence in the highest density CC in human cells among vertebrates is caused by the fact that: a) the human genome has all the known types of constitutive heterochromatin (C-and Q-HRs); b) among higher primates, the highest quantity of chromosomal C-HRs are in the human karyotype; and c) the level of conductivity of the human body is due to the quantity of Q-HRs in its genome (see more details. [81,90].

We assume that the chromosome segments of the higher eukaryotes have undergone their own evolution in the direction: C-heterochromatin ? G+ and Q+ bands ? Q-heterochromatin as response of a cell nucleus for the demand of multicellular organisms in denser packaging of non-coding DNA for the increase of the heat-conducting effect of CC between the nucleus and cytoplasm [70]. For example, at a later stage of evolution of the mammals in Africa in the ancestors of three higher primates (Homo sapiens, Pan troglodytes, Gorilla gorilla) besides C-heterochromatin, a new type of constitutive heterochromatin, Q-heterochromatin, appeared. Obviously, this is related to the increase of the metabolism intensity in their organism, and, accordingly, the further improvement of the intracellular thermoregulation. In this case the Q-heterochromatin is not only a new type of constitutive heterochromatin, but possibly an additional 'center of condensation and attraction' for more dense packaging of adjacent inactive chromatin, thus, increasing the heat conducting effect of CC in the interphase cell of three higher primates [90].

If our reasoning is really relevant to real events in the evolution of animals, then for example, it is not difficult to explain why, for example, a crocodile has not become a warm-blooded animal. It is believed that this large reptile is cold-blooded because he has a 3chambered heart which arterial blood is poorly oxygenated, and so the body cannot maintain a high level of metabolism. However, it is unlikely that anyone will seriously consider that this disadvantage can be added to the lack of high-calorie food. It seems highly probable that the main reason for poikilothermy of a crocodile is his particular chromosome; as with all reptiles crocodile's chromosome give bad differential staining. This means that in these cells the density of CC is low, which hampers the effective transition of excess metabolic heat from the nucleus to the cytoplasm. Perhaps crocodile lies for so long after eating of another food portion due to the fact that under accelerated metabolism or excessive physical activity there is may be a risk of overheating of the body in the deep parts of the body. Warm-blooded animals solve this problem by effectively removing of excess metabolic heat through the dense layer of the CC, as they have more perfect intracellular thermoregulation. In any case, it is necessary to remember that warm-blooded animals at rest consume 5-10 times more energy than the coldblooded organisms of comparable size. Birds and mammals are able to regulate the consumption and storage of thermal energy and maintain a constant body temperature, what is radically different from that of modern reptiles, for which an opportunity to raise the body temperature depends on external sources of heat.

We have no comparative experimental studies on the degree of density of the CC layer in the cells of cold -and warm-blooded vertebrates. And yet there is one study that indirectly testifies in favor of our hypothesis. Thus, Bernardi and Bernardi [110] extensively studied the guanine-cytosine (GC)-rich isochores of cold-blooded (fishes, amphibians and reptiles) and of warm-blooded (birds and mammals) vertebrates. Both the non-coding DNA and the sequences that code for proteins (structural genes) turned out to be much richer in GC in warm -than in cold-blooded animals. Though for the time being we do not know how the GC-rich isochores could influence the appearance of homoeothermic, nevertheless all the above data indicate the existence of a relationship between DNA composition and the appearance of warm-blooded organisms.

Of course, the CS in its present form is the result of long evolution and without it there would not be long-range transport of thermal energy, chemical signals and the products of metabolism in the body of multicellular organisms. However, as we believe, CS with its appearance not least is obliged to necessity of CT in multicellular organisms (for more details see [81,90]).

15 d) Cell thermoregulation and origin of sex

It seems highly probable that the CT is related to the origin of specialized cells, tissues and organs, although it is considered to be the result of favorable mutations in structural genes.

Probably, the first specialized cells, tissues and organs were associated with the sex. As it is known, sex in the modern sense is only in eukaryotic organisms. Regarding the origin of sex, there are many hypotheses, but all associate this process with the evolution of the structural genes. We support the view that the emergence of sex is related to the evolution of the noncoding part of the genome (in the broad sense of the word), and structural genes are related to the development, mainly of secondary sexual characteristics [87,[111][112][113][114].

In particular, we believe that sex, as a product of meiosis and mitosis has appeared as a result of the influence of temperature on some of the stages of cell division. Namely, the low temperature could effect upon duration of prophase stage of mitosis. As it is known, in the case of long delays cell division under prophase the homologous chromosomes can conjugates each other. In this case, at the anaphase stage the daughter cells will be dispersed into non-sister chromatids, as in normal mitotic division, but whole parent chromosomes, i.e. mitosis turns into meiosis. But to do so happen the presence of mitotic chromosomes is necessary. There is reason to believe that

mitotic chromosomes and sex is also the product of a long evolution of non-coding DNAs in eukaryotic genomes [53,112].

If sex appearance is the result of complex evolutionary processes in the distant past, about which we can only make guesses, the mechanisms of sex differentiation can be tested experimentally. In particular, we postulated that sex differentiation is affected by the temperature either. Namely, the sex differentiation (SD) in animals and human is determined by the amount of constitutive HRs in the chromosomes of the undifferentiated embryonic gonads (UEG) via cell thermoregulation. It is assumed the medulla and cortex tissue cells in the UEG differ in vulnerability to the increase of the intracellular temperature. If the amount of the HRs is enough for efficient elimination of heat difference between the nucleus and cytoplasm in rapidly growing UEG cells the medulla tissue survives. Otherwise it doomed to degeneration and a cortex tissue will remain in the UEG. For artificial regulation of the SD it is proposed to remove a layer of cortex or medulla in the UEG depending on the objective and task of the research (for more details see [111][112][113][114]).

We also believe that the inactivation of one X chromosome in mammalian cells is associated with the CT. As it is known, Lyon [115] proposed the singleactive X-chromosome hypothesis to explain the observation that in the mouse, females heterozygous for X-linked fur color genes are patchy mosaics of two colors. To quote Lyon: "... (1) that the heteropicnotic Xchromosome can be either paternal or maternal in origin in different cells of the same animal; (2) that it is genetically inactivated". According to the Lyon this mechanism provides dosage compensation for X-linked genes because each cell, male or female, has only one X-chromosome that is transcribed.

The point that I am trying to convey is that: a) Xinactivation is not involved in the SD, As Lyon [116] stated; b) ?-chromosome is not being inactivated, but it is heterochromatinized in order to compensate the lacking in the female karyotype the largest block of the constitutive HRs on Y chromosome in the interest of the CT. Thus it would be more correct to speak about compensation of the heterochromatin dosage, and not only about the dosage (double) of genes (details see. [63,111]).

That CT can be related to the inactivation of one of X-chromosome in humans shows such fact, that the relatively low level of BHC in women compared with men at the population level [81,82]. This may be due to the fact that CC in interphase cells of women do not have such density as the men CC. Apparently, facultative heterochromatin of inactivated X-chromosome is still inferior to constitutive heterochromatin on the Y chromosome in their ability to condense (compacting) CC in the female body cells.

It is very little known about possible role of CT in individual development. Here we rely primarily on data collected at the level of the human body. In particular, it was found that individuals differ significantly from each other in BHC. At this the following regularity patterns have been revealed: a) on the average BHC of males is higher than that of females; b) individuals differ in BHC from different age groups, on the average human BHC level is steadily changed decreasing with age; c) natives of low altitude regions of southern latitude differ on the average by higher BHC than population of high altitudes and northern latitude [81,82]. In addition, it was found that individuals suffering from the so-called "diseases of civilization" (alcoholism, drug addiction and obesity)

Volume XV Issue III Version I significantly differ in the level of BHC from healthy individuals in the population. [89].

We assume that inherently these differences are related with different quantity of chromosomal Q-HRs in the genome, the biological effect of which manifests itself through CT in the form of different BHC. Of course, we are far from thinking that the basis of individual development rests solely with the CT. We just want to emphasize that CT is probably another factor that can effect upon individual development.

16 VIII. Conclusion

A change in environmental temperature is one of the most common stresses experienced by a wide range of organisms from bacteria to plants and animals. The response of prokaryotic and eukaryotic systems to heat-shock stress has been investigated widely in a large number of organisms and model cell systems. A sudden temperature up shift poses a serious threat to the integrity of almost all cellular macromolecules. The structure of membrane lipids, DNA, RNA and proteins is altered as the temperature rises. The expression of heatshock proteins (HSPs) is a universal response found in all living cells (reviewed in: [117,118]). All organisms from prokaryotes to plants and higher eukaryotes respond to cold shock in comparatively similar manner. Generally, cells respond to cold stress by expression of a small group of proteins, the so termed cold shock proteins (reviewed in: [119,120]).

Apart from protein-mediated transcriptional control mechanisms, translational control by RNA thermometers is a widely used regulatory strategy. It is becoming increasingly clear that certain messenger RNAs are not simply a substrate for ribosomes but contain control elements that modulate their own expression in a condition-dependent fashion. Structural changes in such sensory RNAs are induced by specific environmental changes (reviewed in: [121]).

The role of the circulatory system (CS) has been discussed above in maintaining temperature homeostasis of endothermal organisms. However, the CS cannot influence directly the temperature inside the cells, as those are linked with the CS indirectly -through the intercellular space. Thus, the CS influence on inner cellular temperature homeostasis is limited and its effect, in general, comes to transferring surplus heat from the intercellular space.

That is why it seems that the problem of maintaining the inner cellular temperature homeostasis is solved by cells themselves, and we call it the cell thermoregulation (CT) [70,91].

Apparently, the physiological thermoregulation functions relatively independently from CT as evolutionally new adaptive system [81,82,84]. From our point of view, CT can be the missing link, which should fill the "gap" between the thermoregulation systems, functioning at the molecular level and the whole organism. It is likely that we faced with physiological problem which is a new and alien for classical courses of physiology.

It is possible that our attempts to find a common physical denominator in physiological, ontogenetic and pathologic situations that are so different may seem very far-fetched. Moreover, there will be opponents who believe that mechanisms of physiological thermoregulation in man are sufficiently perfect; otherwise he could not master almost all the land on Earth so rapidly and effectively. Indeed, the modern human occupies a more widespread range of environments than any other species, extending from the northern arctic regions to humid tropical forests and arid zones, living at altitudes from sea level to over 5 000 meters above sea-level. The range of climatic conditions to which human populations are exposed today closely corresponds to the total variation present on this planet. Life at high altitude imposes environmental stresseslow oxygen pressure, low humidity, cold, and increased exposure to high solar radiation. Though, unlike heat or cold stress, high altitude hypoxia can be alleviated only slightly, if at all, by behavioral or cultural adjustments.

As we suppose, during his evolution man, possibly owing to chromosomal Q-HRs, had an additional and very flexible tool to ensure more effective thermoregulation, allowing him to master almost all the oykumene, and, more importantly, during this process he acquired a developed and more functionally perfect neocortex capable of retaining and processing more information than other higher primates, which fact subsequently led to the development of a language and abstract thinking [54]. In essence, all that was said comes to one simple thought: how does man as a homoeothermic being differ from other mammals as concerns preservation of a constant internal environment the main component of which is temperature homeostasis. In the long run, if our arguments are correct they could help understand certain aspects of the origin of human intellect.

Assuming that intellect has a fully terrestrial origin and man is not fortuitously endowed with it, we have the right to ask ourselves: what basically distinguishes man from other mammals, namely, features of structure or features of functioning of these structures? As far as we know, Homo s. sapiens is not only devoid of a more or less large anatomic structure, but also has no protein or enzyme that has no analogue in the animal world. The fundamental structural characteristic of man is the presence of chromosomal Q-HRs in its genome which he has inherited together with the chimpanzee and the gorilla -from one common ancestor. In this context the only difference of H. s. sapiens is the wide quantitative Q-HRs variability in his genome, to the understandings of its biological and physiological significance the present work was devoted. Based on our limited knowledge, we still suspect that chromosomal HRs in the genome of higher eukaryotes probably have no functions in the traditional in biology sense, and are possibly maintained by natural selection in the genome only owing to a number of important effects they have on the organism. But unlike other known forms of variability (biochemical, immunological, anthropogenetic, morpho-physiological, etc.), chromosomal HRs have no phenotypic manifestations.

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Of course we are far from the idea that the cell thermoregulation is the only effect of chromosomal HRs. It will not be surprising if it turns out that HRs has not one but several important effects on cell functioning in higher eukaryotes.

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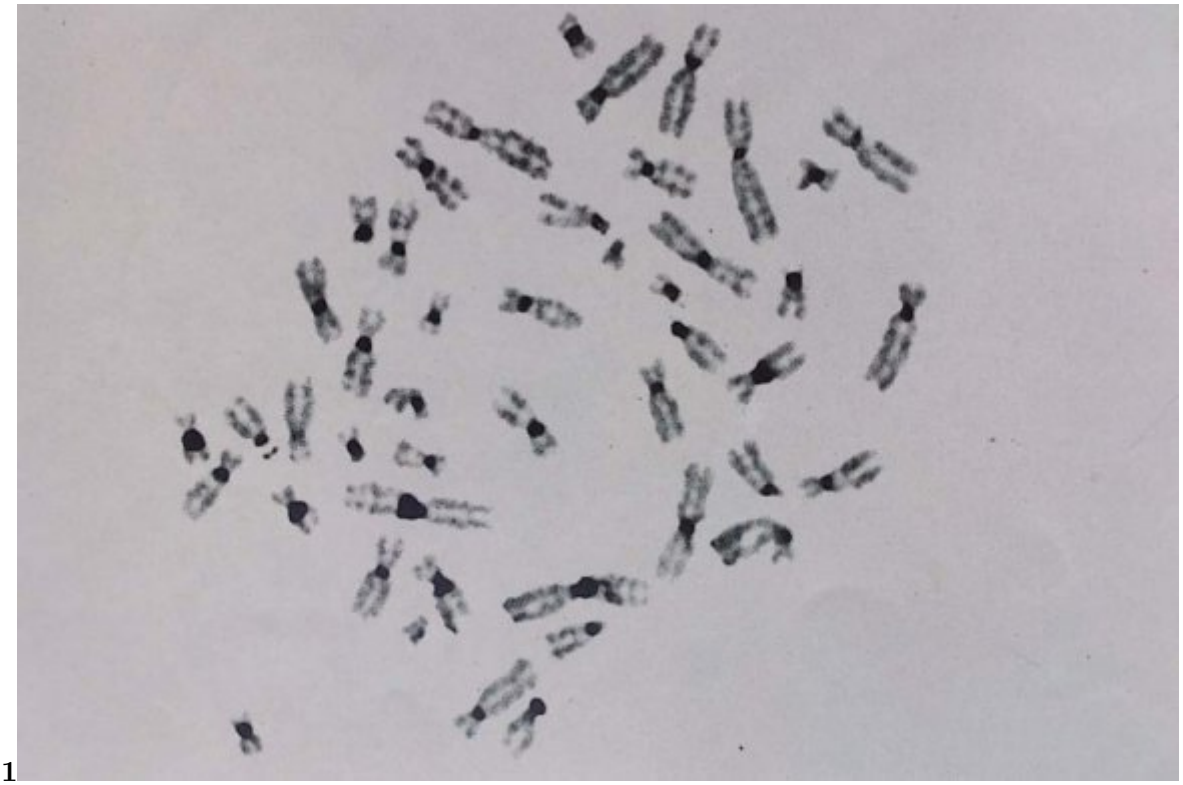
[1]

[1] © 2015 Global Journals Inc. (US) Heterochromatin: The Visible with Many Invisible Effects

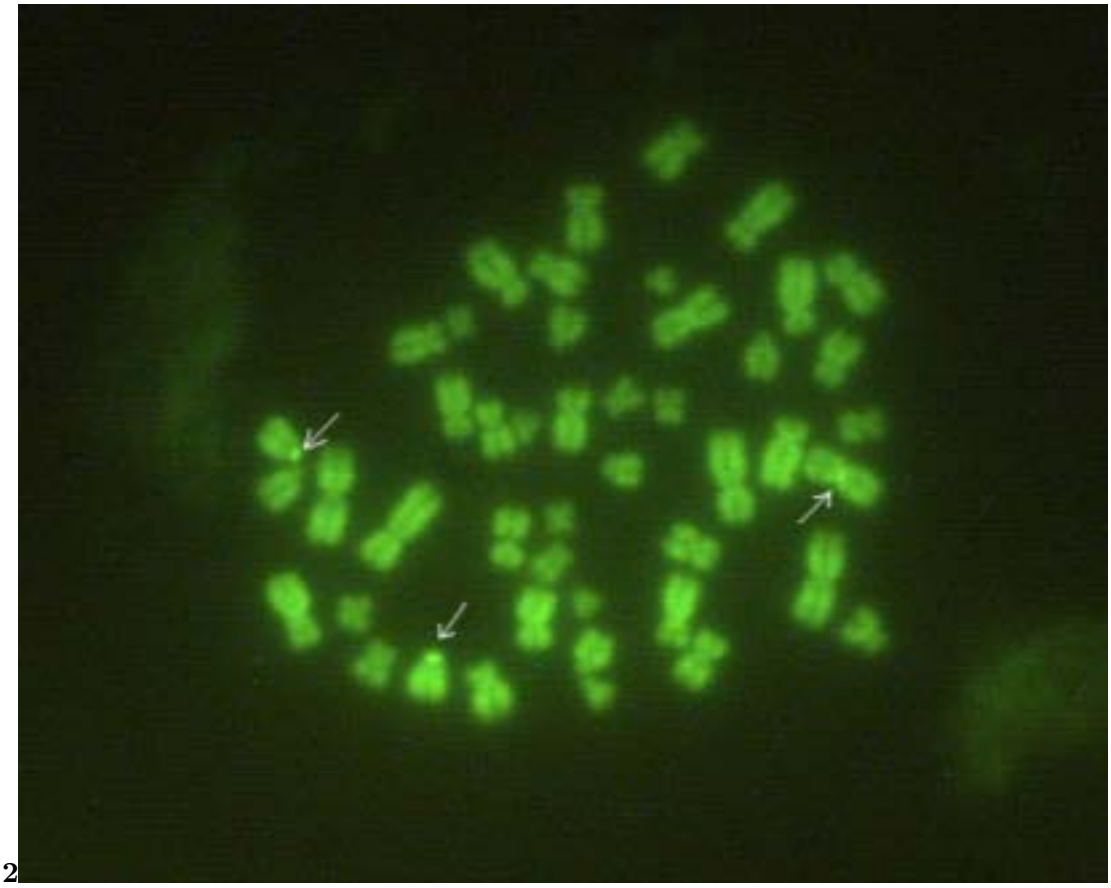
7

Figure 1: 7 Volume



1

Figure 2: Figure 1 :



2

Figure 3: Figure 2 :

Location of Q-HRs	I (n = 520)	II (n = 1122)	III (n = 449)	IV (n = 297)	V (n = 48)	VI (n = 327)
3	358 (0.344)*	759 (0.354)	378 (0.420)	236 (0.397)	53 (0.552)	425 (0.649)
	34.3**	31.0	34.4	22.6	29.8	27.8
4	32 (0.031)	130 (0.058)	29 (0.022)	16 (0.027)	5 (0.052)	18 (0.027)
	3.1	5.0	1.8	1.5	2.8	1.2
13	332 (0.319)	769 (0.343)	379 (0.422)	309 (0.520)	55 (0.573)	573 (0.821)
	31.8	30.0	34.4	29.6	30.9	35.1
14	63 (0.060)	113 (0.059)	69 (0.077)	93 (0.156)	10 (0.104)	112 (0.171)
	6.0	5.2	6.3	8.9	5.6	7.3
15	86 (0.083)	262 (0.117)	86 (0.094)	140 (0.235)	24 (0.250)	147 (0.224)
	8.2	10.2	7.7	13.4	13.5	9.6
21	125 (0.120)	260 (0.116)	105 (0.116)	135 (0.230)	18 (0.188)	155 (0.237)
	12.0	10.1	9.5	13.1	10.1	10.1
22	48 (0.046)	214 (0.095)	64 (0.071)	113 (0.190)	13 (0.135)	136 (0.207)
	4.6	8.3	5.8	10.8	7.3	8.9
Total	1044	2563	1100	1044	178	1530
Mean number of Q-HRs	2.1	2.28	2.45	3.52	3.71	4.68
Statistics			$\chi^2 = 4.769$; df = 5; P = 0.445;			

3

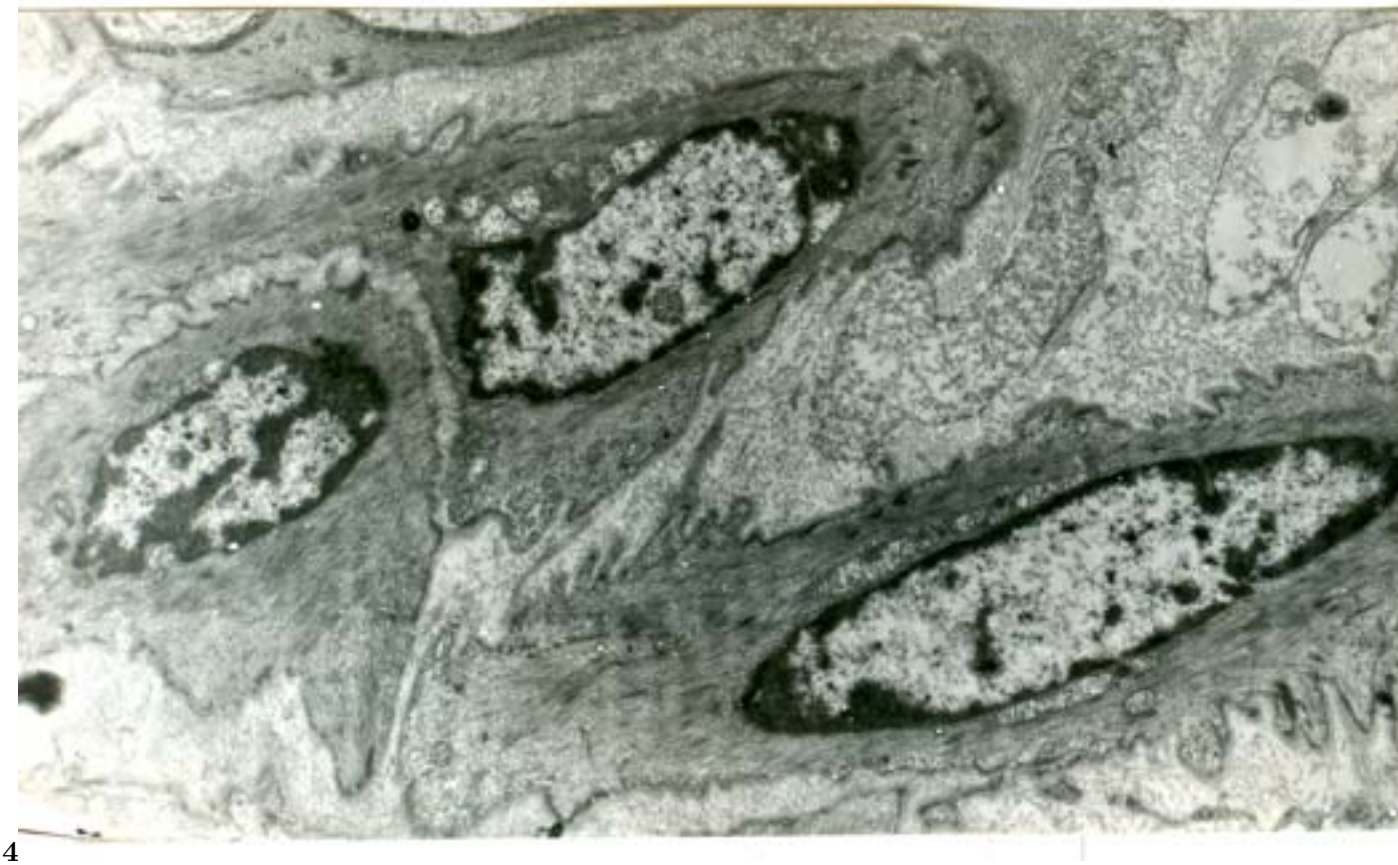
Figure 4: Figure 3 :


1.8 e
2.2 d
1.8 c
1.8 b
2.2 a
2.4 k
3.5 h
3.3 f
3.4 g
2.1 - 2.7 i
3.7 q
4.6 m
3.3 l
4.6 p
4.7 n
4.6 o

Figure 5:

Number of Q-HRs	Large Y ≥ F (n = 53) I	Medium F > Y > G (n = 102) II	Small Y ≤ G (n = 32) III
0	3		
1	5	1	
2	21	12	2
3	11	26	1
4	6	28	10
5	7	22	13
6		10	4
7		3	2
Total	139	406	150
Mean number	2.62	3.98	4.69
Statistics	$t_{I,II} = 6.077$; df = 153;		P =<0.001*
	$t_{II,III} = 2.748$; df = 132;		P = 0.007*
	$t_{I,III} = 7.223$; df = 83;		P =<0.001*

Figure 6:



4

Figure 7: Figure 4 :

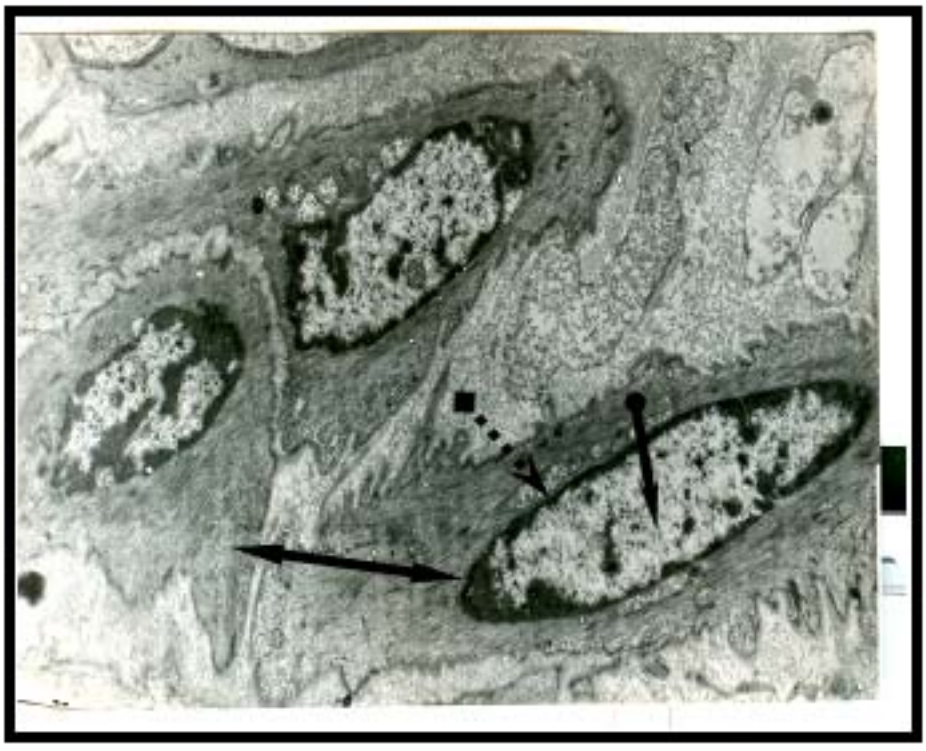


Figure 8:

1

The following consistent data have been obtained:

Figure 9: Table 1 :

3

) [63,64];

Figure 10: Table 3

3

[Note: 15) different age groups have different m values, thegreatest number of Q-HRs is characteristic of neonates, while the lowest -of elderly subjects (Table4)[57,65];]

Figure 11: Table 3 :

4

Heterochromatin: The Visible with Many Invisible Effects

0 1 2 Number of Q-HRs	4 19 23 (n=145)	(n=112)	(n=23) 7 3 20 4 41 11 Kyrgyz I 1 II 2 III 3	4 9 60 (n=389)	Popu (n=2
3 4 5 6 7 8 Total	38 37 16 5 3 458	19 16 7 2 270	2 3 44	85 97 76 38 20 1520	58 60 44 17 7 1 881
Mean number of Q-HRs	3.16	2.41	1.91	3.91	3.69
Statistics	t I, II = 4.01; P = <0.001*		df = 255;	t I, II = 1.808; df =	P = 0.071
	t I, III = 4.58; P = <0.001*		df = 38;	t I, III = 5.068; df =	P =
	t II, III = 1.64; P = >0.100		df = 133;	t II, III = 4.259; df =	P =

1 -Newborns; 2 -18 -25 years; 3 -60 years and older.
* -these differences are statistically significant.

Figure 12: Table 4 :

6

[48]

Number of Q-HRs	Mo (n = 277)	Co (n = 200)
0	46	9
1	81	29
2	100	49
3	39	54
4	9	34
5	2	24
6		4
7		1
Total	444	572
Mean number	1.60 ± 0.06;	2.86 ± 0.10
Statistics	t = 10.40; df = 410; P =<0.0	

Figure 13: Table 6 :

57

borers and controls [49]

Number of Q-HRs	Na (n = 271)	Russian children (n = 113)
I		
0	36	9
1	68	21
2	102	27
3	40	39
4	19	12
5	6	3
6		2
7		
Total		
Mean number 1.84±0.07		
Statistics t I, II = 3.82; t I, III = 0.63; t I, IV = 8.2; t II, III = 2.92; t II, IV = 3.07; t II, IV = 6.40;		
df = 382;	df = 312;	df = 395; df = 154;
P =<0.001* P =>0.50;		

* -these differences are statistically significant.

Figure 14: Table 5 :Table 7 :

8

Heterochromatin: The Visible with Many Invisible Effects

0 Number of Q-HRs	11 (19.6) Obese females 5 (11.4) Kyrghyz (N = 56) Russians (N = 44) I II		2 (2.0) Kyrghyz (N = 100) III	Contr Ru (N IV
1	24 (42.9)	18 (40.9)	11 (11.0)	7 (
2 3 4 5 6 7 Total	19 (33.9) 2 (3.6) 68	19 (43.2) 2 (4.5) 62	32 (32.0) 19 (19.0) 22 (22.0) 11 (11.0) 2 (2.0) 1 (1.0) 294	24 33 31 (1.
Mean number of Q-HRs Statistics	1.21 ± 0.11 t I, II = 1.29; df = 99; P = >0.20; 1.41 ± 0.11 t I, IV = 10.41; df = 144; P =<0.0			

* -these differences are statistically significant.

Figure 15: Table 8 :

9

0	7 (14.5)	10 (17.5)		18 (8.9)	46 (8.3)
1	23 (47.9)	17 (29.8)		37 (18.3)	119 (21.4)
2	12 (25.0)	22 (38.5)	12 (12.0)	72 (35.6)	194 (34.9)
3	6 (12.5)	6 (10.5)	13 (13.0)	35 (17.3)	122 (21.9)
4		2 (3.5)	36 (36.0)	29 (14.4)	57 (10.2)
5			30 (30.0)	9 (4.5)	16 (2.9)
6			9 (9.0)	2 (1.0)	2 (0.4)
Total	65	87	411	459	1193
Mean number of Q-HRs	1.35 ± 0.128	1.53 ± 0.135	4.11 ± 0.113	2.27 ± 0.094	2.15 ± 0.51
Statistics	t I, II = 0,96;	t I, III = 16.17;	t I, IV = 5.79;	t I,V = 5.81;	t II, III = 14.66;
	df = 103;	df = 118;	df = 106;	df =64;	df = 112;
	P > 0.300;	P < 0.001*;	P < 0.001*;	P < 0.001*; P < 0.001*;	
					12;
	df = 118;	df = 611;	df = 232;	df = 143;	df = 328;
	P <0.001*;	P < 0.001*;	P < 0.001*;	P < 0.001*;	P > 0.200

[Note: t II, IV = 4.50; t II, V = 3.76; t III, IV = 12.52; t III, V = 15.81; t IV, V = 1. -these differences are statistically significant.]*

Figure 16: Table 9 :

10

2		14	5	19
3	2	12	9	23
4	5	29	8	42
5	14	7	4	25
6	8	3	1	12
7	3	7		10
8	2	3		5
Total	181	306	95	582
Mean number	5.32 ± 0.206	4.08 ± 0.189	3.51 ± 0.209	4.28
Statistics		t I, II = 3.975; df = 107; P =<0.001;*		
		t II, III = 1.656; df = 100; P =0.101;		
		t I, III = 6.083; df = 59; P =<0.001;*		

*[Note: * -these differences are statistically significant.]*

Figure 17: Table 10 :

11

2		10	9	19
3		12	11	23
4	9	26	7	42
5	9	14	2	25
6	7	4	1	12
7	5	3	2	10
8	2	2	1	5
Total	174	291	117	582
Mean number	5.44 ± 0.220	4.10 ± 0.168	3.54 ± 0.275	4.28
Statistics		t I, II = 4.607; df = 101; P =<0.001;* t II, III = 1.786; df = 102; P = 0.077; t I, III = 5.349; df = 63; P =<0.001;*		

*[Note: * -these differences are statistically significant.]*

Figure 18: Table 11 :

12

2		10	9	19
3	4	10	9	23
4	6	31	5	42
5	10	10	5	25
6	12			12
7	6	4		10
8	5			5
Total	240	252	90	582
Mean number	5.58 ± 0.198	3.87 ± 0.151	3.21 ± 0.208	4.28
Statistics		t		

[Note: I, II = 6.591; df = 106; P =<0.001 t II, III = 2.474; df = 91; P = 0.015* t I, III = 7.356; df = 69; P =<0.001* * -these differences are statistically significant.]*

Figure 19: Table 12 :

13

2	5	14		19
3	6	17		23
4	16	23	3	42
5	7	7	11	25
6	2	5	5	12
7		6	4	10
8		2	3	5
Total	139	294	149	582
Mean number	3.86 ± 0.179	3.97 ± 0.185	5.73 ± 0.239	4.28
Statistics		t I, II = 0.380; df = 108; P = 0.704; t II, III = 5.111; df = 98; P = <0.001* t I,III = 6.395; df = 60; P = <0.001*		

*[Note: * -these differences are statistically significant.]*

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