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Helicobacter Pylori Vaccine

Antiperspirant Aluminum Chloride

Highlights

Prevalence of Beta-Lactamase

Adverse Histopathological Effects

Discovering Thoughts, Inventing Future

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Adverse Histopathological Effects of Antiperspirant Aluminum Chloride on Skin

By Dr. Mubeen Khan, Dr. Ashfaq Ul Hassan, Dr. Rohul Afza, Dr. Sangeeta Gupta, Dr. Manmeet kour & Dr. Rajinder kumar

SKIMS, India

Abstract- The antiperspirating agents are the daily household products used globally by both the genders to minimize excessive sweating. Approximately about 90% of U.S population regularly uses antiperspirants. The most consistently used components since the commercial introduction of antiperspirants in 1903 are the aluminium salts.

Aluminium chloride is used as a catalyst in the process of Friedel Crafts. It is a salt of aluminium and chloride. It is widely used in the manufacturing of many petrochemicals, in the manufacturing pharmaceuticals, dyes intermediates and other organic chemicals, in the production of rubber; lubricants and wood preservatives, and in cosmetics as an astringent; active ingredient in antiperspirants.

Keywords: *dermis, follicle, keratin, glands, almunium chloride.*

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Adverse Histopathological Effects of Antiperspirant Aluminum Chloride on Skin

Dr. Mubeen Khan [α], Dr. Ashfaq Ul Hassan[σ], Dr. Rohul Afza [ρ], Dr. Sangeeta Gupta [ω], Dr. Manmeet kour [¥] & Dr. Rajinder kumar [§]

Abstract- The antiperspirating agents are the daily household products used globally by both the genders to minimize excessive sweating. Approximately about 90% of U.S population regularly uses antiperspirants. The most consistently used components since the commercial introduction of antiperspirants in 1903 are the aluminium salts.[1]

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Keywords: dermis, follicle, keratin, glands, almunium chloride.

I. Introduction

The use of chemicals is a wide spread practice worldwide for enhancing and improving lifestyle. But along the benefits of these products there is also the potential for adverse effects to the people and the environment.[4] It has been seen that daily transdermal exposure over long periods of time of metal containing compounds in personal care products has raised some health concern.[5-7]

The global cosmetic and skin care industry is a highly profitable market worldwide that is concerned with utilization of raw materials, product testing, sophisticated laboratory equipment and new technology testing that is said to focus within the safe limit parameters of cosmetics and toiletries usage development. As such, these cosmetic giant companies spend lavishly more on TV advertising than any other commercial enterprise. Consumers are introduced and used in various cosmetics and personal care products without full disclosure on its package labeling. The average person is misled to believe that such product ingredients have been adequately tested and are safe for public usage. Ironically, this is far from accurate.[8] Moreover, males and females individuals, from infancy to old age utilize a huge multivariate variety of shampoos, body soaps antiperspirants and skin creams preparations, some with no known peer knowledge or concern of the preparation's hazardous potential.

Thorough scanning of the available literature revealed, dearth of literature regarding the gross and histological effects of aluminium salts (aluminium nitrate and aluminium chloride) on skin. Therefore a curious desire developed to conduct evidence based study of the effects of aluminium chloride on the skin of mammal, the albino rabbit.

II. Materials and Methods

The present study was carried out on twenty four inbred adult albino rabbits. The numbers of animals used and procedures to minimize the suffering of the animals are in accordance with ethics committee on animal experiments of Government medical college Jammu. IEC no. pharma/2012/2818.The rabbits were procured from the Central Animal House of Government Medical College, Jammu. Animals were housed in with dust free rice husk as bedding material under laboratory conditions with controlled environment of temperature of 25±2℃, humidity (16% ± 10%) and 12 hours light/dark cycle (16- 18) as per committee for the purpose of control and supervision of experiment on animals (CPCSEA), Indian guidelines. They were provided standard feed and water ad libitum, before subjecting them for experimentation, animals were given a week's time to acclimatize with laboratory conditions.

The animals were divided into following three main groups (A, B and C) as follows:

Group A: Experimental group - 12 animals
Group B: Control group - 12 animals

These groups were further subdivided into group A1, A2, B1 and B2, containing 6 animals each.

Group A1 received 10% aluminium chloride.
Group A2 received 20% aluminium chloride.
Group B received distilled water.

Group B1 animals were taken as control for group A1 animals. Group B2 animals were taken as control for group A2 animals.

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About 2cm× 2cm area of skin on posterior surface of each ear of each rabbit was used as test areas. The test areas were shaved 24 hours prior to application of drug. Powdered form (98% purity) of aluminium nitrate and aluminium chloride was used. Solutions were prepared in distilled water at 10% and 20% concentrations daily before application.

0.5ml of solution was applied daily with the help of a clean glass rod to the test areas on experimental animals. After application, each experimental animal was kept in individual cages until the applied solution dried up at ordinary room temperature and atmosphere. Procedure was repeated daily for next fifteen days whereas only distilled water was applied to the control groups. On day sixteenth of the treatment right sided test areas of all groups were first examined using a hand lens. Then after proper local anesthesia with 1ml of 2% xylocaine subcutaneously, 1cm^2 of the test areas were excised under proper aseptic conditions. The wounds left were properly cared for with povidine iodine till complete healing. Povidine iodine was applied twice a day locally on the wound. Left sided test areas were kept without treatment for next 30 days, on 46th day these test areas were first grossly examined using a hand lens and then 1cm^2 of the test areas were excised after proper local anesthesia again using 1ml of 2% xylocaine subcutaneously and wounds were taken care of with povidine iodine applied locally twice a day till they healed completely. The macroscopic or gross changes of the skin were seen with the help of hand lens while the histological changes were observed after the tissues were chemically fixed in neutral buffered formalin solution and later processed. Five-micron thick sections were sectioned and stained with Harris's Haematoxylin and eosin stain.

III. Observations

With low and high (10% and 20%) concentration aluminium chloride after 15 days of treatment: - Hyperplasia of epidermis along with hypertrophy of stratum corneum and intercellular oedema in epidermis was observed. Skin treated with 20% Aluminium nitrate showed marked no. of cysts filled with keratin along with epidermal erosions . Dermal oedema, widening of dermal papillae as well as vascularization in dermis was marked with aluminium nitrate 20% as compared to that with aluminium chloride 20%. There was decrease in number of hair follicles, sweat glands and sebaceous glands but increase in number of inflammatory cells and fibroblasts was observed

With low and high concentration of aluminium chloride after one month of stoppage of treatment:-

Slight hyperplasia of epidermis and slight hypertrophy of stratum corneum persisted .Dermis showed slight oedema. Hair follicles, sweat glands and sebaceous glands showed slight increase in number with decrease in number of fibroblasts and inflammatory cells `

IV. Discussion

The aim of the present study was to evaluate if there are any changes in the skin after use of antiperspirants. The results of present study compares favorably with previous studies.

Findings in epidermis with 10% aluminium chloride are consistent with the findings of the Lansdown[9], Nasir et al.[10] After one month of stoppage of treatment with 10% aluminium chloride the epidermal changes reverted back to normal skin in the present study. Similar results have also been reported by Nasir et al.[11]

The epidermis showed marked hypertrophy of stratum corneum and hyperplasia of epidermis along with marked intercellular oedema and keratin cysts in the present study after 15 days of treatment with 20% aluminium chloride. These findings are almost in accordance with the findings of Lansdown[9], Nasir et al.[11]

After one month of stoppage of treatment with aluminium chloride 20% the changes reverted back to normal with almost complete reversion. Similar changes were also demonstrated by Nasir et al.[11]

In the present study the dermis showed slight oedema and vascularization, few hair follicles and fibroblasts along with inflammatory cells, rare sweat and sebaceous glands after 15 days of treatment with 10% aluminium chloride whereas dermis showed moderate oedema, vascularization, inflammatory cells, slight fibroblasts and rare sweat and sebaceous glands after 15 days of treatment with 20% aluminium chloride. In addition dermal papillae were elongated and widened. After one month of stoppage of treatment with 10% aluminium chloride and 20% aluminium chloride findings were moderate hair follicles, however sweat and sebaceous glands, vascularization and fibroblast were slight. But there is no literature available to compare these findings.

V. Conclusion

The detailed study showing effects of Aluminium chloride (the antiperspirant) was conducted and the observations were noted, critically analyzed and discussed with the findings of previous workers and hence it was concluded that maintenance of a healthy life style is crucial in daily well being. The antiperspirants containing aluminium chloride even in low dose concentrations, may still cause well defined histological damage to the skin and its appendages, especially after a prolong time period of continuous application but the changes almost reverted back to normal after one month of stoppage of application. And

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if the duration of application is further continued permanent histological changes are eminent.

Table : Epidermal changes in the skin as treated with Aluminium Chloride

	Control	After 15 Days of Treatment		After One Month of Stoppage of Treatment	
Different Histological Findings		Aluminium Chloride 10%	Aluminium Chloride 20%	Aluminium Chloride 10%	Aluminium Chloride 20%
Hypertrophy of Stratum Corneum	Nil	Moderate	Marked	Slight	Slight
Hyperplasia of Epidermis	Nil	Moderate	Marked	Nil	Nil
Intercellular Oedema	Nil	Moderate	Marked	Nil	Nil
Cysts filled with Keratin	Nil	Slight	Slight	Nil	Nil
Erosion of Epidermis	Nil	Nil	Nil	Nil	Nil

Table : Dermal changes in the skin treated with Aluminium Chloride.

Changes		After 15 Days of Treatment		After One Month of Stopping of Treatment	
	Control	Aluminium Chloride 10%	Aluminium Chloride 20%	Aluminium Chloride 10%	Aluminium Chloride 20%
Oedema	Nil	Slight	Moderate	Rare	Rare
Vascularization	Nil	Slight	Moderate	Slight	Slight
Inflammatory cells	Nil	Slight	Moderate	Rare	Rare
Fibroblasts	Slight	Slight	Moderate	Slight	Slight
Hair follicles	Moderate	Slight	Slight	Moderate	Moderate
Sebaceous glands	Slight	Rare	Rare	Slight	Slight
Sweat glands	Slight	Rare	Rare	Slight	Slight

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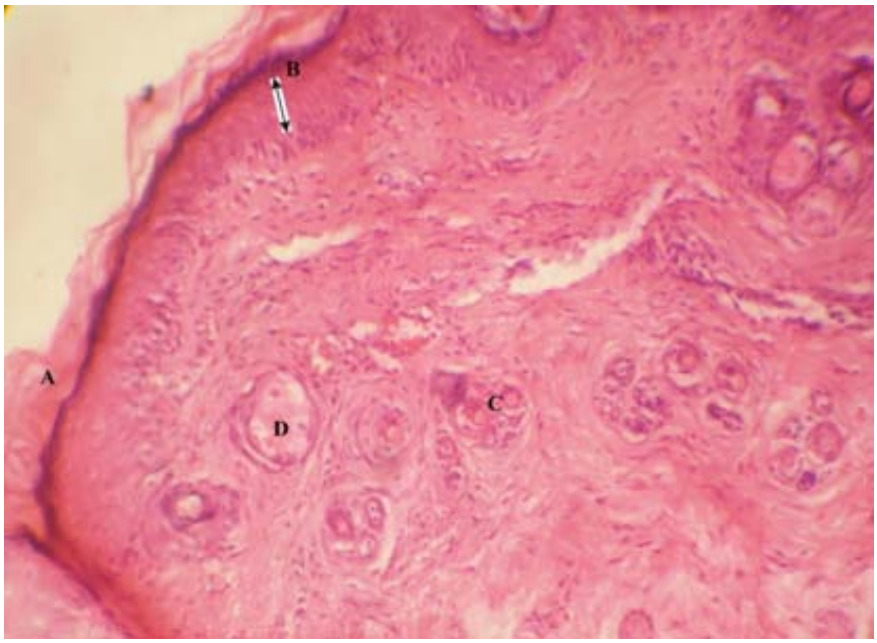


Figure 1: Photomicrograph of longitudinal section of right ear skin of Albino rabbit after 15 days of treatment with 10 % Aluminum chloride showing hypertrophy of Stratum Corneum(A), Epidermal hyperplasia(B), Sweat Glands(C) and Sebaceous Glands(D) (H & E Stain 200X)

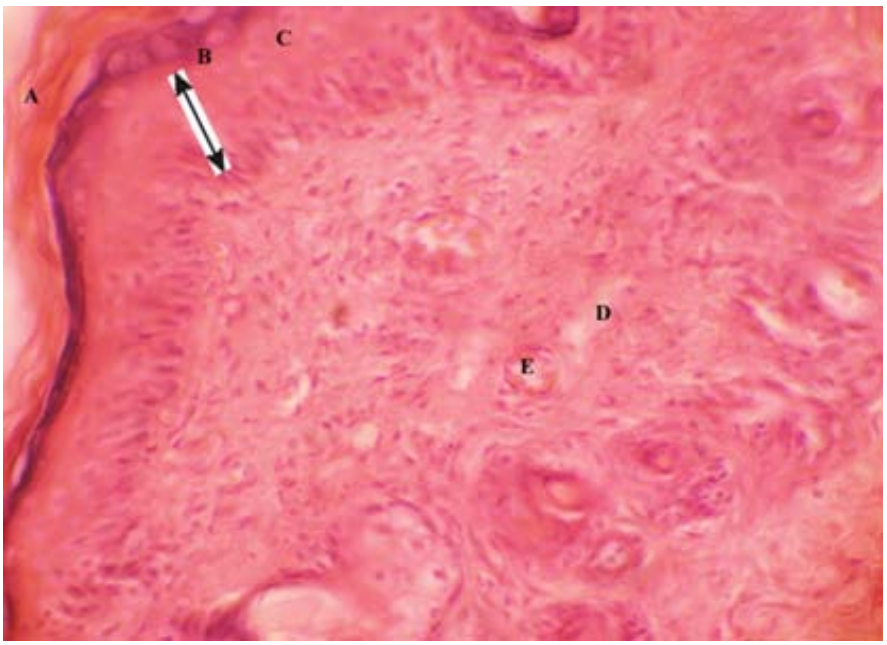


Figure 2 : Photomicrograph of longitudinal section of right ear skin of Albino rabbit after 15 days of treatment with 10 % Aluminum chloride showing hypertrophy of Stratum Corneum(A), Epidermal hyperplasia (B), intercellular edema in Epidermis (C), Dermal Edema (D) and Vascularization (E) (H & E Stain 200X)

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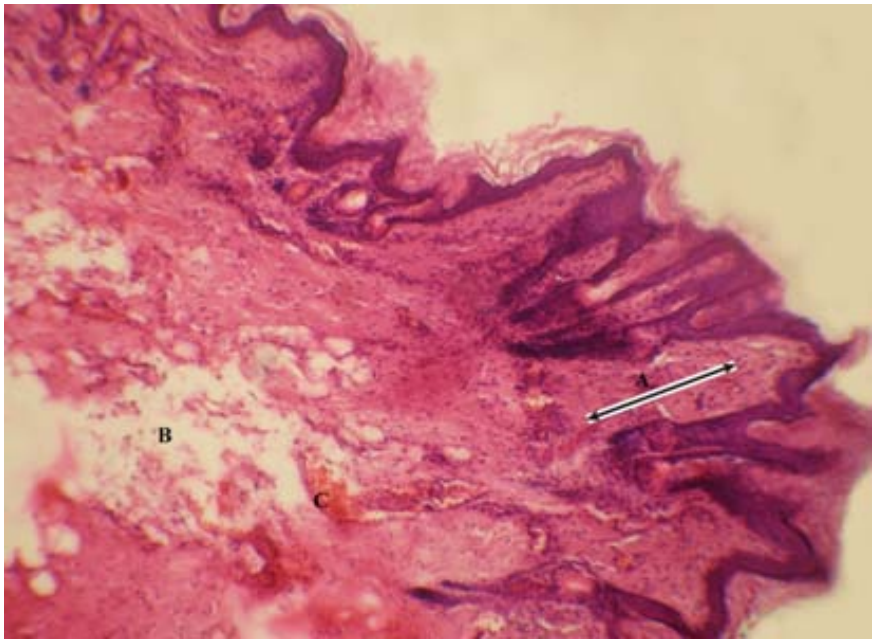


Figure 3 : Photomicrograph of longitudinal section of right ear skin of Albino rabbit after 15 days of treatment with 20 % Aluminum chloride showing elongation of dermal papillae(A), Dermal Edema(B) and Vascularization(C) (H & E Stain 100X)

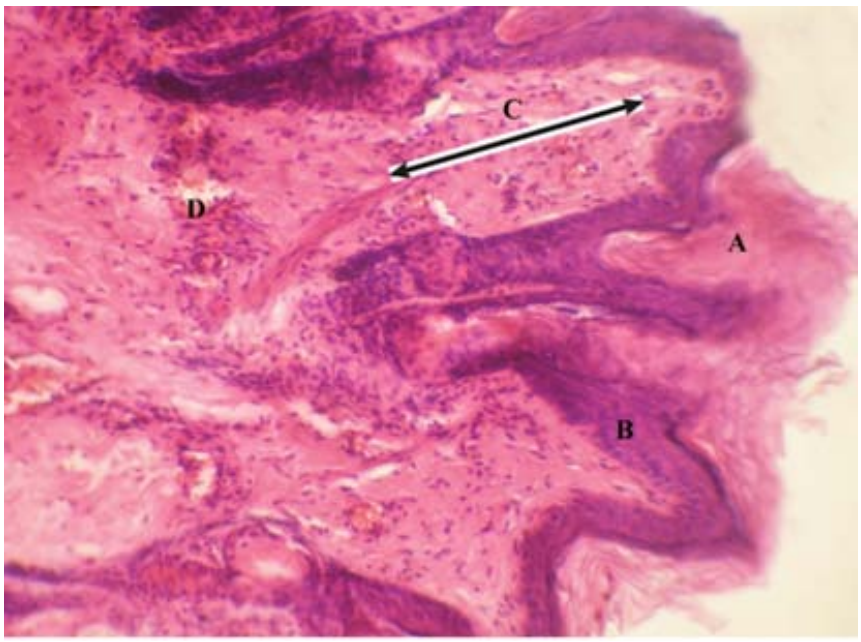


Figure 4 : Photomicrograph of longitudinal section of right ear skin of Albino rabbit after 15 days of treatment with 20 % Aluminum chloride showing hypertrophy of Stratum Corneum(A), hyperplasia of Epidermis(B), elongation of dermal papillae (C)) and Vascularization(D) (H & E Stain 200X)

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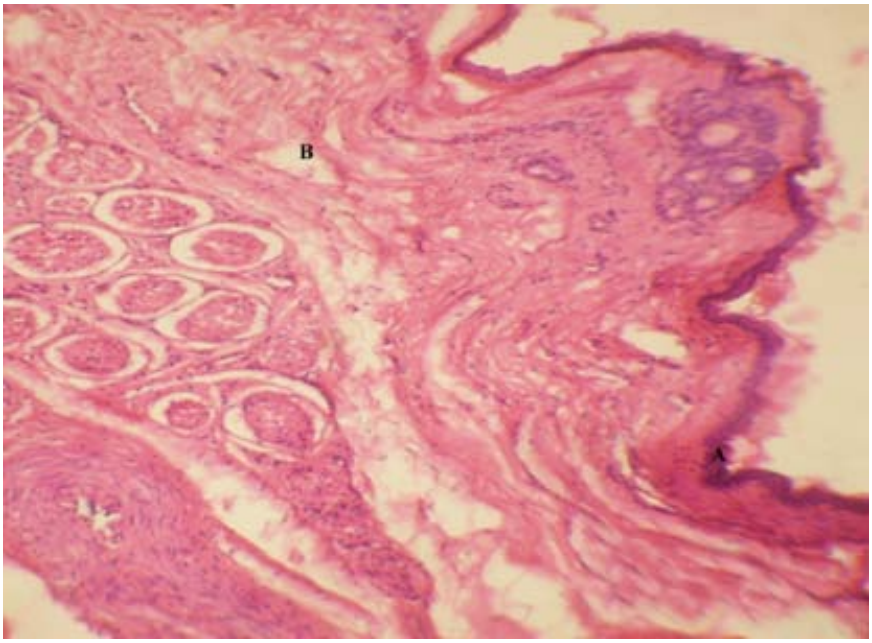


Figure 5 : Photomicrograph of longitudinal section of right ear skin of Albino rabbit after 15 days of treatment with 20 % Aluminum chloride showing slight Epidermal hyperplasia (A) and Dermal Edema(B) (H & E Stain 100X)

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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.

Keywords: heterochromatin, Q-heterochromatin, C-heterochromatin, condensed chromatin, cell thermoregulation, human body heat conductivity.

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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-and-geographic 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.

Keywords: heterochromatin, Q-heterochromatin, C-heterochromatin, condensed chromatin, cell thermoregulation, human body heat conductivity.

I. Introduction

Though 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.

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.

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 [1-4]. 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 C–heterochromatin [5-8]. 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 Q-heterochromatin are defined by a single term, "constitutive heterochromatin", they are undoubtedly significantly different intrachromosomal structures [Fig. 1 and 2].

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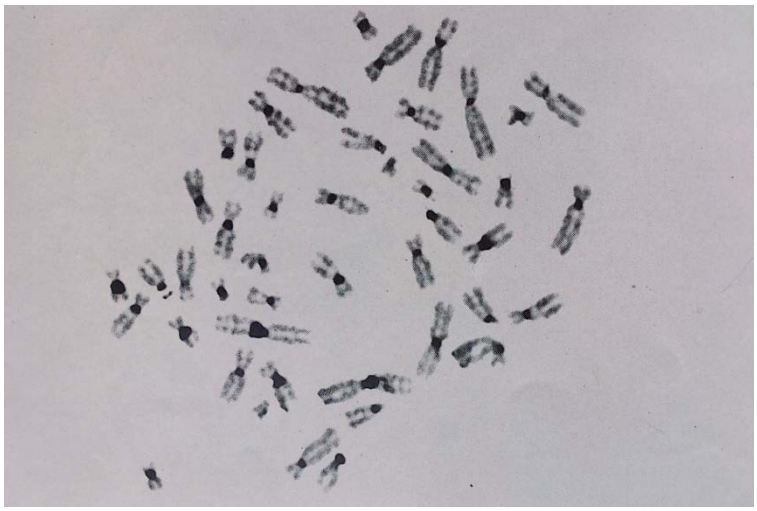


Figure 1 : Chromosomal C-heterochromatin regions (C-HRs) of the human karyotype after C-staining. C-HRs (dark bands) is located on all human chromosomes.

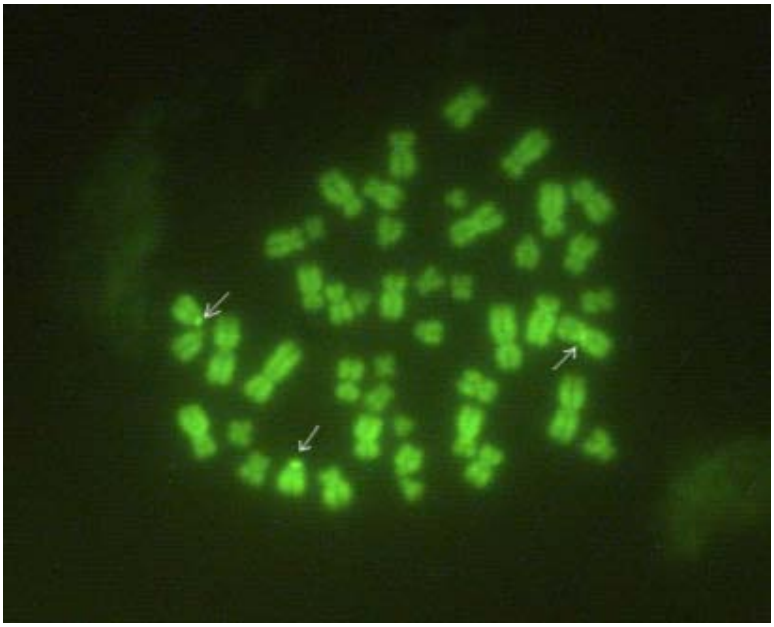


Figure 2 : Q-heterochromatin regions (Q-HRs) of the human chromosomes after Q-staining. Q-HRs of large sizes and 5th degree intensity of fluorescence on the short arms of both chromosomes 13 and Q-HR of medium size and 5th degree of fluorescence intensity in the pericentric region of chromosome 3.

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 [8,10-14]. Individuals differ in the number, location, size, and intensity of staining (fluorescence) of these specific chromosomal regions [8,15,16].

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 C-band homeomorphisms... From interpopulation comparisons, C-band means show a tendency to maintain a constant amount of constitutive heterochromatin".

III. 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

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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, Mikloś [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 [25-31]. 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 non-homologous 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.

Gershenson [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 crossing-over.

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

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adaptive nature, providing them with quick adaptation to changing environmental conditions [40-42].

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.

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 [11-13]. 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 ($Y \geq F$), (b) medium ($F>Y>G$), and (c) small ($Y \leq G$) [44].

The following consistent data have been obtained:

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 Q-variants 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 [44-46]. 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 [47-52] (Table 1);

Table 1 : Distribution and mean number of chromosomal Q-HRs per individual in certain samples of individuals of Eurasia and Africa [53]

Number of Q-HRs	I	II	III	IV	V	VI	VII
0	57	58	94	24	10	1	0
1	116	123	221	80	13	1	1
2	141	175	363	141	51	11	21
3	56	99	242	111	85	8	54
4	13	51	137	65	58	13	78
5	2	14	50	23	49	9	79
6			13	5	24	2	55
7			2		3	2	29
8					4	1	6
9							3
10							1
Mean number of Q-HR	1.63	2.01	2.28	2.44	3.52	3.71	4.68

I – mountaineers (n=385); II – northern Mongoloids (n=520); III – highland Mongoloids (n=1122); IV – Russians in Kyrghyzstan (n=449); V – steppe Mongoloids (n=297); VI – Indians of northern India (n=48); VII – lowland Negroids (n=327).

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4) 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 2) [54];

Table 2 : Chromosomal Q-HRs frequencies in seven Q-polymorphic autosomes in native populations of Eurasia and Africa [55].

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;					

*n = sample size; * – Q-HRs frequency from the number of chromosomes analyzed;*
*** – Q-HRs frequency as percentage of the overall number of chromosomal Q-HRs;*
I – Northern Mongoloids of Siberia; II – Highland Mongoloids of Pamir and Tien Shan; II – Steppe Mongoloids of Central Asia; IV – Russians; V – Indians of Northern India; VI – Lowland Negroids of subequatorial Africa.

5) human populations do not differ from each other in the relative content of Q-HRs on seven autosomes (see Table 2) [54-56];
6) the amount of Q-HRs in the genome is best determined by the value of their mean number per individual in a population (*m*) [44,47-52,57-59];
7) decreases or increases in *m* are due to simultaneous but proportional decreases or increases in the absolute number of Q-HRs on all the seven Q-polymorphic autosomes (see Table 2) [47-50,52,54];
8) consistent interpopulation differences in the quantitative content of Q-HRs in their genome were established [51,52,57-62];
9) these differences proved to be related to features of the ecological environment of the place of permanent residence, and not to racial and ethnic composition of the population (Figure 3) [44,47-52,57-59,122];

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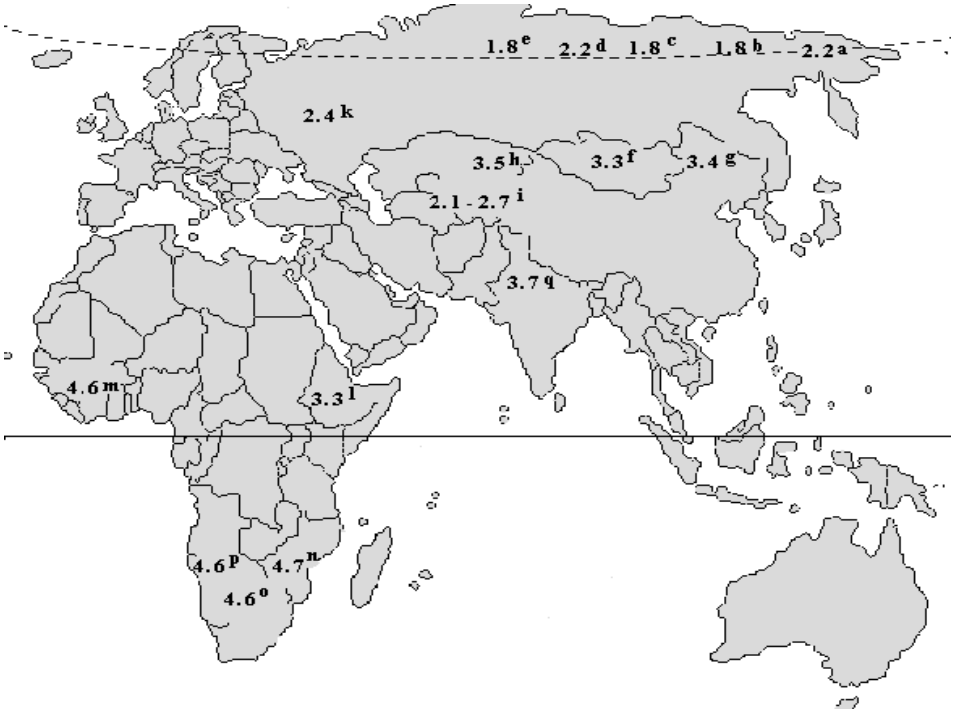


Figure 3 : The mean number of Q-HRs per individual in the native populations of Eurasia and Africa (Reproduced from Ibraimov, 2003, with permission of the publisher): a = Chukchi of Chukotsk (n = 132); b = Yakuts of Yakut ASSR (n = 127); c = Selkups of eastern Siberia (n = 90); d = Nenets of eastern Siberia (n = 117); e = Khants of eastern Siberia (n = 54); f = Mongolians of the MPR (n = 72); g = Chinese of northern China (n = 124); h = Kazakhs of southern Kazakhstan (n = 101); i = Kirghiz of Pamir and Tien Shan (n = 603); k = Russians of Bishkek (n = 200); l = Ethiopians of Ethiopian uplands (n = 52); m = Guinea-Bissau Negroes (n = 13); n = Mozambique Negroes (n = 148); o = Zimbabwe Negroes (n = 34); p = Angola Negroes (n = 132); q = Indians of northern India (n = 58).

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 [47-52, 59] (see Fig. 3);
11) the presence of individuals in the population with different numbers of Q-HRs in the karyotype (from 0 to 10) is due to the fact that Q-HRs are unevenly distributed on seven potentially Q-polymorphic autosomes (see Table 2) [54];
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 (Table 3) [63,64];

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Table 3 : Distribution of the numbers and mean number of autosomal Q-HRs in males with Y chromosomes of various sizes [63].

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*		

15) different age groups have different *m* values, the greatest number of Q-HRs is characteristic of neonates, while the lowest – of elderly subjects (Table 4) [57,65];

Table 4 : Distribution of the numbers and mean number of chromosomal Q-HRs in Kyrgyz, Kazakh and Russian samples in various age groups [65,83]

Number of Q-HRs	Populations								
	Kyrgyz			Kazakhs			Russians		
	(n=145) I [1]	(n=112) II [2]	(n=23) III [3]	(n=389) I [1]	(n=239) II [2]	(n=33) III [3]	(n=83) I [1]	(n=60) II [2]	(n=80) III [3]
0	4	7	3	4		2	1		4
1	19	20	4	9	16	5	4	4	6
2	23	41	11	60	36	7	9	7	28
3	38	19	2	85	58	12	14	14	23
4	37	16	3	97	60	6	30	17	14
5	16	7		76	44	1	16	13	5
6	5	2		38	17		6	4	
7	3			20	7		3	1	
8					1				
Total	458	270	44	1520	881	84	321	224	212
Mean number of Q-HRs	3.16	2.41	1.91	3.91	3.69	2.55	3.87	3.73	2.65
Statistics	$t_{I, II} = 4.01$; df = 255; P = <0.001*			$t_{I, II} = 1.808$; df = 6.26; P = 0.071			$t_{I, II} = 0.502$; df = 141; P = 0.575		
	$t_{I, III} = 4.58$; df = 38; P = <0.001*			$t_{I, III} = 5.068$; df = 420; P = <0.001*			$t_{I, III} = 5.895$; df = 161; P = <0.001*		
	$t_{II, III} = 1.64$; df = 133; P = >0.100			$t_{II, III} = 4.259$; df = 270; P = <0.001*			$t_{II, III} = 4.980$; df = 138; P = <0.001*		

[1] – *Newborns;* [2] – *18 – 25 years;* [3] – *60 years and older.*

* – *these differences are statistically significant.*

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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 5) [66].

Table 5 : Distribution of the numbers and mean number of chromosomal Q-HRs in newborns and deceased babies [66]

	Kyrgyz		Russians	
Number of Q-HRs	Newborns I (n=145)	Deceased II (n=17)	Newborns III (n=37)	Deceased IV (n=5)
0	4			
1	19		3	
2	23		7	
3	38		5	
4	37	9	12	2
5	16	5	7	2
6	5	3	3	1
7	3			
Total	458	79	133	24
Mean number of Q-HRs	3.16±0.13	4.58±0.23	3.59±0.23	4.8±0.37

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 7) are characterized by extremely low amounts of Q-HRs in their genome [47-49];

Table 6 : Distribution and mean number of chromosomal Q-HRs in mountaineers and control (Russian nationality) [48]

Number of Q-HRs	Mountaineers (n = 277)	Control (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 =<0.001	

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Table 7 : Distribution and mean number of chromosomal Q-HRs in natives of Far East Siberia, Russian children, oil-borers and controls [49]

Number of Q-HRs	Natives (n = 271) I	Russian children (n = 113) II	Oil-borers (n = 43) III	Control (n = 200) IV
0	36	9	4	9
1	68	21	13	25
2	102	27	19	49
3	40	39	5	54
4	19	12	2	34
5	6	3		24
6		2		4
7				1
Total	498	267	74	572
Mean number	1.84±0.07	2.36±0.12	1.72±0.15	2.86±0.10
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; df = 311; df = 89; P =<0.001* P =>0.50; P =<0.001* P =<0.01* P =<0.01* P =<0.001*			

** – these differences are statistically significant.*

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);

Table 8 : Distribution and mean number of Q-HR per individual in groups of obese females and in control samples

Number of Q-HRs	Obese females		Controls	
	Kyrghyz (N = 56)	Russians (N = 44)	Kyrghyz (N = 100)	Russians (N = 100
	I	II	III	IV
0	11 (19.6)	5 (11.4)	2 (2.0)	4 (4.0)
1	24 (42.9)	18 (40.9)	11 (11.0)	7 (7.0)
2	19 (33.9)	19 (43.2)	32 (32.0)	24 (24.0)
3	2 (3.6)	2 (4.5)	19 (19.0)	33 (33.0)
4			22 (22.0)	31 (31.0)
5			11 (11.0)	1 (1.0)
6			2 (2.0)	
7			1 (1.0)	
Total	68	62	294	283
Mean number of Q-HRs	1.21 ± 0.11	1.41 ± 0.11	2.94 ± 0.14	2.83 ± 0.11
Statistics	$t_{I, II} = 1.29$; df = 99; P = >0.20; $t_{I, III} = 9.72$; df = 156; P =<0.001*; $t_{I, IV} = 10.41$; df = 144; P =<0.001*; $t_{II, IV} = 9.13$; df = 123; P=<0.001*; $t_{III, IV} = 0.62$; df = 189; P =>0.50;			

** – these differences are statistically significant.*

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Table 9 : Distribution and mean number of Q-HRs per individual in alcoholics, drug addicts and controls

Number of Q-HRs	Alcoholics		Drug addicts	Controls	
	Kyrghyz (n = 48)	Russians (n = 57)	(n = 100)	Kyrghyz (n = 202)	Russians (n = 556)
	I	II	III	IV	V
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; df = 103; P > 0.300;	$t_{I, III}$ = 16.17; df = 118; P < 0.001*;	$t_{I, IV}$ = 5.79; df = 106; P < 0.001*;	$t_{I,V}$ = 5.81; df =64; P < 0.001*;	$t_{II, III}$ = 14.66; df = 112; P < 0.001*;
	$t_{II, IV}$ = 4.50; df = 118; P <0.001*;	$t_{II, V}$ = 3.76; df = 611; P < 0.001*;	$t_{III, IV}$ = 12.52; df = 232; P < 0.001*;	$t_{III, V}$ = 15.81; df = 143; P < 0.001*;	$t_{IV, V}$ = 1.12; df = 328; P > 0.200

* – *these differences are statistically significant.*

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 Q-heterochromatin [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".

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 are the following: (1) HRs are fixed by evolution in the genome of all higher eukaryotes; (2) HRs are in a condensed condition during the whole of a cell cycle; (3) they are organized, as a rule, from short, nontranscribed, tandemly jointed, highly repetitive DNA (hrDNA) sequences; as now established, HRs can consist not only of satellite sequences (satDNA); (4)

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HRs are located in centric and telomere chromosomal domains, as well as in the regions forming nucleolus-organizing regions; (5) HRs are replicated at the end of the S period of a cell cycle; and (6) a wide variability in the quantitative contents within and between species.

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).

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 [6,19,25,72-75] (Figure 4).

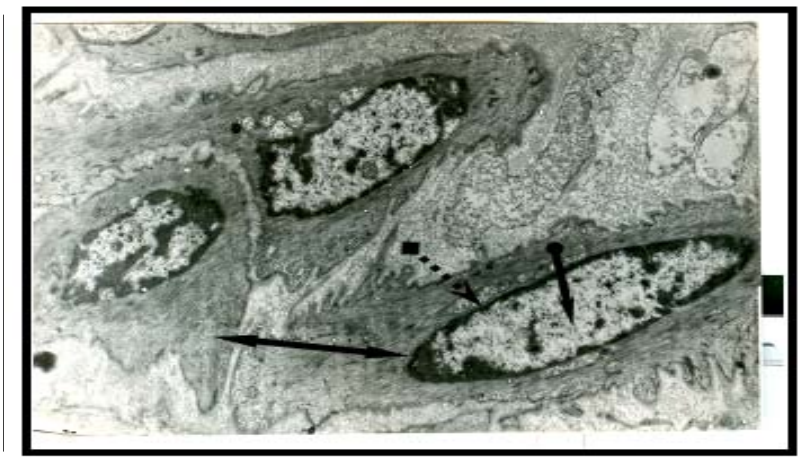


Figure 4 : Electron micrograph of smooth muscle cell of a bull (x 8000). In nuclei can be seen condensed chromatin (heterochromatin) and decondensed chromatin (euchromatin)

◆·····➤ peripheric layer of condensed chromatin; ●——➤ euchromatin; ◄——►cytoplasm

(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 [77].

(3) The amount of DNA per cell was found to bear no relation to the degree of evolutionary complexity ('C value paradox'). Redundant DNA of most eukaryotic organisms is complexed with proteins in highly compact structures designated as CC. Heterochromatins are a particular case of the differential packaging of the chromosome [78].

(4) Euchromatin and heterochromatin differ significantly in the levels of organization that are found during the interphase period. The majority of the euchromatin loses mitotic ultrastructural organization above the level of chromatin loops. On the other hand, heterochromatin retains all the hierarchies of folding present during metaphase, although in a more relaxed state. During interphase the centromeric heterochromatin remains compact and frequently several centromeric regions are associated together, forming chromocenters [78].

(5) More direct evidence for a close association of interphase chromatin with the nuclear membrane has recently been demonstrated in unfixed nuclei [79].

(6) The centromeres of chromosomes with nucleolus-organizing regions consistently associated with

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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.

(7) 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 – Q-heterochromatin – appeared at a later stage of evolution of the animals in the ancestors of three higher primates (*Homo sapiens, Pan troglodytes, Gorilla gorilla*) [8-10].

(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];

(11) 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 Q-heterochromatin, 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 so-called '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.

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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 non-living 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.

Table 10 : Distribution of the numbers and mean number of chromosomal Q-HRs and time of occurrence of the peak temperature on the surface of the right palm [84]

Number of Q-HR	1 to 5 minutes (n = 34) I	6 to 10 minutes (n = 75) II	11 mts and over (n = 27) III	Total (n = 136)
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;*			

* – *these differences are statistically significant.*

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].

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Table 11 : Distribution of the numbers and mean number of chromosomal Q-HRs and the temperature difference between the surfaces of the right palm and the oral cavity [84]

Number of Q-HR	0.1 °C to 1.0 °C (n = 32) I	1.0 °C to 2.0 °C (n = 71) II	2.1 °C to 3.0 °C (n = 33) III	Total (n = 136)
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;*			

** – these differences are statistically significant.*

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.

Table 12 : Distribution of the numbers and mean number of chromosomal Q-HRs and temperature amount of the right palm at the moment the peak temperature occurrence [84]

Number of Q-HR	0.1 °C to 1.0 °C (n = 43) I	1.0 °C to 2.0 °C (n = 65) II	2.1 °C to 3.0 °C (n = 28) III	Total (n = 136)
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	$t_{I, II} = 6.591$; 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.*

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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.

Table 13 : Distribution of the numbers and mean number of chromosomal Q-HRs and the temperature of the surface of the right palm [84]

Number of Q-HR	Below 35.0 °C (n = 36) I	35.1°C to 36.0°C (n =74) II	36.1°C and over (n = 26) III	Total (n = 136)
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*			

** – these differences are statistically significant.*

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,

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we had to modify the standard technique of physicists so that it was acceptable to the human [84].

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 Q-heterochromatin in human genome. Certainly, the thickness of peripheral layer of CC around cellular nucleus depends on total amount of chromosomal C-heterochromatin in the genome. But as we suppose, packaging density (compactization) of CC itself is basically connected with the amount of chromosomal Q-heterochromatin 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 [15,16,44-46,57-62,86,89]. 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 Q-heterochromatin 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.

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 [44,47-51,57-59,89,122]. 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.

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 semi-arid 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

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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 [47-51,53,54,57-59,87,91,122].

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

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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 Q-heterochromatin 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, 2) and, hence, the appearance of individuals with a various BHC who

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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 Q-heterochromatin 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 Q-heterochromatin [67].

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].

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 cells 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

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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 CT, 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.g.: due to the different intensity of cell metabolism in different

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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 warm-blooded, 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 3-chambered 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 cold-blooded 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

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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]).

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 non-coding part of the genome (in the broad sense of the word), and structural genes are related to the development, mainly of secondary sexual characteristics [87,111-114].

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 [111-114]).

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 single-active 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 X-chromosome 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) X-inactivation is not involved in the SD, As Lyon [116] stated; b) X-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)

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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.

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 heat-shock 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 stresses - low 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.

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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.

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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Prevalence of Beta-Lactamase Producers in ICUs of a Tertiary Care Teaching Hospital of North India

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Abstract- *Objectives:* The aim of this study was to identify prevalence rates, sites and types of infection, the most common bacteria, and their antimicrobial resistance patterns, especially beta-lactamase producers present in Intensive care units (ICUs) of a tertiary care hospital.

Methods: Clinical samples obtained over a period of 12months from January 2014 to December 2014 from six ICUs of a tertiary care hospital were analyzed. Identification of micro organisms to species level and their antimicrobial susceptibility testing was performed as per CLSI guidelines. For control, 500 samples each from the environment & staff of ICU were collected & processed in the same way.

Keywords: *intensive care units, prevalence, betalactamase producers, cross-infection.*

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Prevalence of Beta-Lactamase Producers in ICUs of a Tertiary Care Teaching Hospital of North India

Dr. Poonam Sharma [α], Dr. Sarbjeet Sharma [σ] & Dr. Jasvir kaur [ρ]

Abstract- ***Objectives:*** The aim of this study was to identify prevalence rates, sites and types of infection, the most common bacteria, and their antimicrobial resistance patterns, especially beta-lactamase producers present in Intensive care units (ICUs) of a tertiary care hospital.

Methods: Clinical samples obtained over a period of 12months from January 2014 to December 2014 from six ICUs of a tertiary care hospital were analyzed. Identification of micro organisms to species level and their antimicrobial susceptibility testing was performed as per CLSI guidelines. For control, 500 samples each from the environment & staff of ICU were collected & processed in the same way.

Results: Of the total 1545 clinical samples collected during the study period, 522 were culture positive. The percentage of Gram negative and gram positive organisms isolated from them was 79.88% (417/522) and 19.37% (101/522) respectively and that of Candida was only 0.76% (4/522). Further, 50.8% (212/417) of Gram negative and 56.4% (57/101) of Gram positive isolates from clinical samples were beta-lactamase producers. The latter were maximum in clinical samples followed by environmental and staff samples.

Conclusion: Prevalence of beta-lactamase producing isolates in environmental and staff samples in addition to clinical samples indicates towards the possibility of cross infection by these organisms from the environment and staff to the patients. Therefore infection control strategies such as hand hygiene, rational antibiotic use, training and performance feedback can lead to significant reduction in the cross infection rates.

Keywords: intensive care units, prevalence, betalactamase producers, cross-infection.

I. Introduction

Intensive care units (ICUs) are of great value in the control and treatment of the severe illnesses that affect the human body. In spite of their invaluable and well-established role, ICUs lead to some degree of morbidity to patients, and nosocomial infection is clearly related to that.

Exposure to life-saving invasive procedures, serious underlying disease of patients and increased patient contact with healthcare personnel put patients admitted to the ICU at higher risk of acquiring nosocomial infections. ICU staff and the equipment used for patient care during the hospitalisation are the primary sources of cross-transmission of nosocomial pathogens.

Nosocomial infections increase patient morbidity, length of hospital stay, hospital costs, and may also increase mortality rates. When serious infections are suspected, treatment must be commenced immediately to increase the likelihood of a satisfactory outcome for the patient. Empirical knowledge, to select appropriate antibiotics, must be used so that the most likely infecting organisms are treated.

The prevalence of ICU-acquired infections varies between 4.4% and 88.9% being significantly higher in developing countries than in developed countries (1). Furthermore, device-associated infection rates in developing countries, especially ventilator-associated pneumonia (VAP) followed by central venous catheter-related bloodstream infections (CRBSIs), occur at a higher frequency than in European countries and USA (2,3).

The aim of this study was to identify the prevalence rates, sites and types of infection, the most prevalent microorganisms, and the antimicrobial resistance patterns especially the beta-lactamase producers present in ICUs of a tertiary care hospital.

II. Materials and Methods

The present study was conducted in 6 intensive care units of a tertiary care teaching hospital .We retrospectively analyzed consecutive culture-positive isolates and studied the antimicrobial susceptibility patterns of micro- organisms during the period from January 2014 to December 2014. The BacT/Alert (bioMerieux) was used for blood culture. Identification of micro organisms to species level and antimicrobial susceptibility testing was performed by the Vitek method. The interpretation of antimicrobial susceptibility results was done as per Clinical and Laboratory Standard Institute (CLSI) guidelines (4). For control, 500 samples each from the environment & staff of ICU were collected & processed in the same way. Informed consent was taken from staff before collecting samples. This study was conducted on hospitalised patients from

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whom samples were received in microbiology department so the article didn't need an approval from ethical committee.

a) Statistical Analysis

Statistical analysis was conducted. The chi-square test and odds ratio was applied for the comparison of categorical variables. *P* values less than 0.05 were considered as statistically significant.

III. Results

Total number of clinical samples collected during one year period were 1545. Out of which, 522 were culture positive as shown in Table1.

Table 1: Distribution of various clinical samples obtained from ICUs

S.no.	Samples	Total no.	Positive
1	Blood	704	158 (22.4%)
2	Urine	498	118 (23.7%)
3	Pus	160	124 (77.5%)
4	Suction tip	100	83 (83%)
5	Respiratory	47	33 (70.2%)
6	Body fluids	27	02 (7.4%)
7	Central lines	09	04 (44.4%)
		1545	522 (33.8%)

The percentage of Gram negative organisms isolated from clinical samples was79.88% (417/522), the percentage of gram positive organisms was 19.37% (101/522) & that of Candida was 0.76% (4/522) as shown in Table 2.

Table 2 : Distribution of various organisms in clinical samples

S.No.	ORGANISM	TOTAL No.
1	ACINETOBACTER	151
2	E.COLI	105
3	S. AUREUS	93
4	ENTEROBACTER	89
5	PSEUDOMONAS	29
6	KLEBSIELLA	21
7	CITROBACTER	16
8	ENTEROCOCCUS	06
9	PROTEUS	06
10	CANDIDA	04
11	CONS*	02
	Total	522

**Coagulase Negative Staphylococcus*

The prevalence of Gram positive and Gram negative isolates in environmental & staff samples is shown in Table 3. The prevalence of β-lactamase producing Gram negative and Gram positive isolates in clinical, environmental & staff samples is shown in Table 4 & 5 respectively.

Table 3 : Prevalence of various organisms in ICU, staff & environment.

S.No.	ISOLATES	Environment	Staff
1	Gram positive	50(10%)	34 (6.8%)
2	Gram negative	78(15.6%)	208 (41.6%)
3	Positive samples	128 (25.6%)	242 (48.4%)
4	Sterile samples	372 (74.4%)	258 (51.6%)
	Total samples	500	500

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Table 4 : Prevalence of Beta-lactamase producing Gram negative isolates in clinical, environmental & staff samples

SNo.	ORGANISMS	CLINICAL ISOLATES		ENVIRONMENTAL ISOLATES		ISOLATES FROM STAFF	
		TOTAL	BETA LACTAMASES PRODUCING	TOTAL	BETA LACTAMASES PRODUCING	TOTAL	BETA LACTAMASES PRODUCING
1	ACINETOBACTER	151	88 (58.3%)	12	0	20	2 (10%)
2	E.COLI	105	56 (53.3%)	22	08 (36.3%)	52	10 (19.2%)
3	ENTEROBACTER	89	31 (34.8%)	14	02 (14.3%)	10	0
4	PSEUDOMONAS	29	15 (51.7%)	10	02 (20%)	46	10(21.7%)
5	KLEBSIELLA	21	13 (61.9%)	20	10 (50%)	70	22 (31.4%)
6	CITROBACTER	16	09 (56.3%)	0	0	06	0
7	PROTEUS	06	0 (0%)	0	0	04	0
	Total	417	212 (50.8%)	78	22 (28.2%)	208	44 (21.2%)

Table 5 : Prevalence of Beta-lactamase producing Gram positive isolates in clinical, environmental & staff samples

S.No.	ORGANISMS	CLINICAL ISOLATES		ENVIRONMENTAL ISOLATES		ISOLATES FROM STAFF	
		TOTAL	BETA LACTAMASES PRODUCING	TOTAL	BETA LACTAMASES PRODUCING	TOTAL	BETA LACTAMASES PRODUCING
1	MSSA	36	17(47%)	18	08 (44.4%)	14	04 (28.6%)
2	MRSA	57	40 (70%)	06	04 (66.7%)	08	04 (50%)
3	CONS	02	0	26	0	12	00
4	ENTEROCOCCI	06	01 (16.7%)	0	0	0	0
	Total	101	57 (56.4%)	50	12 (24%)	34	08 (23.5%)

IV. Observations

1. Maximum number of infections in ICU were Blood stream infections followed by Urinary tract, wound and respiratory tract infections.
2. Among the clinical isolates, the most prevalent bacterial agent was Acinetobacter 28.9% (151/522), followed by organisms of family Enterobacteriaceae and *Staphylococcus aureus,*
3. Concerning resistance patterns for *S. aureus*, 61.3% were resistant to methicillin and 100% had sensitivity to vancomycin.
4. Isolates obtained from staff samples were more than the ones obtained from clinical samples. More than 50% *S.aureus* obtained from staff & environmental samples were Methicillin resistant (MRSA) however all were sensitive to Vancomycin.
5. Among the clinical isolates, 50.8 %(212/417) of Gram negative isolates and 56.4 %(57/101) of Gram positive isolates were beta latamase producers.
6. The most frequently used antimicrobials in ICUs were cephalosporins, imipenem, levofloxacin, piperacillin-tazobactum and metronidazole. Actually, empirical treatment schemes are based on knowledge of local microbiota
7. *E.coli* & Klebsiella sp were the most common isolates recovered from environment & staff of ICU. Acinetobacter followed by *E. coli* were the more prevalent isolates from clinical samples
8. Prevalence of Gram negative organisms was more than gram positive in all the 3 groups as shown in Table 6.

Table 6 : Comparison of various isolates in the 3 groups

ISOLATES	TOTAL PERCENTAGE	GRAM POSITIVE%	GRAM NEGATIVE %	BETA LACTAMASES PRODUCERS
CLINICAL	33.8	19.4	79.8	51.9
ENVIRONMENTAL	25.6	10	15.6	26.56
STAFF	48.4	6.8	41.6	21.48

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9. Beta lactamase producers were maximum in clinical samples followed by environmental and staff samples as shown in Table 6.
10. By calculating the odds ratio, isolates from clinical samples were twice more likely to be beta lactamase producers than the ones from environmental samples (odds ratio=2.98) and isolates from clinical samples were four times (odds ratio=3.94) more likely to be betalactamase producers than from staff samples.
11. By using chi-square test no significant (p=0.2) association was found between isolates from environmental and staff samples.

V. Discussion

In this study, Gram-negative bacteria were more common than Gram-positive bacteria, which is in accordance with the other studies (5,6,7). Treatment becomes challenging in gram-negative organisms causing serious infections in ICUs including pneumonia, bloodstream infections, wound or surgical site infections and meningitis. These organisms also exhibit multidrug resistance, and therapeutic alternatives have declined due to stagnation in novel antimicrobial agents (7,8).

In the present study, blood stream infections were most common, followed by urinary tract, wound and respiratory infections. However in the study by Boyles S (9) respiratory infections were more common in ICU followed by wound, blood stream and urinary tract infections. The probable reason could be that the sample size in their study was much larger (14000 patients) than ours.

Acinetobacter species was the most common pathogen isolated which is in accordance with the study by Datta P et al (6, 7). The prevalence of MRSA among clinical, environmental and staff samples was more than 50% which shows that more stress should be laid on hand hygiene in our ICUs as improved hand hygiene can reduce acquisition of antimicrobial resistant bacteria, particularly MRSA (10).

There has been increase in incidence of beta lactam resistant organisms in ICUs of our hospital which is in accordance with a study conducted by Shaikh S et al (11). Among the clinical isolates, 50.8% of Gram negative isolates and 56.4% of Gram positive isolates were beta lactamase producers. This data confirms that in the intensive care medical environment, the most virulent in general are the most resistant and are the most frequently found organisms (12,13).

Prevalence of beta-lactamase producers in environmental and staff samples apart from clinical samples indicates towards the possibility of cross infection by these organisms from the environment and staff to the patients. Infection control strategies such as hand hygiene, rational antibiotic use, training and performance feedback can lead to significant reduction in the cross infection rates. In addition patients colonized or infected with beta lactamase-producing organism should be placed under contact precautions to avoid hospital transmission (14).

Hand hygiene is the most important way of decreasing the spread of infections in ICUs especially in developing countries like ours. Initial empirical therapy with broad-spectrum antibiotics is a life-saving strategy, which improves clinical outcome and reduces selection of resistant organisms. However, it is imperative to de-escalate these antibiotics according to culture and antibiotic susceptibility results. Antibiotic cycling can be used as an effective approach to control antibiotic resistance. Strict antibiotic policies in ICUs can prevent the use of long term antibiotics and shorten the duration of the antimicrobial therapy (15).

Conducting infection surveillance and control activities in ICUs and rational antibiotic utilisation policies are valuable measures for infection control. These measures provide current knowledge about antibiotic resistance patterns, early recognition and management of outbreaks, which is essential for infection control (16).

Increasing drug resistance and spreading of multidrug-resistant (MDR) pathogens in the ICU environment results in limited therapeutic options and prolonged hospitalisations. Consequently, the prevalence of ICU-acquired infection, healthcare costs and mortality rates are higher in developing countries due to limited resources associated with the quality of care (17).

In conclusion, our study shows that multidrug resistant bacteria are on rise in our hospital. The rise in beta-lactamase producers emphasizes the importance of stringent infection control practices, rational prescribing policies and need for development of new drugs and vaccines. Also, there is a need for the continuous evaluation of the local antibiotic resistance patterns for the formulation of a rational antibiotic policy. Limiting use of antibiotics to patients with clear evidence of infection rather than colonization is essential & discontinuation of antibiotics when their possible benefits have been obtained is also critical. Further, new drugs are required to replace the increasingly obsolete classes of antibiotics that currently exist and there is need for strict compliance with infection control practices.

Conflict of Interest Statement

We declare that we have no conflict of interest.

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The Proteins of Type IV Secretion System as Promising Candidates for *Helicobacter Pylori* Vaccine

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Abstract- *Helicobacter. pylori* is a component of class 1 carcinogens and there is a close association between the incidence of gastric cancer and high prevalence of infection with this bacterium. The risk of gastric cancer associated with *H. pylori* infection in industrialized and developing countries is estimated to be 80% and 70% respectively. CagA is the important virulence factor in this bacterium and all of the strains involved in gastric cancer are CagA positive. This factor is secreted into host cells by type IV secretion system. CagA and type IV secretion system in *H. pylori* encoded by the cag pathogenicity islands (cag PAI) that encodes 30 proteins which are necessary for the pilus formation and function of type IV secretion system, so regarding to the role of this secretion system in secreting CagA and its function in pathogenesis and cancer development in humans and the role of different proteins of this secretion system such as canal and pilus formation and their necessity for function of these structures, it is possibly they are be appropriate candidates for design vaccine, because with inhibiting these proteins can stop canal and pilus formation and finally hinder CagA secretion into the host cells.

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The Proteins of Type IV Secretion System as Promising Candidates for *Helicobacter Pylori* Vaccine

Azad Khaledi [α], Abbas Bahador [σ] & Davoud Esmaeili [ρ]

Abstract- ***Helicobacter. pylori*** **is a component of class 1 carcinogens and there is a close association between the incidence of gastric cancer and high prevalence of infection with this bacterium. The risk of gastric cancer associated with *H. pylori* infection in industrialized and developing countries is estimated to be 80% and 70% respectively. CagA is the important virulence factor in this bacterium and all of the strains involved in gastric cancer are CagA positive. This factor is secreted into host cells by type IV secretion system. CagA and type IV secretion system in *H. pylori* encoded by the cag pathogenicity islands (cag PAI) that encodes 30 proteins which are necessary for the pilus formation and function of type IV secretion system, so regarding to the role of this secretion system in secreting CagA and its function in pathogenesis and cancer development in humans and the role of different proteins of this secretion system such as canal and pilus formation and their necessity for function of these structures, it is possibly they are be appropriate candidates for design vaccine, because with inhibiting these proteins can stop canal and pilus formation and finally hinder CagA secretion into the host cells.**

I. Review

Helicobacter pylori is a spiral-shaped gram-negative bacillus that it colonizes half the world's population (1). Chronic infection with this bacterium causing an increased risk for several infectious diseases such as gastritis, duodenal ulcers, hyperplasia, neoplasia and ect (2).

H. pylori is one of the ancient microorganisms and its spread between human societies is return to sixty thousand years ago (3). *H. pylori* colonize the human gastric for years and even decades without anyadverse consequence (4). The risk factors for acquiring *H. pylori* are including poverty, the use of common sleeping devices, living in very crowded sittings such as boarding houses which raise the possibility of infection(5). *H. pylori* is component of the family of class 1 carcinogen and there is a high correlation between the incidence of gastric cancer and high prevalence of infection with this bacterium (6). Gastric cancer is the second common cancer worldwide and the fourteenth cause of death in the world and it is considered as a main epidemiological problem in the 21st century (7). The risk of gastric cancer associated with *H. pylori* infection in industrialized and developing countries are estimated to be 80%, and 70% respectively (8). *H. pylori* infection is usually asymptomatic chronic gastritis and between infected people the rate of chronic gastritis or gastric ulcer are 10%-15 % (8). *H. pylori* infection, exposure to nitrosamines, high-salt diet, smoking and low consumption of fruits and vegetables are major risk factors for gastric cancer. The high prevalence of *H. pylori* infection in the world and its role in gastric cancer and other diseases, and the emergence of antibiotic resistance strains have caused different therapeutic and prevention methods recommended against infection with bacterium (9) . It should be noted, only patients with symptoms are treated and asymptomatic patients are at risk of serious problems such as atrophic gastritis and gastric cancer as well after cure, recurrence or reinfection might be take place (10), particularly in developing countries (11). Thus the need for vaccines in general that can control infection is felt.

The immune mechanisms against *H.pylori* is mediated by innate and adaptive immunity, the innate immunity is including gastric acidity, gastric peristalsis, loss of gastric epithelial cells, gastric mucosa, saliva and etc (12). In total, acquired immunity is consists of the cellular and humeral immunity. Despite stimulate antibody production, clearance and complete protection against *H. pylori* infection is caused by cellular immunity (13). So to eradication of this bacterium, The strong Th1 response to protection (IFNɣ production is necessary for protection) and Th2 response (IL-10) to reduce inflammation during *H. pylori* infection is required (13).

Some *H. pylori* native and recombinant antigens such as urease, Heat Shock proteins, CagA, VacA, HP-NAP, catalase (14) HpaA (15), SOD (16) are used as vaccine and the efficacy of therapeutic and prophylactic immunization of these antigens have been shown. several studies tried to discover more protective antigens in mice including Hp0410 (neuraminyllactose-binding hemagglutinin HpaA homologue) (17), Tpx (thiol peroxidase) (18) outer membrane proteins, alkyl

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hydroperoxide reductase (19), but other studies have attempted to use from proved previous protective antigens in new forms to show their treatment aspect and prophylaxis efficiency in mice (20). The first evidence of the efficacy of protection against *H. pylori* has been provided by urease immunization in mouse model and showed that the both types of recombinant vaccines UreB or UreA are effective when they used in the oral forms (21). The protective role of HP-NAP has been evaluated in mouse model, in orally the mice with recombinant HP-NAP along with LTK63, LTK63 non-mutant strains as adjuvant were immunized and following challenge with *H. pylori* showed protection against gastric colonization of the majority of vaccinated mice (22). The protective efficacy of native purified VacA given along with LTK63 as an adjuvant was proved in oral immunization in mice (23). Other studies demonstrated the same (24). Recombinant CagA in companying with LTK63 was used in mice and the results showed this combination to be protective against gastric colonization upon consequence *H. pylori* trial intragastrically challenge (25). Combination of CagA, VacA and HP-NAP was used as a therapeutic vaccine in the model of *H. pylori* experimental infection of beagle dog and presented good efficacy without any side-effects owing to immunization. Following challenge, the decrease in *H. pylori* colonization and gastric inflammation was observed in vaccinated dogs (26). A study revealed recombinant vaccine proteins CagA + VacA + HP-NAP has been immunogenic and safe in clinical phase (27). The emphasis of all studies on that protection against *H. pylori* would be acquired by vaccination through animal models; but unfortunately complete protection is seldom achieved, it appear that this depend on optimization of the antigen mixture, adjuvant and route and regimen of immunization and to get this aim the appropriate combination is very important(28). In addition, efficiency in animals is not essentially indicative of efficacy in humans(28). Due to inadequate knowledge upon mechanisms of protective immunity against *H. pylori* till this moment there has been no licensed vaccine against *H. pylori*, Until now there has been no licensed vaccine against *H. pylori*. The reasons for this are: inadequate knowledge about the mechanisms of protective immunity against *H. pylori*, thus extensive research is needed to identifying the mechanisms of protective immunity against *H. pylori* and the vaccine formulations should be known to be able to preventing and treatment of infection(28), regarding known role of CagA and other main carcinogens factors, the supposition is that the vaccine should be targeting specifically these factors (28). In other words, a vaccine is valuable for us to prevent gastric cancer rather than prevent colonization of *H. pylori* in human(28). The studies upon new vaccine candidates, efficient adjuvants, regimens and routes of application is go on yet (28).

In continue we want to explain in this brief about type IV secretion system and introduce its proteins as good candidates for vaccine. In several gram-negative bacteria, such as *Neisseria gonorrhoeae*, *Bordetella pertussis*, *Agrobacterium tumefaciens* and *Brucella suis* have type IV secretion system and in these bacteria this system is used to transfer macromolecules (such as DNA, nucleic acid and protein complexes), (29). Type IV secretion system in *H. pylori* encoded by the cag pathogenicity islands (cag PAI) that encodes 30 proteins which are necessary for the pilus formation and function of type IV secretion system (29). Type IV secretion system is a molecular pump that facilitates the interaction between host and pathogen or injects toxins into the host cells (30). According to the medical literature in the human *H. pylori* species, type IV secretion system is divided into three different groups, first group (Tfs3, group 1) which plays an important role in shaping the genome plasticity of *bacterium*, the second group is called Com B system which plays an important role in insertion and integration of environmental DNA fragments into the itself genome. At last the third group there is only in *H. pylori* pathogenic strains which play role in translocation of protein effectors (such as CagA) into the eukaryote cells (27). CagA toxin and type IV secretion system is encoded by cag PAI, this pathogenicity island is a 40 kDa fragment of DNA and transfer of it occurs horizontally (31). Based on the nomenclature used for *A. tumefaciens* T4SS, this system generally contains 12 protein which these proteins are called Vir (30). The *H. pylori* cag PAI encoding T4SS (Cag-T4SS) initially have been identified by comparing the sequence with those of the VirB /D *A. tumefaciens (30)*. These proteins assemble together to form three interlinked subparts: a cytoplasmic / inner membrane complex, a double membrane - spanning channel and an external pilus (32). The cytoplasmic / inner membrane complex is consists of three NTPases (HP0544, HP0532 , HP0524), HP0529 and HP0530; the trans-membranes pore complex (HP0532, HP0528, HP0527; as well as called 'the core complex') creates a channel from the inner to the outer membrane; the HP0546 and HP0539 proteins create external pilus (32). Other components are crucial for the creation of the T4SS compound: the role of HP0523 is insertion of the system in the periplasm and finally HP0544, with the unknown role, is frequently related to HP0544 (32).

Regarding to the role of type IV secretion in secretion of CagA and its role in pathogenesis and cancer formation in humans and the role of different proteins of type IV secretion such as canal and pilus formation and their necessity for function of these structures, it is possibly they are be appropriate candidates for design vaccine, because with inhibiting these proteins can stop canal and pilus formation and finally can prevent of CagA secretion into the host cells, of course these proteins should be used in combination

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with *H.pylori* virulence factors in multi-component vaccines.

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Conflict of interest

None declared.

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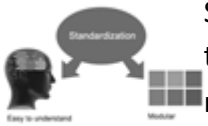


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4. Manuscript's Category,

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31. Adding unnecessary information: Do not add unnecessary information, like, I have used MS Excel to draw graph. Do not add irrelevant and inappropriate material. These all will create superfluous. Foreign terminology and phrases are not apropos. One should NEVER take a broad view. Analogy in script is like feathers on a snake. Not at all use a large word when a very small one would be sufficient. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Amplification is a billion times of inferior quality than sarcasm.

32. Never oversimplify everything: To add material in your research paper, never go for oversimplification. This will definitely irritate the evaluator. Be more or less specific. Also too, by no means, ever use rhythmic redundancies. Contractions aren't essential and shouldn't be there used. Comparisons are as terrible as clichés. Give up ampersands and abbreviations, and so on. Remove commas, that are, not necessary. Parenthetical words however should be together with this in commas. Understatement is all the time the complete best way to put onward earth-shaking thoughts. Give a detailed literary review.

33. Report concluded results: Use concluded results. From raw data, filter the results and then conclude your studies based on measurements and observations taken. Significant figures and appropriate number of decimal places should be used. Parenthetical remarks are prohibitive. Proofread carefully at final stage. In the end give outline to your arguments. Spot out perspectives of further study of this subject. Justify your conclusion by at the bottom of them with sufficient justifications and examples.

34. After conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print to the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects in your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form, which is presented in the guidelines using the template.
- Please note the criterion for grading the final paper by peer-reviewers.

Final Points:

A purpose of organizing a research paper is to let people to interpret your effort selectively. The journal requires the following sections, submitted in the order listed, each section to start on a new page.

The introduction will be compiled from reference matter and will reflect the design processes or outline of basis that direct you to make study. As you will carry out the process of study, the method and process section will be constructed as like that. The result segment will show related statistics in nearly sequential order and will direct the reviewers next to the similar intellectual paths throughout the data that you took to carry out your study. The discussion section will provide understanding of the data and projections as to the implication of the results. The use of good quality references all through the paper will give the effort trustworthiness by representing an alertness of prior workings.

Writing a research paper is not an easy job no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record keeping are the only means to make straightforward the progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear

· Adhere to recommended page limits

Mistakes to evade

- Insertion a title at the foot of a page with the subsequent text on the next page
- Separating a table/chart or figure - impound each figure/table to a single page
- Submitting a manuscript with pages out of sequence

In every sections of your document

· Use standard writing style including articles ("a", "the," etc.)

· Keep on paying attention on the research topic of the paper

· Use paragraphs to split each significant point (excluding for the abstract)

· Align the primary line of each section

· Present your points in sound order

· Use present tense to report well accepted

· Use past tense to describe specific results

· Shun familiar wording, don't address the reviewer directly, and don't use slang, slang language, or superlatives

· Shun use of extra pictures - include only those figures essential to presenting results

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Choose a revealing title. It should be short. It should not have non-standard acronyms or abbreviations. It should not exceed two printed lines. It should include the name(s) and address (es) of all authors.



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Abstract:

The summary should be two hundred words or less. It should briefly and clearly explain the key findings reported in the manuscript--must have precise statistics. It should not have abnormal acronyms or abbreviations. It should be logical in itself. Shun citing references at this point.

An abstract is a brief distinct paragraph summary of finished work or work in development. In a minute or less a reviewer can be taught the foundation behind the study, common approach to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Yet, use comprehensive sentences and do not let go readability for briefness. You can maintain it succinct by phrasing sentences so that they provide more than lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study, with the subsequent elements in any summary. Try to maintain the initial two items to no more than one ruling each.

- Reason of the study - theory, overall issue, purpose
- Fundamental goal
- To the point depiction of the research
- Consequences, including definite statistics - if the consequences are quantitative in nature, account quantitative data; results of any numerical analysis should be reported
- Significant conclusions or questions that track from the research(es)

Approach:

- Single section, and succinct
- As a outline of job done, it is always written in past tense
- A conceptual should situate on its own, and not submit to any other part of the paper such as a form or table
- Center on shortening results - bound background information to a verdict or two, if completely necessary
- What you account in an conceptual must be regular with what you reported in the manuscript
- Exact spelling, clearness of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else

Introduction:

The **Introduction** should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable to comprehend and calculate the purpose of your study without having to submit to other works. The basis for the study should be offered. Give most important references but shun difficult to make a comprehensive appraisal of the topic. In the introduction, describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will have no attention in your result. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here. Following approach can create a valuable beginning:

- Explain the value (significance) of the study
- Shield the model - why did you employ this particular system or method? What is its compensation? You strength remark on its appropriateness from a abstract point of vision as well as point out sensible reasons for using it.
- Present a justification. Status your particular theory (es) or aim(s), and describe the logic that led you to choose them.
- Very for a short time explain the tentative propose and how it skilled the declared objectives.

Approach:

- Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done.
- Sort out your thoughts; manufacture one key point with every section. If you make the four points listed above, you will need a least of four paragraphs.

- Present surroundings information only as desirable in order hold up a situation. The reviewer does not desire to read the whole thing you know about a topic.
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Materials:

- Explain materials individually only if the study is so complex that it saves liberty this way.
- Embrace particular materials, and any tools or provisions that are not frequently found in laboratories.
- Do not take in frequently found.
- If use of a definite type of tools.
- Materials may be reported in a part section or else they may be recognized along with your measures.

Methods:

- Report the method (not particulars of each process that engaged the same methodology)
- Describe the method entirely
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures
- Simplify - details how procedures were completed not how they were exclusively performed on a particular day.
- If well known procedures were used, account the procedure by name, possibly with reference, and that's all.

Approach:

- It is embarrassed or not possible to use vigorous voice when documenting methods with no using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result when script up the methods most authors use third person passive voice.
- Use standard style in this and in every other part of the paper - avoid familiar lists, and use full sentences.

What to keep away from

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings - save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part a entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Carry on to be to the point, by means of statistics and tables, if suitable, to present consequences most efficiently.You must obviously differentiate material that would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matter should not be submitted at all except requested by the instructor.



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Content

- Sum up your conclusion in text and demonstrate them, if suitable, with figures and tables.
- In manuscript, explain each of your consequences, point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation an exacting study.
- Explain results of control experiments and comprise remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or in manuscript form.

What to stay away from

- Do not discuss or infer your outcome, report surroundings information, or try to explain anything.
- Not at all, take in raw data or intermediate calculations in a research manuscript.
- Do not present the similar data more than once.
- Manuscript should complement any figures or tables, not duplicate the identical information.
- Never confuse figures with tables - there is a difference.

Approach

- As forever, use past tense when you submit to your results, and put the whole thing in a reasonable order.
- Put figures and tables, appropriately numbered, in order at the end of the report
- If you desire, you may place your figures and tables properly within the text of your results part.

Figures and tables

- If you put figures and tables at the end of the details, make certain that they are visibly distinguished from any attach appendix materials, such as raw facts
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- In spite of position, each table must be titled, numbered one after the other and complete with heading
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The Discussion is expected the trickiest segment to write and describe. A lot of papers submitted for journal are discarded based on problems with the Discussion. There is no head of state for how long a argument should be. Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implication of the study. The purpose here is to offer an understanding of your results and hold up for all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of result should be visibly described. Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved with prospect, and let it drop at that.

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- Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work
- You may propose future guidelines, such as how the experiment might be personalized to accomplish a new idea.
- Give details all of your remarks as much as possible, focus on mechanisms.
- Make a decision if the tentative design sufficiently addressed the theory, and whether or not it was correctly restricted.
- Try to present substitute explanations if sensible alternatives be present.
- One research will not counter an overall question, so maintain the large picture in mind, where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

- When you refer to information, differentiate data generated by your own studies from available information
- Submit to work done by specific persons (including you) in past tense.
- Submit to generally acknowledged facts and main beliefs in present tense.

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Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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