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Hereditary Immunity in Cancer

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ABSTRACT

The Cancer War against the biggest current threat to global human health (1971 – 2xxx) failed dismally because the bankruptcy of its theoretical bases. New insights in cancer biology and origin are sorely needed. The goal of this chapter is to widen immunological evidence of the entirely innovative hypothesis of xenogamous origin, parasite subsistence and sexual transmission of human cancer. The search was based on a multidisciplinary integrative reassessment and reinterpretation of relevant current data about hereditary immunity of cancer and against cancer. The main focus was on manifestations of hereditary immunity over consecutive stages of cancer subsistence, beginning from the invasion of victim's genome with cancerous gamete and finishing by sexual transmission of cancerous genome between people. The evidence of hereditary immunity has been revealed at any of the stages. The subsistence of cancer within a prey's body at the expense of substances derived from the body is crucial for the progression of cancer. The subsistence is supported by constitutive immunity of cancer cells to the host's immune defense and cell regulation. These new notions encourage new proposals for cancer prevention by restriction of cancerous fertilization and for cancer healing by pathogenetically grounded chemotherapy. Contents: 1. Introduction; 2. Manifestations of Hereditary Immunity in Cancer [In first Discovery of Hereditary Immunity to Cancer; Over Observations of Cancer Prevalence (Ethnic and Racial Differences in Cancer Prevalence, Population Differences in Cancer Prevalence, Racial Differences in the Liability to Cancer); Over Observations of Diseased Persons (Over Cancer Invasion of a Victim's Body, Over Embryogenesis of Cancer, Anatomy and Physiology

of a Ripe Cancer, Differences in the Locations of Cancer Sub-Units, The Foreignness of Cancer for it Prey)] 3. Immunology of cancerous tissues and cells (Hereditary Immunity of Cancer to Victim's Regulatory Management, Hereditary Immunity of Cancer to Victim's Immune Defense) 4. Conclusion.

Keywords: Cancerous genealogy; cell regulation; embryogenesis; constitutive immunity; genome intrusion; immune response; parasite-pray; self-procurement; sexual transmission; xenogamy;

INTRODUCTION

Cancer is now among the first dozen of biggest threat to global human health. Although the date of first cancer appearance is unknown, but its written history starts nearly 4600 years ago from the Egyptian papyrus of around 2625 B.C.E., when the Egyptian physician Imhotep described "bulging tumors of the breast" [1]. For therapy, he honestly stated, "There is none". One can suppose that cancer is more ancient than the statue of Sphinks. For many subsequent centuries, cancer was not a widely observed disease, the cancerous killing and its prevalence continued to grow very slow. Today, the term "cancer" has more than 100 distinct clinical forms of the disease. Each of the forms is named following the organ affected by its initially detected unit. The causes of such dangerous progression are unknown. However, up to the beginning of third millenium cancer was not seen as a transmissible disease. The cancer pandemic has become the quintessential product of modernity.

The current War on Cancer, the "cancer crusade" forced by the U.S. National Cancer Act of 1971 provided a massive stimulus for cancer research, prevention, and healing. The Act made big promises, promoted the U.S. National Cancer Institute (NCI) and gave the NCI a token measure of independence. Since the 1971 Act, the NCI has spent about $90 billion on science, treatment, and prevention of cancer [2]. Now, over 40 years later, the disease continues to spread throughout the nation (and the world) with growing intensity. Cancer figures now among the leading causes of death worldwide, accounting for 8.2 million deaths in 2012 [3]. According to Sharon Begley, "Cancer is on track to kill 565,650 people in the United States this 2013 year – more than 1,500 a day, equivalent to three jumbo jets crashing and killing everyone aboard 365 days a year" [4].

The efficacy of means exploited currently for cancer prevention and treatment appears to be very low. For instance, Provenge, a recent immune treatment for metastatic prostate cancer, costs $93,000 and extends life by about four months [5]. Cancer chemotherapy has a 97 percent fatality rate. Really, as Imhotep stated, "There is none" for the therapy of cancer. The over 40 years long war on cancer is proclaimed today as a dismal failure [6]. Over 40 years "We Fought Cancer… And Cancer Won" [4].

The Cancer War failed because the bankruptcy of its theoretical bases. The NCI elaborated the strategy of the War, but the theoretical base was oriented exclusively 50 years old ago and

there has been no revised hypothesis of carcinogenic somatic mutations. The initially accepted paradigm of the origin and pathogenesis of cancer, the 'somatic mutation hypothesis'[7] appeared to be impotent. Most research and treatment questions that vexed the cancer community 40 years ago remain unanswered. The promises of a 'somatic mutation hypothesis' appeared unpaid [8,9]. A need has emerged to develop a more enlightening paradigm that captures the essentials of the cancer.

Compared to the areas in which medical research had its most dramatic successes, cancer presents fundamentally different challenges. Meagre progress in the knowledge of cancer calls for new research approaches. New insights in cancer biology, its origin, the circle of life, pathogenesis, immunology, clinical progression and epidemic spread are sorely needed [9,10].

Only one hypothesis can pretend to present today an radically different view on the origin, pathogenesis, immunology and pandemic spread of human cancer: the hypothesis of a parasite origin of sexually transmitted human cancerous disease [8,11]. The hypothesis forms the innermost kern of recently elaborated xenogamous (intrusive) paradigm of cancer, which united the issues about cancer's origins, genetics, mode of existence, pathogenesis, and epidemic spread [12]. The creation of the entirely different paradigm has been initiated by a set of small pioneer publications offered an absolutely new view on the origin of cancer and its pathogenesis, as well as on the way of its transmission from the diseased persons to the susceptible one [8,11,13]. This article aids the most exhaustive search of cancer immunology based on the hypothesis.

The need of this research is justified by the impotency of current oncology to prevent and heal cancerous disease which is now the biggest threat to global human health. The failure arose because current medicine lucks appropriate knowledge of cancer immunology in the aspects of cancer origin, subsistence, pathogenesis and the manner of it epidemic spread. This approach unites first consecutive analyze of the stages of cancer subsistence beginning from cancerous invasion of a victim body, the potencies of cancer progression within of it prays, its impact of on the victim and the sequel of its circle of life by the transmission between humans.

For decades, cancer immunity researches have focused on the factors of individual responsive immunity elaborated by lymphatic system. The idea of genetic immunity in cancer, highly controversial at the time, was proposed just recently [11,13]. The goal of this search was to reveal the functions of hereditary immune traits over consecutive stages of the disease.

Hereditary or constitutional immunity is genetically determined ability of a living structure to resist relevant impact of either ecological (e.g. infectious) or physiological agents [14-18]. The existence of hereditary immunity to infections was known over many hundreds of years. Nevertheless, W. Boyd [14] was probably the first who stated near 50 years ago in his handbook on the fundamentals of immunology that this kind of immunity was a fundamental trait and he expressed his regret for the lack of scientific knowledge of this type of resistance.

For many decades of 19th Century, the discovery of hereditary immunity was out of the mainstream of fundamental immunology. It has been considered as being beyond importance, comprehension and utilization. Even at the threshold of the last quarter of 20th century, a little bit has been known about these kinds of immunity. Moreover, a little bit has been done to explore this area. Almost all immunologists and pathologists focused their attention on responsive immunity elaborated by lymphatic system of vertebrates. However, another form of immunity, namely the constitutionally predetermined ability to prevent disease has often been overlooked. Immunity of Invertebrates, Plants, Fungi, Bacteria, Viruses and other kinds of living beings were out of the mainstream of immunology [19].

The situation began to change at the threshold of the third millennium. First generalization and theoretical comprehension of the data about hereditary immunity have been performed. The mechanisms and functions of hereditary immunity were revealed and characterized for the first time [17,18]. Some primary proposals to exploit the new knowledge in the contra-infectious health care have been formulated and realized [18,20]. What is more, the functions of hereditary immunity were revealed and characterized for the first time in the origin and pandemic spread of most flagrant "non-infectious" diseases of today (obesity, atherosclerosis, osteoporosis, senescense, mental disorders, cancer) [9,10,12,18,21-29].

MANIFESTATIONS OF HEREDITARY IMMUNITY IN CANCER

In First Discovery of Hereditary Immunity to Cancer

The existence of hereditary immunity to cancerous diseases was unknown before the early beginning of 20th century. Alfred Scott Warthin (Figure 1) was the first whose observations made him convinced that there are hereditary immunity to cancer and hereditary susceptibility to it. He worked up the histories of several generations of some stabled families and present first description and genealogy of a classic cancer prone and cancer immune families in the early 1900's [30].

Figure 1: Aldred Scott Warthin **(1866 – 1931)** MD, PhD, Chairman of the Department of Pathology at the University of Michigan at Ann Arbor.

A.S.Warthin published his last study of hereditary cancer in 1925 [31]. He also commented that his observations had been met with little favor among cancer surgeons. (Some things never change). Relatively little attention was given to the heredity in "cancer families" until the 1960s when Henry T. Lynch described two large cancer kindreds and reported the first family with the complex of some associated malignant diseases that is now called as Lynch Syndrome [32]. Over the 20th century the insight into inheritance of the phenomenon has although been concentrated around the Lynch Syndrome. However from the late 1960s until the beginning of 21th century, progress in understanding Lynch Syndrome continued to be slow.

Over Observations of Cancer Prevalence

Although human cancer occurs everywhere in the world, there are very wide population, ethnic, and racial variations in its mortality rates (Figures 2, 3, 4 and Table 1). The variations express the differences in the intensity of hereditary immunity among relevant groups of peoples.

Table 1: The ratios of the highest rates to the lowest rates in worldwide cancer incidence. According to [34].

Cancer	The values of rates per 100,000		
	Highest rate	Lowest rate	Ratio
Skin melanoma	28.9 (Australia)	0.1 (Kuwait, Thailand)	289
Nasopharinx	28.5 (Hong Kong)	0.1 (Quito, Ecuador)	285
Larynx	20.4 (Basque Country)	0.1 (Qidong, China)	204
Prostate	102.0 (Atlanta, Georgia)	0.8 (Qidong, China)	127.5
Lung	119.1 (Maoris, NZ)	1.0 (The Gambia)	119.1

Ethnic and racial differences in cancer prevalence

The rates of cancer incidence (Figure 2) show the widest variations. The rates for all cancer sites in males revealed an over eight-fold differences that ranged from 493.8 per 100,000 in Tasmania, Australia, to a low of 59.1 in The Gambia, that shows also lowest rates for cancer of colon, rectum, pancreas, bronchus, lung, thyroid gland, myeloid leukemia, bladder, tongue, mouth and testis. Rates for U.S. males were 351.3 for blacks (SEER) and 330.4 for whites [33]. One can expect the key to the origin of cancer will be found in the ecology of The Gambia innate ethnos, which provided him with more than 5-fold resistance to cancer in contrast to the USA blacks and whites. Prostate cancer, one of the most common cancers in men, is especially frequent in men of African origin. Prostate cancer incidence rates in African Americans are 1.5–fold greater than rates in Americans of European origin [33].

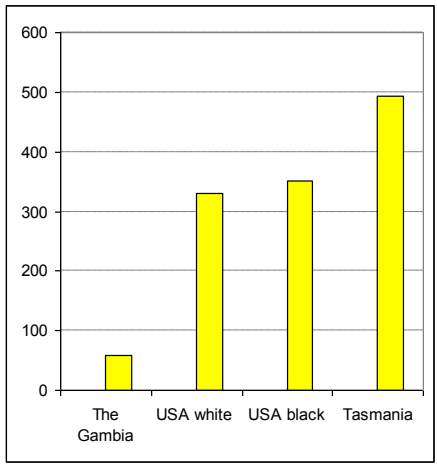

Figure 2: Ethnic variation in cancer incidence rates. According to [12].

Population differences in cancer prevalence

The rates used (Figure 3) are the number of cancer deaths per 100,000 populations. They are ranked from the highest to the lowest [33]. The data revealed four-fold difference between the lowest (54.4 in Thailand) and highest (235.4 in Hungary) male cancer mortality rates. The group of five most cancerous countries unites Hungary, Luxembourg, Belgium, France and Uruguay. Amongst a group of five least cancerous countries Mexico, Ecuador and Panama shares their neighborhood with Thailand and Kuwait [33]. One can suppose in contrast to Hungary the population of Thailand could be named immune to cancer.

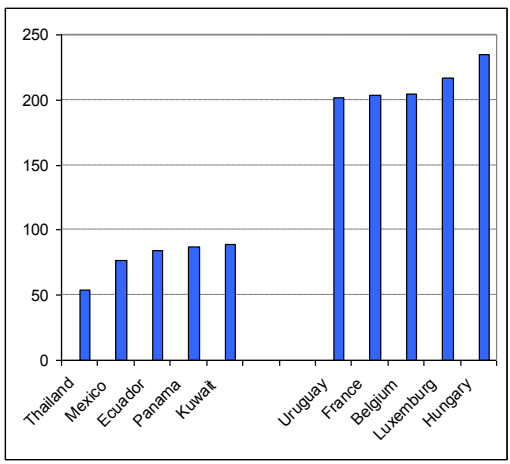

Figure 3: Variation in male cancer mortality rates among different populations. According to [12].

The largest ratios of the highest rates to the lowest rates in worldwide cancer incidence among

males were for melanoma of the skin, nasopharynx, and larynx, with ratios of 289, 285, and 204, respectively (Table 1).

For melanoma of the skin, the area reporting the highest rate was the Australian Capital Territory with 28.9 per 100,000; the lowest rate, 0.1, was reported among Kuwaitis in Kuwait and among persons in Khon Kaen, Thailand. For nasopharynx, the highest rate was 28.5 in Hong Kong while the lowest was 0.1 for Quito, Ecuador. For larynx, the highest rate was 20.4 in Basque Country, Spain, and the lowest rate, 0.1, was for men in Qidong, China. Prostate cancer rates were highest for black men in Atlanta, Georgia (102.0) and lowest in Qidong, China (0.8 per 100,000). The worldwide range in lung cancer incidence among men ranges from a high of 119.1 in New Zealand Maoris to 1.0 per 100,000 in The Gambia. U.S. black men in New Orleans experienced a lung cancer rate of 115.9, just lower than that for Maoris in New Zealand.

Racial differences in the liability to cancer

Inter racial differences compose one of the main riddles of cancer manifestations that should be decoded. For instance the rates of male skin and pancreas cancer incidence referenced by primary two sites and races can not be explained from the viewpoint of current paradigm

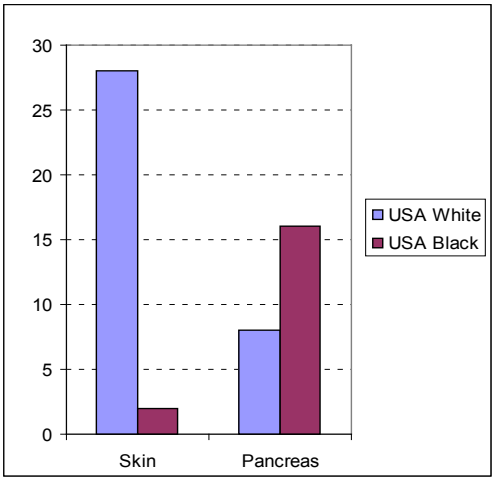

Figure 4: Opposite rates of male cancer incidence by primary site and race*. According to [35].*Rates are per 100,000 persons of the 2000 U.S. standard population.

The above discussed new observations (Figures 2, 3, 4 and Table 1) are intrigued although seen very mysterious in the light of the orthodox postulates about of cancer. This is one of the main riddles of cancer manifestations that should be decoded. At the same time, they evidenced the existence of ethnoses (and persons) with very high grades of natural i.e. genetic immunity to cancer and thus reveal very important milestones in the way to the deciphering of both the origin of cancer and the genetic components of the disease pathogenesis. A more complete understanding of cancer origin, pathogenesis and epidemic spread will come from the discovery of relevant

subjects in opposite ethnic and racial groups. One of the mile stones could be the traits of ethnoses and populations which reveal opposite values of the rates of cancer prevalence. Another milestone could be revealed by the analysis and comprehension of both individual and intra-individual diversity in natural immunity to cancer.

Over Observations of Diseased Persons

Over cancer invasion of a victim's body

Cancer is initiated by the appearance in the human body of deviant cell lineages that are habitual regulators of cell dividing and tissue growth are unable to control. The uncontrollability is predetermined by the constitutional immunity of cancerous cells to the mediators of habitual regulation of cell dividing and tissue growth [8,11]. This intrinsic trait of cancerous cells is their ultimate evolutionary adaptation for carcinogenesis. Such deviant cell lineages appear in the human body as a result of genome transformation performed over the heterozygous crossbreeding between parental gametes with partially different (divergent) genotypes (Figure 5). Over xenogamous formation of a descendant's zygote, its genome becomes admixed with carcinogenic genes [10].

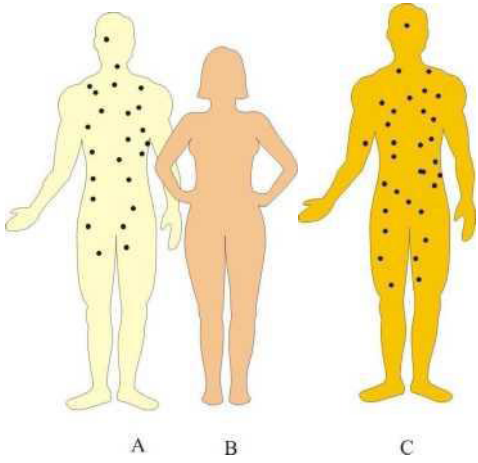

Figure 5: A hypothetic variant of the transmission of human cancer.

A - Father, the carrier of cancerous gamete;

B - Mother, the carrier of non-cancerous gamete;

C - Their cancerous son, which was developed from the zygote uniting the genomes of father's and mother's gametes.

Xenogamous mating between members of genetically different species, subspecies, ethnoses and families led to the intrusion of a genome with components of deviant genetic information that induced intra-individual diversity of cell lineages [22]. Some of the cells appear to own the main

trait of cancerous cells, genetic immunity to habitual regulators of cell division. The descent and consequent subsistence of human cancer includes regular obligatory alternation of successive descendants, which formed a hypothetical pathway of tumor development from gametes-zygote to an advanced-stage cancer (Table 2).

Table 2: Successive forms in cancer progression and subsistence (according to [36] updated)

Parents	Genomic forms	Unicellular forms			Multicellular forms	
Habitual parent	Habitual parent's genome	Habitual gamete	Cance-rous zygote	Earliest cancerous cells	Fetal micro-locations of cancer	Tumors
Cancerous parent	Cancerous parent's genome	Cancerous gamete				

The coexistence in a xenogamous zygote of both habitual and deviant, for instance, cancerous genes is a result of well-known of heterozygous interbreeding, which is responsible for the formation of the intra-individual biodiversity characteristic of any kind of human pathology [12,21,29]. After the development of the zygous form, the descendant organism consists of both habitual and deviant cells. The activity of cancerous genes leads to the appearance in the invaded human body of a set of deviant cell lineages provided with relevant cancerous abilities. They are able to resist the habitual regulation of cell division and tissue growth as well as withstand the victim's immune response. The lineages and their extracellular associates first form the micro-locations of cancer units and then their clinically detectable locations, the cancerous tumors.

Over embryogenesis of cancer

The early post-zygotic stages of human embryogenesis are not sufficient for current discovery. It is necessary only to accentuate that divergence between normal and aberrant cell clones could begin far before antenatal embryogenesis. Earliest cancerous cells are formed fetal micro-locations dispersed around the body in accordance with general rules of embryonic differentiation of tissues and their dislocations inside appropriate organs [36].

Analogous phenomenon of mosaic disposition has a brilliant track record in the fields of infectious diseases. Like the clones susceptible to infectious agents, any aberrant cell clones are usually present among the clones of habitual cells but in a far lesser quantity [21,37]. In one case of sickle cell anemia, aberrant erythrocytes consisted of 22 percent of the total number of red blood cells. Analogous phenomenon of dispersion mosaicism has a brilliant track record in the fields of infectious diseases. Individual variations in the sizes and focal locations of relevant susceptible cell clones can be seen also during the observation of many infectious diseases (Figure 6).

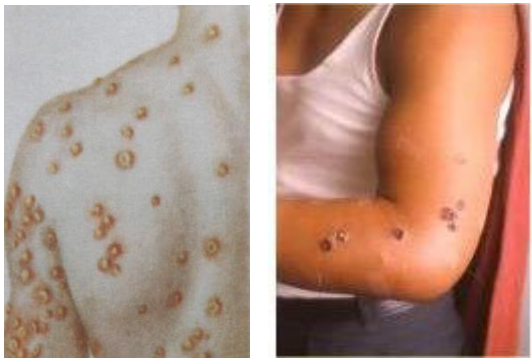

Figure 6: Dapple dispersion of susceptible cell clones revealed by smallpox (1) and anthrax (2) infections.

Dispersion of observed clones can be extremely variable in the number and size of locations. The number of patches may be less than a dozen in a minor illness (Figure 6), or they may number in the thousands in a more severe case of the same kind of disease. Beyond the edge of aberrant location, the regular tissue is normal. All the discussed traits of the dispersion of cell clones susceptible to relevant infectious agents (places of locations, their number and sizes) are formed before postnatal ontogenesis [18,21]. This may mean that distribution of aberrant clones is programmed by genomes.

Cancerous cells also appear in and stochastically disperse around the victim's body before postnatal ontogenesis and initially exist in it as subpopulations (units) of smaller but different sizes. For instance, prostate cancer is a form of malignancy which mainly develops in the prostate. Its additional units become visible later and are mainly located in the bones and lymph nodes. Prostate cancer tends to develop in men over the age of 50 [38]. The genomic roots of these traits should be subject to special investigation. In contrast to their steadfast locations, cancerous units enlarge during their postnatal life.

The primordial and late appearing subpopulations of cancerous cells and the tumors formed by them far later reside stably in their initial places in different areas of the body. They do not metastasize. In reality we can only observe non-simultaneous appearance of several identical tumors in different parts of a diseased body. This explanation of the reasons and propelling forces of cancer's discretion has been proposed and developed only recently [8,9,11].

Anatomy and physiology of a ripe cancer

The somatic mutation hypothesis allows the existence of only one cancerous cell clone in an affected body. First doubts about this hypothesis were revealed by integrative analyses of epidemiological and clinical observations [8], according to which the multiple cancers comprise two or more primary cancers occurring in an individual that originate from a primary site or tissue and are neither an extension nor a recurrence or metastasis [39].

Cancer patients have a 20% higher risk of a new primary cancer compared to the general population. Approximately one third of cancer survivors aged >60 years were diagnosed more than once with another cancer. As the number of cancer survivors and older people increases, the occurrence of multiple primary cancers is also likely to increase [39-43].

Such observations prompted the idea of the possible existence of a number of appropriate clones in cancerous tissue. This means that like any other multicellular being, cancer may contain a variety of different cells and associated extracellular structures that are under different genetic regulation and may perform different functions at different stages of cancer development [8,9]. According to the xenogamous theory of carcinogenesis, any ripe cancer should consist of a number of subunits of various sizes that are positioned in different areas of the afflicted body. Each subunit contains cellular and tissue structures. In contrast to the somatic mutation hypothesis, the existence in a cancer of a number of different clones was recently documented very well.

Recent studies [44] together with the set of data discussed above, allow us to suppose that like any other multicellular being, cancer contains a variety of different cells that are under different genetic regulation and possess different behaviors. Cancer consists of a couple of functionally heterogeneous cell lineages that vary with respect to their distinctive structural or physiological functions and potentials. The heterogeneity within a tumor cell lineage may also determine the differences within the tumors and their locations. Cancer is able to maintain its structural stability through many generations and the diversity of cancer composition remains stable over its sequential long-term propagation [44]. This means that both animal and human cancers have developed many adaptations that enable these aberrant lineages of mammalian cells to exist as a multicellular parasite [8,9].

Cancer cells are the driving force of tumor development and progression yet these transformed cells cannot do it alone. Assemblages of ostensibly normal tissue and bone marrow-derived (stromal) cells are recruited to constitute tumorigenic microenvironments. Most of the hallmarks of cancer are enabled and sustained to varying degrees through contributions from repertoires of stromal cell types and distinctive sub-cell types. Their contributory functions are becoming increasingly better understood, as are their reciprocal communications with neoplastic cancer cells that mediate their recruitment, activation, programming, and persistence [45].

Such complicated traits cannot belong to a lone cell. Besides, their acquisition cannot be achieved by single mutation. This conclusion discredits the basis of the somatic mutation hypothesis but supports the compromising idea of cancer occurring as a consecutive accumulation of mutation upon mutation on a single normal cell [45,46]. The new versions of the somatic mutation hypothesis do not discuss cancer transmission between humans either.

Cancerous tumors are composed of multiple cell types: stromal, immune or malignant cells. Malignant cells can also show sub-clonal heterogeneity, where different clones carry various somatic mutations and show variable oncogenic potential or drug sensitivity. Finally this sub-

clonal population can change during the progression of the cancer [47].

Cancer is sustained by the production of aberrant cells that vary in many morphological and physiological properties. The repopulation dynamics of 150 single lineages from ten human colorectal cancers were followed. The revealed functional heterogeneity of the cell lineages varied with respect to their distinctive structural or physiological functions and potentials. Some clones were able to become dormant and undetectable only to become abundant in later generations [44].

Heterogeneity within a couple of tumor cell lineages may also determine the differences within the kinds of tumors and their locations. Cancer maintains its heterogeneous structural stability through many generations. The diversity of cancer composition remains stable over its sequential long-term propagation [44]. The presence of various slow-growing dormant clones was also evidenced by the re-emergence of previously minor clones after chemotherapy, and their ability to initiate new tumors (although of a smaller size) over subsequent transplantations of the tumors in experiments [48].

Incipient micro-populations of cancerous cells are formed, distributed and dispersed in the afflicted body before postnatal ontogenesis in the form of distantly separated micro-populations and their initial sizes are different but very small. The number of present subpopulations may be less than a dozen in a minor case of illness, or they may number in the hundreds in a severe course of disease. Beyond the edge of the subunits, the tissues are seen immune to cancerous invasion zones. The majority of any cancerous body consists of such unaffected, i.e. hereditary immune zones.

The cancerous subunits are dispersed around the body either stochastically or in a manner not yet understood. Accordingly, the formation of subunits before postnatal ontogenesis is the reason they are not eliminated by the mechanisms of adaptive immunity performed by the lymphatic system [9].

It was supposed that cancerous units in primordially different locations become clinically detectable at different times after initiation of malignant growth; this allowed for the differences in their initially smaller sizes. The differences in initial cancer cell masses and their subunits around the body predestined individual diversity in the course and severity of cancer when the disease begins to develop [10].

At a relevant time in a victim's life, the uncontrollable growth of such micro-subpopulations becomes visible in the form of detectable extra cell masses of cancerous tissue, the malignant tumors. The largest of the primordial subpopulations achieves the size of detectable tumor far earlier than the smaller ones, thus forming the first apparent cell mass, usually called the 'primary' tumor. The subpopulations of initially lesser sizes may become visible in the form of 'secondary' detectable tumors.

In most of it cases cancer consists of some separate units that are dispersed around the victim's body in a stochastic maner. However, they keep their physiological unity that is demonstrated by a set of unique manifestations evidenced just recently in post- surgical and experimental observations. Communications between cancerous units was hypothesized in [49] and confirmed in a host of other studies, many of which are reviewed in [12,50]. It was noted that large tumors inhibit the growth of smaller tumors and thwart the inception of new tumors [50-52].

Extirpation of larger tumors triggers the accelerated proliferation of smaller, dormant or slower-growing cancerous units. The removal of a unit could accelerate the growth of other units which were inhibited before. The accelerated progression of cancerous units after foregoing resection was noted in experimental [53-55] and clinical [56,57] studies. Acceleration in the rate of growth of inattached units was found after 70% ectomy of cancerous liver [58].

Resection of bigger tumors was followed by a 32-fold increase in the rate of the growth of other units [59]. More importantly, the early extirpation of the first apparent cancer unit does not prevent the subsequent appearance of "secondary" units [60,61]. This may mean that at the time of the resection, the secondary tumors already existed in the form of undetectable micro-populations. It is proposed that cancerous units produce humoral factors able either to promote or inhibit tumor growth and angiogenesis. Removal of the primary tumor reduces the production of growth inhibitors and pro-apoptosis factors and signals, which accelerates the growth of smaller subunits [59].

These important finding have been directly confirmed in a number of well-documented clinical case studies involving various types of cancer. For instance, in eight cases of testicular cancer, resection of voluminous tumors caused a dramatic exacerbation of the disease [62]. Excision of primary melanomas precipitated the appearance of new subunits in three skin cancer patients [63,64]. In one case of pancreatic cancer, excision of the primary adenocarcinoma caused the appearance in the liver of numerous previously undetectable subunits [65]. Analogous effect on cancer physiology can be induced by radiological procedures as well as the current means of cancer chemotherapy. Thus the widely performed futile billion squanders on the use of surgery, radiology and current chemotherapy of cancerous disease should be stopped. They are not only futile for cancerous patients but even very dangerous for them.

Differences in the locations of cancer sub-units

According to well established knowledge [66], every new entity is initiated by the process of fertilization involving the fusion of male and female gametes to form a zygote, the unicellular form of the entity born during the fusion of gametes and their genomes. In the case of carcinogenic fertilization, the zygote's genome will contain carcinogenic components. Immediately following fertilization, the zygote undergoes a series of extremely rapid mitotic divisions (cleavages) wherein the enormous volume of its cytoplasm is divided into numerous smaller cells (blastomeres). In

the case of the carcinogenic zygote, some of the blastomeres may contain cancerous components in their genomes.

By the end of cleavage, the blastomeres form an unfilled spheroid known as a blastula and then change their positions relative to one another. This series of extensive cell rearrangements leads to the formation within the embryonic entity of three germ layers: the ectoderm, the endoderm, and the mesoderm. The layers interact with one another and rearrange themselves to produce tissues and organs. The developing entity enters the stage of organogenesis.

During organogenesis, certain cells undergo long migrations from their places of origin to their final locations. These migrating cells include the precursors of blood cells, lymph cells, pigment cells, and gametes. Many organs are formed of cells from more than one germ layer. For instance, most facial bones are derived from cells that have migrated ventrally from the dorsal region of the head. A specialized portion of zygote cytoplasm gives rise to cells that are the precursors of the gametes (either the sperm or egg).

The gametes and their precursor cells are set aside for the function of reproduction. The separation of somatic cells (which give rise to the individual body) and germ cells (which contribute to the formation of a new generation) is often one of the first differentiations to occur during animal development. The germ cells eventually migrate to the gonads, where they differentiate into gametes. The development of gametes is usually not completed until the organism has become physically mature. Gametogenesis begins during development but is completed in the sexually mature adult. At maturity, the gametes may be released and participate in fertilization to begin a new embryo.

At least two paradoxes can be seen in the disposition of either primordial or later appeared malignant tumors. Firstly, in contrast to assumed ubiquitousness of primordial tumors there are both more favorite and far less favorite sites of their dispositions. The primordial tumors are mainly disposed at prostate, lung, bronchus, colon, urinary bladder, skin, kidney, rectum, pancreas, stomach. Besides, hypopharynx, bones and joints, floor of mouth, nasopharynx, gallbladder, oropharynx, oral cavity. trachea, peritoneum and pleura are far less favorable for the disposition of primary tumors (Table 3). Secondly, there are only some most common sites where the late appeared tumors are preferably dispose - the lungs, bones, liver, and brain. Other places of a body are seen far less accessible for appeared tumors. One question arise immediately – are these unfavorable places immune to the invasion of cancer?

Table 3: Opposite rates of male cancer incidence by primary site and race (Rates are per 100,000 persons of the 2000 U.S. standard population) [67].

Cancer sites		All Races	White	Black
Sites of Highest Rates				
1.	Prostate	156.9	145.0	226.0
2.	Lung & Bronch	85.0	79.9	95.1
3.	Colon	36.9	36.0	46.1
4.	Urinary Bladder	36.0	37.9	18.3
5.	Skin	25.6	28.0	2.0
6.	Non-Hodgkin Lim	22.6	23.1	16.0
7.	Kidney	20.8	20.7	23.1
8.	Rectum	15.8	15.5	15.9
9.	Pancreas	13.2	13.0	15.7
10.	Stomach	9.2	8.1	15.5
Sites of Lowest Rates				
1.	Hypopharynx	1.2	1.1	2.4
2.	Bones /Joints	1.1	1.1	0.8
2.	Mouth	0.9	0.9	1.1
4.	Nasopharynx	0.8	0.7	1.1
5.	Gallbladder	0.8	0.6	1.1
6.	Oropharynx	0.7	0.7	1.2
7.	Oral cavity	0.4	0.4	0.6
8.	Trachea	0.3	0.3	0.2
9.	Peritoneum	0.1	0.1	0.1
10.	Pleura	0.0	0.0	0.1

The differences discussed above demonstrate the inequality of human body parts in their ability either to resist cancer installation or to accept and keep the cancerous sub-units. The inequality is although evidenced by expressive intraindividual differences in the disposition of cancerous units around afflicted body. Hereditary immunogenic way of the existing of such variation as well as its reasons have not been discussed anywhere before.

Over stages of organogenesis, the earliest primordial cancerous cells are carried to different areas of the embryo's body before postnatal ontogeny in the same manner that is used to create other embryonic tissues and organs. After the end of their dispersion and initial multiplication, the cells exist like the primordia of future tumors, sleeping cell masses of smaller but different sizes. The carcinogenic components in the cells genomes may dispose at various places of the afflicted entity, probably according to their intrinsic predilection. After that the cells continue to exist inside the infected body in the form of several distantly separated micro-populations, the cancerous subunits, and provided with life-supporting stuffs and energy by the organism. The development of detectable tumor is usually delayed for decades.

At the appropriate time of the host's life (mainly after 40 years of age), probably according to a specific program of cancer ontogenesis and aging, the potentially cancerous micro-populations receive their specific impulse to awaken. This means that human cancer possesses its own schedule, an intrinsic biological watch; i.e., the genetic program of its development from zygote and primordial cancerous cells to transmission between humans. This programmed cancer subsistence is different of that of its victim. This is a specific cancerous germ line - the lineage of

cells culminating in the germ cells. The possession of these unique genomic traits provided cancer with many benefits of undoubtedly adaptive importance. The program favors those cancerous cell lineages whose schedule of life does not allow early restriction of reproductive, or transmissive, functions of the afflicted person as well as the period of its effective care for offspring before its victim is 40 years of age.

Foreignness of cancer for it prey

It should be especially accentuated exceptional foreignness of cancer for its host**.** All cancer looks alien in the body afflicted by them. This is applicable both to the bodies of cancerous tumors (Figure 7) and to their microscopic cellular tissue structures.

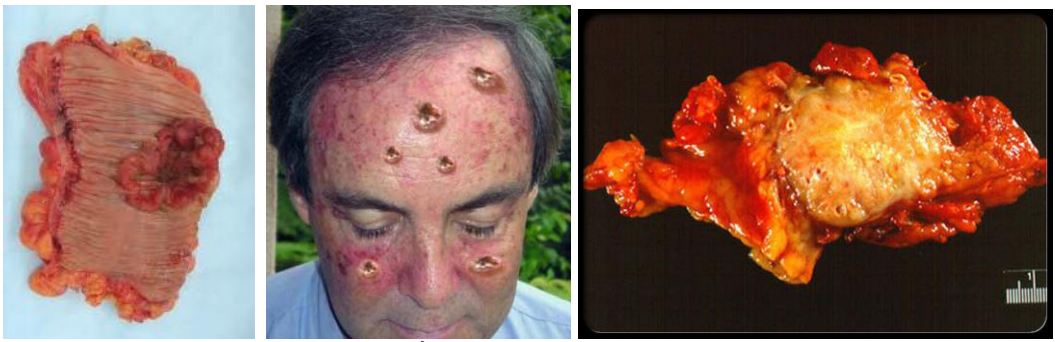

Figure 7: Visual foreignness of cancerous tumors

a) Cancer disposed on normal colon tissue (photograph courtesy of adruniverse.blogspot.com)

b) Multiple cancer subunits on facial skin (photograph courtesy of adruniverse.blogspot.com).

c) Cancer (yellow color) intruded into the pancreas (photograph courtesy of Emedicinehealth IMAGE COLLECTION).

The cancer cells look abnormal and foreign under the conventional light microscope (Figure 8). Although they are considered versions of cells which compose the tissue of the supposed cancer origin; in reality, light microscopy cannot identify the tissue and site of malignancy origin [68].

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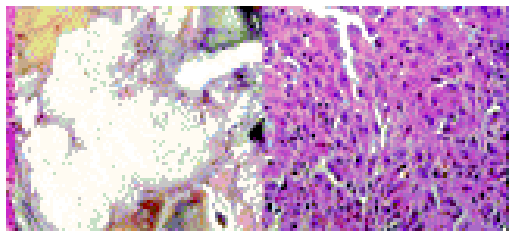

Figure 8: Gross and microscopic features of sarcomatoid renal cell carcinoma presented by [69] as well as any other form of cancer disease attest the foreignness of cancerous malignancy.

There exist a plenty of various morphological and physiological manifestations of the foreignness of cancer for its prey. Some of them may remind the similar but not identical traits of those ones if any of infectious and parasite diseases. Their influence is revealed in any other features of cancer both unique and universal all-pathological traits of malignancy as well. The presence of cancerous foreignness was surely evidenced in lung and breast cancers (over 90%) by dogs' scent [70].

IMMUNOLOGY OF CANCEROUS TISSUES AND CELLS

Hereditary Immunity of Cancer to Victim's Regulatory Management

Any living being is constitutionally provided with a physiological system that maintains normal body structure within its genetically predetermined shape, size and function. A special part of this very important and effective system is dedicated to managing the starting and revival of body structures and functions on molecular, subcellular, cellular, tissue and organ levels. Habitual cells of normal organisms grow and divide to form new cells as the body needs them. When cells grow old and die, new cells take their place. The regulation is realized on the cellular level and performed by means of molecular humoral agents.

In the case of cancer invasion, this orderly process goes wrong. The mighty system of body management and maintenance appears to be impotent, even in relation to some its initially smallest parts, the subunits of cancer. Cancerous cells grow and divide independently of habitual physiological management. That occurs because cancer cells and tissues possess absolute constitutional immunity to the agents of habitual physiological management of cell division and tissue formation. Constitutional (hereditary) immunity of the cells against relevant physiological regulators can be created by structural incongruence between regulators and their receptors. The existence of such specific immunity is considered the obligatory prerequisite to malignity [9].

Cancer cells continue dividing and forming the masses of relevant tissue when the afflicted body does not need them. Furthermore, the cancerous cells of older generations do not die when their peers would. The extra cells form the masses of tissue called malignant tumors. This innate (constitutional) trait of cancerous cells is of most adaptive, pathogenic importance. This innate immunity of cancerous cells functions in all stages of cancer and maintains its initiation, development and subsequent progression.

Hereditary Immunity of Cancer to Victim Immune Defense

Human cancer invades its victim because there is no immunity. The malignant cells and tissues are inherently protected from destruction by cell and humoral mechanisms launched by the victim's lymphatic system of responsive immunogenesis. Cancerous cells are not recognized by the victim's immune system as non-self because their surface does not contain relevant molecules of the major histocompatibility complex that are essential to the antigen-processing pathway. Such traits allow the cancer to evade the surveillance performed by the victim's system of

immunogenesis. This protection is predetermined by the germ line of the formation of cancerous cells directly from the zygote over the prenatal development of the afflicted organism [8]. This trait of cancer ontogeny is undoubtedly of evolutionary adaptation, providing the parasite with a lifelong ability to escape rejection by the victim's immune response.

CONCLUSION

The above investigation was devoted to the revealing and characterization of the traits of constitutional (hereditary) immunity in cancer origin, pathogenesis and epidemic spread. The search was based on entirely innovative hypothesis - the hypothesis of genome intrusion of cancer origin over carcinogenic transformation of reproductive genomes in consequence of xenogamous mating and consequent intrusion of the offspring genome with foreign carcinogenic component. The goal of this article was to widen immunological evidence of the entirely innovative hypothesis of xenogamous origin, parasite subsistence and sexual transmission of human cancer.

The main focus was on manifestations of hereditary immunity over consecutive stages of cancer subsistence, beginning from the invasion of victim's genome with cancerous gamete and finishing by sexual transmission of cancerous genome between people. The evidence of hereditary immunity has been revealed at any of the stages. The newly performed immunological updates to the hypothesis were based on multidisciplinary integrative reassessment and re-sensing of both well-known and recent data about cancer epidemiology, immunology, genetics, pathogenesis and clinical manifestations from the viewpoint of up-to-date, all-pathological, immunological, genetic, anthropological and evolutionary discoveries.

The first pioneer conclusion of performed discovery is that human cancer is a foreign biological entity adapted, in it evolution, to invade inside of human body and exist in it at the expense of stuffs and functions of the intruded organism. The evolutionary emergence of cancer should be predetermined by genome transformations that created, in evolution, inter-taxon differences in the molecular constitution of inherent physiological systems responsible for the regulation of cell dividing and tissue growth.

Cancerous disease is a result of ecological functions performed by the subsistence of cancer inside of invaded human body despite out the counteraction of afflicted organism. The circle of cancer life is also figured in the innovative paradigm for the first time. Except some unique genomic traits, mainly those providing it with the ability to invade victim, reproduce in it and be transmitted to the bodies of new prays, cancer may be considered as analogous to the plethora of parasites existed in the world.

The development of individual cancer is initiated by the appearance in the afflicted body of a deviant cell clone (or clones) inherently immune to the prey defence systems. These clones are foreign (alien, non-self) to the afflicted body with many of its traits. They are although able to grow independently of physiological control of normal cell replication. Hereditary immunity of

cancerous cells to habitual physiological control of normal cell replication and tissues grow should be considered as their evolutionary adaptation to parasitic way of life. This trait of cancerous cells provides the success of their invasion and subsequent progression inside of afflicted body. The surmounting of cancer hereditary immunity against normal cell regulation may become a goal of the development of effective cancer chemotherapy.

The emergence of cancerous clones and their dispersion around the body in the form of discrete micro-populations are performed before postnatal ontogeny in the manner used in the dispersion of other embryonic tissues and organs. That is why the lymphatic system of individual adaptive immunity does not recognize the deposited cancer cells as foreign and does not destroy them. This circumstances provide cancer cells with hereditary immunity against the wictim's responsive immunogenesis.

Human hereditary immunity to cancer could be revealed even at the stage of conception - in the cases of structural incongrueence between habitual and cancerogenic gametes. But in current reality of our technical potencies it is evidenced by the existense of demonstrative racial, ethnic, population inter-individual and differences in the prevalence of cancer. What is more, the existence human hereditary immunity to cancer is confirmed by expressive intraindividual differences in the disposition of cancerous units around afflicted body. The differences of this kind demonstrate the inequality of human body parts in their ability either to resist cancer installation or to accept and keep the cancerous sub-units. Some humans are born with total defence against cancer where as others people bodies possess only seldom susceptible localities. Probably the more susceptible persons can not be raised and born.

These new notions provide innovative framework and landmarks for the location of evoluutionary roots of cancer origin and current subsistence. There remains much to learn about this extraordinary unique and extremely complex disease. According to the paradigm, the search for a coveted clue to the genomic roots of cancer would be oriented on the discovery of structural and functional differences between the genomes of cancerous and normal cells. The notions should also encourage new research ideas and proposals for cancer prevention and therapy.

The prevention of cancer should be oriented on the principle approved in the prophilaxis of other sexually transitted invasions. Appropriate genetic tests must be performed before conception. The cancerous genealogies of expectant moms and dads must be discovered in detail. Their genomes must also be tested for the risk of cancer in their potential children. The results can provide early warnings about cancer, the deadliest disease. The warnings can help people to make rationale decisions about their marital plan. This kind of protective parenting is now on its way to becoming a mainstream medical test.

The discovery of hereditary immunity in cancer leads to the revision of cardinal perspectives in the healing of cancer. All previous efforts of medicine in the chemotherapy but especially in the

surgical and radiological healing of cancer appeared futile while they are opposed by the biology of cancer and pathogenesis of cancerous disease. Current medicine must stop the futile billion squanders on the unreasoned surgical and radiological cure of cancerous disease but readdress the billions on the search of pathogenetically grounded chemotherapeutics.

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