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The Common Origin of Multicellularity and Cancer: Lessons from the Fossil Record

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Abstract

Despite the methodological limitations in the study of fossil record and some confusion in the literature about the diagnostic distinction between real neoplasia and other types of proliferation or even malformations in species very distant from mammals, paleopathological studies have revealed many cases of *bona fide* benign as well as malignant neoplasms in animals and land plants since Paleozoic Era. Further, almost all types of modern neoplastic diseases have been documented in ancient *Homo sapiens* bone remains. It is worth to note that, despite the major changes in the structure of animal populations, the prevalence of malignant as well benign neoplasms has remained relatively constant (and in some cases it has even increased) among the different taxa of animals for hundred million years. This suggests that malignancies as well as benign neoplasms are rooted quite deeply in the evolutionary life of organisms. This seemingly unremarkably fact represents a remarkable riddle for evolutionary biologists. If natural selection, working on living organisms has been powerful enough to produce complex adaptations, from the eye to the immune system, why has it been unable to eliminate or even reduce the incidence of cancer, even though many apparently less harmful traits have been eliminated during species evolution? Based on the fact that, both today and in the fossil record, cancer seems to occur in organs that have experienced a decline or loss of their regenerative ability we suggested that cancer may be an ultimate, even futile, reparative attempt. Therefore, the permanence of cancer by hundred million years might be understood as if its existence is coupled to the normal regenerative mechanisms of the organisms without which no pluricellular organism could survive. This interpretation, encoded in the so-called hypothesis of the biological sense of cancer, was built within the broad framework of tissue organization field theory (TOFT) by assuming that cancer is primarily a disease of higher levels of organization, that is, an organismic, organ- or tissue-based disease rather than a cellular one.

Keywords: multicellularity, cancer, fossil record, paleopathology, TOFT

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1. The Many Routes to Multicellularity and Cancer

In the ancient seas of the Earth, about a billion (10^9) years ago, multicellular organisms began to evolve from eukaryotic unicellular ancestors. There is convincing evidence that this process was not unique, and that multicellularity has evolved independently many times in the history of life: once in animals (*metazoa*), once in land plants (*embryophytes*); once in each sac (*ascomycetes*) and club (*basiodiomycetes*) fungi; once in green algae (*chlorophytes*) and at least one in both red algae (*rhodophytes*) and a complex group that includes brown algae called heterokontophytes (Aktipis *et al.* 2015).

Remarkably, however, regardless of the different evolutionary lines of multicellular organisms, all of these processes share two central features as a precondition to preserve and restore the organismic homeostasis. First, the capacity for cooperation among their cells—that includes different types and levels of differentiation associated with division of labors, resource transport and creation and maintenance of the extracellular environment. And second, the development of mechanisms designed to regulate cell death and to control normal cell proliferation, although the intimate nature of these mechanisms remains controversial (Sonnenschein & Soto 2021; Sanchez Alvarado & Yamanaka 2014).

A dis-regulation of the latter mechanisms is assumed to be the basis of the *normal architecture-modifying proliferative growth of tissue*, which is collectively called "neoplasia" (etymologically, "new growth"), in which tissue organization and function are altered.

If this new growth has relatively little effects on the organismic homeostasis, it can be defined as benign neoplasia. On the other hand, if it affects the organismic homeostasis in ways that may have profound effects for organism fitness and survival, it can be defined as malignant neoplasia or cancer.

Herein, we define these terms in a broader sense than that clinically defined for humans and, for extension, for mammals. In effect, in clinical settings, the term "benign" is reserved for slow-growing, relatively well differentiated neoplasms that remain localized in the tissue of origin. In contrast, the term "malignant" is used to denote fast-growing neoplasms that invade and destroy adjacent or distant (metastases) tissues and display many additional features such as less cellular differentiation or anaplasia, acceleration of cell cycle and high number of mitotic figures, genomic alterations, increase cell mobility, chemotaxis, changes in the cellular surface, secretion of lytic factors, etc. (Robert 2010). We do not use the classical definition of Ewing (1940) in which "a neoplasm (either benign or malignant) is an autonomous, or relatively autonomous, growth of tissue" (autonomous meaning the ability to disobey the rules that control normal cell proliferation) because this statement, that has guided cancer research for more than 80 years, is actually a postulation rather than a true definition. In effect, pathologists do not use it as an operational tool to diagnose the presence of a tumor. In fact, the means to diagnose cancer have not changed that much since the 19th century, when pathologists began describing the histological pattern of tumors using the light microscope (Sonnenschein & Soto 1999; Mayo Clinic 2023). In addition, if the mechanisms that control normal cell proliferation are still unknown, how can anyone be assured that cancer cells are disobeying those mechanisms?

It is possible that not all features of human cancer are present in species or lineages very distant from mammals such as invertebrates or land plants. In consequence, it might be said that those species or lineages do not get cancer. However, if we do not focus exclusively on human cancer and we adopt the more general definitions stated above, "cancer" or "cancer-like phenomena" (as proposed by some authors) might be present in a much larger collection of multicellular organisms than originally thought (Aktipis *et al.* 2015; Dujon *et al.* 2022).

2. Limitations of the Fossil Record

The broad definition of neoplasia given above distinguishes it from other common proliferations or phenomena such as malformations, hyperplasia, regenerative growths, inflammation, etc. although the boundaries among them are not always very clear. This statement is particularly true for extinct organisms. In fact, the interpretation of neoplasms in the fossil record is one of the more challenging aspects of paleopathology.

In the first place, the material available to paleopathologists consists, in most cases, of osseous remains, apparently limiting the detection of neoplasms to bone tumors of ancient vertebrates and leaving behind the most ancient pluricellular organisms.

However, upon certain circumstances, structures of invertebrates such as exoskeletons and shells could be preserved. In effect, the precipitation or growth of mineralized exoskeletons and shells is widely distributed in invertebrate taxa within the phylum Mollusca as well as the subphyla Crustacea. The composition of these structures varies throughout invertebrates, and, similar to vertebrate bones and teeth, consists of mineral and organic components that can be fossilized depending on special biological, physical, and chemical conditions. Furthermore, upon very rare circumstances, soft tissues can also be preserved. One mechanism that facilitates soft tissue preservation is phosphatization, where the tissue is replaced by calcium-phosphate minerals. However, in these cases, the process does not preserve the physical structure of the organs. Exceptionally rare, intact or almost intact soft-tissue fossils have been found in some rocks. This process is known as Burgess Shale-type (BST) preservation. Burgess Shale is a fossil-bearing deposit exposed in the Canadian Rockies of British Columbia, Canada, famous for the exceptional conservation of fairly tough tissues such as cuticle as thin films, and soft tissues as solid shapes, even those pertaining to organisms of extreme antiquity. Consequently, soft normal and neoplastic tissues might have also been eventually preserved associated with both ancient vertebrates and invertebrates. The BST preservation is not yet completely understood although latest investigations suggest that soft tissue fossil-bearing rocks apparently contain some minerals that inhibit bacteria, preventing the process of decomposition after death. On this basis, scientists hope to elucidate the underlying mechanisms of this process to find more soft-tissue fossils (Keenan 2021).

In the second place, the diagenetic process that affects the fossil remains may produce post-mortem alterations that either simulate or overshadow cancer-linked lesions that occurred during life. In fact, focal and multiple alterations induced in bone by different physical, chemical and/or biological factors may produce erosions that can mimic lesions associated with primary or metastatic neoplasms. On the other hand, the diagenetic process may also superimpose alterations (for example, incrustations) that may hide cancer lesions or modify their original appearance (Capasso 2005). Today, however, methodological progress, especially in the field of archeometry, has improved our capacity to distinguish a variety of lifetime parameters, including cancer images and lesions, from alterations produced after the death of the organisms (Grupe & Harbeck 2014).

In the third place, the difficulty to find neoplasms and especially cancer in the fossil record is associated with two characteristics of the wild life: first, most individuals tend to die at a young age due to starvation, infections or predation, at a time when the incidence of cancer is very low; second, when the age to get cancer is reached, tumor-bearing organisms could be more susceptible to predation than healthy individuals, limiting the possibility to appear in the fossil record. Moreover, predators are thought to prey on individuals that are in poor physical condition. This can explain why benign tumors or early but not metastasized cancer are more commonly detected in organisms in the wild (Perret *et al.* 2020).

In the fourth place, a fossil record represents an instantaneous picture and not a moving process. Consequentially, the chance of determining whether, during the life of an extinct organism, a neoplasm could have affected—and to what extent—its fitness and survival, is an inference based on the peculiar traits of the neoplasm but not a direct observation. In

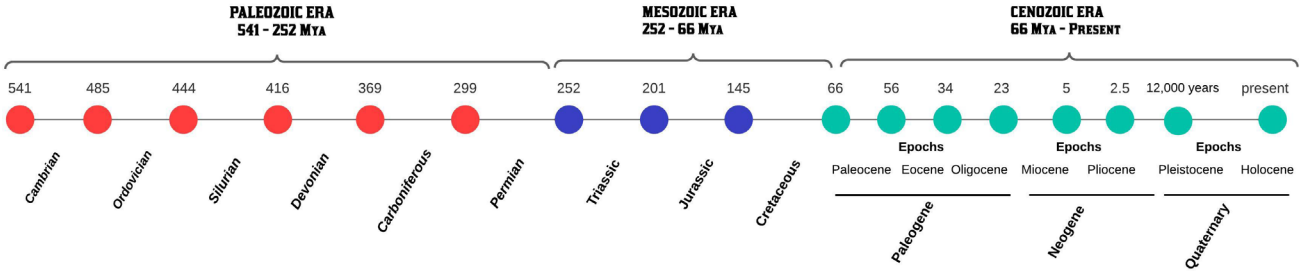

Figure 1. Chronology of the different geological eras, periods, and epochs.

Table 1: Cases of benign and malignant tumors in the fossil record of animals and land plants.

Geological eras		***Species***	***Tumor type and location***	***References***
Paleozoic Era	Invertebrates (trilobites)	*Centropleura loveni* (Cambrian)	Nearly circular prominent bubble-shaped structure. Anterior pleura ridge of thoracic segment	*De Baets et al. 2021; Babcock 1993*
		Conomicmacca hyperion (Cambrian)	Large neoplasia. Posterior pleura region adjacent to the furrow that separates the pygidial axis from the pleuron	*Elicki & Geyer 2013*
		Toxochasmops (Ordovician)	Metaplasia	*Nielsen & Nielsen 2017*
		Bohemoharpes ungula (Silurian)	Neoplasm accompanied by radiating circulatory canals	*Owen 1983*
	Vertebrates	*Dinichthys* (Devonian)	Bone resorption due to a malignant tumor of the soft tissues of the mouth floor	*Capasso 2005; Scheele 1954*
		Phanerosteon mirabile (Carboniferous)	Osteoma including a bone focal hyperostosis	*Capasso 2005; Moodey 1927*
		"Mammalian" forebear (Permian)	Compound odontoma (a benign neoplasia of calcified dental tissue)	*Whitney, Mose, & Sidor 2017*
	Plants	*Odontoperis* (Early Permian) *Pteridiorichnos stipitopteri, Walchia piniformis* (Carboniferous)	Abnormal outgrowths of plant tissues denominated galls. Galls are produced by host plant cells in response to infection by fungi, bacteria, nematodes, insects, mites or other agents.	*Labandeira 2021; Scott, Stephenson, & Collinson 1994; Schachat & Labandeira 2015; Impson, Post, & Hoffmann 2013; Schread 1971*
Mesozoic Era	Vertebrates	*Triassic capitosaurid,* amphibian (Early Triassic)	Parostotic osteosarcoma in a cranial bone	*Gubin et al. 2001*
		Shell-less stem-turtle *Pappochelys rosinae* (Middle Triassic)	Osteosarcoma on the femur	*Haridy 2019*
		Metoposaurus, krasiejowensis (Late Triassic)	Osteosarcoma	*Surmik et al. 2022*
		Comanchean dinosaur (Early Cretaceous)	Hemangioma between two caudal vertebrae	*Moodie 1921*
		Mosasaurus, Pachyrhinosaurus, Vagaceratops irvinenesis, Titanosaurus, Hadrosaurs (Cretaceous)	Osteomas	*Moodie 1921; Rothschild et al. 2003; Rothschild & Martin 1993; Rega, Holmes, & Tirabasso 2010; Souza Barbosa et al. 2016; Norman & Milner 1989*
		Edmontosaurus (Cretaceous)	Metastatic cancer	*Rothschild et al. 2003*
		Apatosaurus, Allosaurus, Vagaceratops irvinenesis (Jurassic)	Osteochondroma	*Capasso 2005; Rega, Holmes, & Tirabasso 2010;Foth et al. 2015*

	Plants	*Viaznikopteris rigida, Dicroidim odontopteroides* (Early Triassic) *Ginkgoites sp., Desmiophyllum sp.* (Cretaceous)	Galls	*Labandeira 2021; Krassilov & Karasev 2008; McLoughlin 2011; Vasilenko 2005*
Cenozoic Era	Vertebrates	*Fishes* (Tertiary and Quaternary) *Sirenian mammals* (Oligocene) *Elephants* (Quaternary)	Osteomas	*Capasso 2005; Przyklady 1965*
		Hesperocyon (Oligocene)	Osteochondroma	*Wang & Rotschild 1992*
		Mammoth (Late Oligocene)	Osteoblastoma	*Krzeminska 2008*
		Ungulates from Argentina, horses, European mammoths, Japanese elephants and in a walrus from Alaska.	Neoplasms of the dental tissues	*Capasso 2005; Cabrera 1934; Patte 1937; Hunter & Langston 1964; Kobayashi 1937*
		Bovidae, Canidae, Nothroterium Ursusus spelaeus	Benign tumors	*Miralles & Crusafont Pairo 1952; Pales & Wernert 1953; Moodie 1929; Scott 1898; Pales 1959*
		Buffalo, Capra, Nothrotherium maquinense	Osteosarcoma	*Conkling 1990; Capasso & Di Tota 1996; Souza Barbosa et al. 2021; Baker & Brothwell 1980*
	Plants	*Taxodium dubium, Alnus julianiformis* (Paleogene)	Galls	*Chen & Appleby 1984; Jiang et al. 2021*
	Pre-human and ancient human populations	*Australopithecus sediba*	Osteoid osteoma	*Quinney et al. 2016*
		Homo ergaster	Osteosarcoma	*Odes et al. 2016*
		Homo erectus	A possible Burkitt lymphoma or an ossifying sarcoma	*Capasso 2005*
		Homo steinheimensis	Meningiomas	*Czametzki, Schwaderer, & Pusch 2003; Czametzki 1980*
		Homo neanderthalensis	Meningiomas, intradiploic epidermal cyst	*Hublin et al. 2009*
		Homo sapiens	Meningiomas, hemangiomas, osteoclastomas, histiocytomas, osteomas, osteocondromas, osteosarcomas, condrosarcomas, hemangiosarcomas, Ewing's sarcoma. Bone metastases of nasopharyngeal, breast and prostatic carcinoma and lytic lesions due to multiple myeloma and melanoma.	*Capasso 2005; Czametzki, Schwaderer, & Pusch 2003; Shimkin 1977; Strouhal 2001; Pahl 1986; Luna et al. 2008; Luna et al. 2015; Arrieta, Mendonca, & Bordach 2018*

fact, strictly speaking, the very existence of a neoplasm (new growth) in a fossil is also an inference, because no "growth" during life can be directly demonstrated in a dead body.

3. The Fossil Record of Cancer

Despite the limitations mentioned in the precedent paragraph and despite some confusion in the literature about the diagnostic distinction between real neoplasia and other types of proliferation or even malformations in species very distant from mammals , the fossil record has revealed many cases of *bona fide* benign as well as malignant neoplasms since Paleozoic Era. Figure 1 shows the chronology of the different geological eras, periods, and epochs. Table 1 summarizes the many cases of benign as well as malignant neoplasms observed in fossils of both animals and plants that will be described below.

3.1. Non-human Organisms: Paleozoic Era (541-252 Million Years Ago)

The most ancient reported neoplastic cases may be traced to the Paleozoic Era. In effect, 23 neoplasia have been detected in fossils of trilobites, an extinct class of marine arthropods with over 20,000 species having been described, that lived for almost 270 million years, from the early Cambrian [Cambrian period lasted 56 million years between 541 to 485 million years ago (Mya) and it was the time when practically all major animal phyla first appeared in the fossil record] up to the late Permian (299-252 Mya). Because trilobites had wide diversity and an easily fossilized exoskeleton, they have left an extensive fossil record. Some of these neoplasms have been attributed to parasitism and/or traumatic injuries while the origin of others remains uncertain. Some examples show simple bulbous swellings with a central crater-like depression that could be produced in slow-healing ulcers induced by infections of pre-existent injuries. In other cases, however, the growth seems to invade and damage adjacent structures resembling the invasive neoplasia observed in human beings and other mammals. Probably the best example has been detected in an incomplete carapace of a specimen of *Centropleura loveni* from the Cambrian (more than 500 Mya): the neoplasia was a nearly circular prominent bubble-shaped structure developed from the anterior pleura ridge of thoracic segment 6. The neoplasia affected not only the part of the pleura from which it originates but also the posterior part of the anteriorly neighboring pleura, the posterior margin of which is indented (De Baets *et al.* 2021; Babcock 1993). A large neoplasia was also observed in a specimen of the bathynotid trilobite *Conomicmacca hyperion* from the Cambrian. The neoplasia was located in the posterior pleura region adjacent to the furrow that separates the pygidial axis from the pleuron and it could have affected the pleural area immediately adjacent to the neoplasm as well as the pygidium growth (Elicki & Geyer 2013).

In addition, in a specimen of *Bohemoharpes ungula* from the Silurian (between 444 and 416 Mya), the neoplasm is accompanied by radiating circulatory canals, similar to the way that tumors often attract blood vessel development (Owen 1983). Further, in a *Toxochasmops* trilobite from the Ordovician (485-444 Mya), putative images of metaplasia were observed in an anomalous growth of tissue although it is not easy to distinguish herein a true neoplasm from a diagenetic process or a regeneration after an injury (Nielsen & Nielsen 2017).

In vertebrates, the earliest known possible case of neoplasm was found in a fossil of an armored large fish from the extinct genus *Dinichthys*, which lived in the late Devonian, about 360 Mya. The case consists of a profound depression on the internal surface of the lower jawbone. The lesion, which certainly occurred during the life of the fish (that is, it was not produced by diagenetic processes) could have been caused by trauma linked to intra-specific aggression among these combative animals; however, the paleopathologists better interpreted it as the result of bone resorption due to a malignant tumor of the soft tissues of the mouth floor (Capasso 2015; Scheele 1954). The armored fishes known as placoderms are considered to be the earliest branch of the jawed fishes and in consequence, they are one of the first groups of vertebrates to appear on the Earth after the jawless fishes.

More direct evidence of neoplasia was obtained from a fossil of the extinct bony fish *Phanerosteon mirabile* that lived in the lower Carboniferous, about 300 Mya. This neoplasia is a classic osteoma including a bone focal hyperostosis (excessive bone growth) similar to that observed in bony fishes living today (Capasso 2015, Moodie 1927).

In terrestrial vertebrates, the oldest case reported up to date is a lesion characterized as a compound odontoma (a benign neoplasia of calcified dental tissue) in a specimen of a "mammalian" forebear, a premammalian synapsid that lived in the late Permian, about 255 Mya. Odontomas are the most common odontogenic tumors and its recognition in such a distant specimen suggests that this condition is unlikely related to characteristics of mammalian dentition but rather evolved much earlier in vertebrate evolution (Whitney, Mose, & Sidor 2017).

The fossil record of tumors in the Paleozoic is not restricted to animals.

Many land plants exhibit abnormal outgrowths of plant tissues (tumors) that are denominated galls. Galls are produced by host plant cells in response to infection by fungi, bacteria, nematodes, insects, mites or other agents. In most cases, galls do not seriously harm the host plant and could be considered benign neoplasia. In the more highly developed galls, these self-limiting neoplastic growths are almost comparable, in the determinate growth of their structures, to a leaf or a fruit (Bayer, Kaiser, & Micozzi 1994). A few of them, however, may be highly deleterious for their hosts. The best—but not the only—example of the latter are the crown galls caused in many plants (such as nut trees, perennial fruit trees, vines and roses) by the soil-inhabiting bacterium *Agrobacterium tumefaciens* that, in some cases, especially when the gall completely encircles the main stem, can severely harm and kill the hosts (Armstrong 1995; Chen *et al.* 2016; Kluepfel *et al.* 2017; Gohlke & Deeken 2014; Zhu *et al.* 2020; Grabowski & Koetter 2019). Figure 2 shows an example of crown galls induced by *Agrobacterium tumefaciens* in a present-day tree.

In the narrow framework of human pathology, crown galls as well as other galls that may affect the survival of the host plant, cannot be considered cancer because they do not invade or metastasize. In effect, the rigid wall of the plant cells as well as the absence of a vascular system able to transport cells, prevents the galls to invade or metastasize in the true sense of these words. However, in the broader sense of malignant neoplasia stated in this work, the galls that are harmful for their hosts may be considered genuinely cancer plants. Recognition of crown galls as true cancer may be traced up to the onset of the 20th century (Smith 1916). Its malignant behavior is also exemplified by the fact that, as with many animal tumors, unless caught very early in tumorigenesis, surgical excision of crown gall tumors from the infected plants is ineffective in controlling the disease (Lacroix & Citovsky 2001).

The physical features of most galls (hardened, three-dimensional and resistant to flattening) allow their

Figure 2. An example of crown galls induced by *Agrobacterium tumefaciens* in a present-day tree (Picture by the Authors).

preservation in the fossil record and provide a basis for evaluating their external and eventually internal structure (Labandeira 2021). In fact, galls on land plants have a spotty but periodically rich and abundant fossil record. Many galls in the fossil record may have been induced by arthropods although in some cases, the causes remain undetermined.

The earliest gall registered is a putative insect or mite-induced gall on a liverwort (an early cryptogam) of the Middle Devonian Period at 385 Mya. Afterwards, gall activity was registered about 315 Mya, during the Carboniferous, on vegetative and reproductive axial organs of horsetails, ferns and probably conifers but not on foliage (Labandeira 2021). The earliest galls in leaves were detected on *Odontoperis* from the early Permian (Scott, Stephenson, & Collinson 1994), followed by the expansion of foliar galling through the late Permian as supported by plant damage, an extensive diversification of small, early *hemipteroid galler* lineages on seed-plant foliage and the paleoclimate record (Schachat & Labandeira 2015).

The nature (whether benign or malignant) of these very ancient neoplasms is unknown but it might be inferred from the behavior of analogous present galls. For example, the anatomical and three-dimensionally preserved rachis gall of the extinct tree-fern *Pteridiorichnos stipitopteri* from the Carboniferous is similar to some modern fern rachis galls caused by gall midges, which do not negatively affect the growth of its host. On the other hand, a beaked gall described on the axes of the extinct conifer *Walchia piniformis* from the Carboniferous is similar to the aphid-induced gall on Norway spruces that, in severe cases, may cause disfigurement, stunting and eventually death of the affected trees (Labandeira 2021; Impson, Post, & Hoffmann 2013; Schread 1971).

3.2. Mesozoic Era (252-66 Million Years Ago)

The first period of the Mesozoic Era was the Triassic (252-201 Mya) that began after Earth's worst-ever life devastation, the Permian-Triassic extinction, also known as the Great Dying, when an unidentified event killed some 90 percent of the planet's species.

Among animals, the earliest cases of neoplasia in the Mesozoic Era were a parostotic osteosarcoma reported in a cranial bone of an early Triassic capitosaurid amphibian that lived between 252 and 247 Mya (Gubin *et al.* 2001) and an osteosarcoma on the femur of a specimen of the extinct shell-less stem-turtle *Pappochelys rosinae* that lived 240 Mya in the middle Triassic (Haridy *et al.* 2019). The appearance of the latter tumor conforms with present-day periosteal osteosarcoma in humans and represents the oldest instance of bone cancer in an amniote. Another case of osteosarcoma has recently been reported in the vertebral intercentrum of a temnospondyl amphibian, *Metoposaurus krasiejowensis*, that lived between 237 and 201 Mya ago in the late Triassic (Surmik *et al.* 2022).

Afterwards, there are many documented cases of benign as well as malignant neoplasms in fossils from extinct animals that lived during the Jurassic (201-145 Mya) and Cretaceous (145-66 Mya). Among benign tumors, the most represented cases were hemangioma, osteomas, and osteochrondoma. The earliest case of hemangioma was reported in a fossil fragment—presumably a vertebral centra—of an unidentified dinosaur that lived between 165 and 145 Mya in the late Jurassic (Rothschild *et al.* 1998). Afterwards, hemangioma have been found between two caudal vertebrae of a not identified Comanchean dinosaur that lived in the early Cretaceous between 145 and 100 Mya (Moodie 1921) and in some late *Cretaceous hadrosaurus* or duck-billed herbivorous dinosaurs which lived about 80 Mya (Rothschild *et al.* 2003). Similarly, osteomas have been described in two Cretaceous specimens belonging to mosasaurus family—an extinct group of large marine reptiles that were positioned at the top of the food chain in the late Cretaceous oceans (Moodie 1921; Rothschild *et al.* 2003), in the left scapula of a specimen of *Pachyrhinosaurus*—a ceratopsid dinosaur of the late Cretaceous—in the right foot of a *Vagaceratops irvinenesis*—an herbivorous ceratopsian dinosaur which lived during the late Cretaceous about 75 Mya (Rega, Holmes, & Tirabasso 2010)—in a bone tail of a titanosaurus, a gigantic long-necked and long-tailed sauropod dinosaur from the late Cretaceous (Souza Barbosa *et al.* 2010) and in some specimens of Cretaceous hadrosaurs (Rothschild *et al.* 2003; Norman & Milner 1989). In the same way, the earliest case of osteochondroma was found in a rib of a specimen of the extinct genus of Apatosaurus, a giant herbivorous sauropod that lived in the late Jurassic between 156 and 150 Mya (Capasso 2005). At least two additional

cases of osteochondroma have been informed: one in a specimen of *Allosaurus*, a large predatory theropod dinosaur which lived in the Upper Jurassic, between 155 and 145 Mya (Foth *et al.* 2015) and another, in a specimen of *Vagaceratops irvinenesis* (Rega, Holmes, & Tirabasso 2010) Other less frequent benign neoplasms or neoplasm-like bone lesion have also been described such as osteoblastoma, desmoplastic fibromas and Langerhans Cell Histiocytosis in some specimens of hadrosaurs (Rothschild, Tanke, & Helbling 2003; Rothschild *et al.* 2020), an ameloblastoma in the lower jaw of a specimen of a dinosaur *Telmatosaurus transsylvanicus* from the late Cretaceous (70-66 Mya) (Dumbravá *et al.* 2016) and an osteoblastic tumor—identified by the presence of a large outgrowth of ovoid appearance with a spiculated microstructural pattern—in the femur of a specimen of the sauropod *Bonitosaura salgadoi* that lived approximately 84 Mya near the end of Cretaceous period (González, Gallina, & Cerda 2017).

Different malignant neoplasms have also been reported—especially in the last few years—in fossil remains from the Jurassic and Cretaceous periods although, in certain cases, diagnosis needs to be further confirmed. Stadtman (Stadtman 1992) reported a probable chondrosarcoma invading the surrounding normal bone in the humerus of a theropod dinosaur (*Allosaurus fragilis*) from the late Jurassic. Another case of chondrosarcoma was reported in a specimen of Vagaceratops irvinenesis from the Late Cretaceous (Rega, Holmes, & Tirabasso 2010).

In the same way, at least two cases of osteosarcoma have been informed: one, in a specimen of *Dilophosaurus wetherilli*, a theropod dinosaur that lived in the early Jurassic, between 200 and 190 Mya (Senter & Juengst 2010) and another, in a specimen of *Centrosaurus apertus*, a herbivorous ceratopsian (horned) dinosaur, which dates from approximately 77·75 Mya (Ekhtiari *et al.* 2020). In addition, a putative thumb-sized brain tumor, was found in a skull fossil of *Gorgosaurus*, a 7.5 m long meat-eater giant closely related to *Tyrannosaurus rex*, that lived 72 Mya (Pickrell 2003). The tumor, possibly an unusual type of bone-forming cancer called an extraskeletal osteosarcoma, filled nearly the entire area formerly occupied by the cerebellum and brainstem and probably impaired the cerebrum, the part of the brain that controls thought and memory.

In addition, two putative cases of multiple myeloma have been described in the cranial bones of both, a specimen of *Torosaurus latus*—a herbivorous horned dinosaur that lived in the Late Cretaceous between 68 and 66 Mya—and an *ornithischian* dinosaur (Capasso 2005). Metastatic cancer has been reported at least twice in fossil remains. The first case was described in a fossil sawed bone section from an unspecified large-sized terrestrial dinosaur that lived between 156 and 148 Mya, in the Upper Jurassic. The permineralized bone contains an ovoid agate filling occupying a large hole whose appearance is that of a lytic zone that is penetrated by irregular trabeculae and that seems to have originally contained a mass of soft tissue. This image together with both the existence of a transition zone between normal bone and the tumorous space characterized by a pattern of bone destruction, and a radiographically detected cortical bone invasion with residual cortical shell, strongly suggest the existence of metastatic cancer (Rothschild *et al.* 1999). Another metastatic cancer was reported in a specimen of *Edmontosaurus* belonging to the family of hadrosaurs, that lived about 70 Mya, in the Late Cretaceous (Rothschild *et al.* 2003). In both cases, the primary origin of metastatic cancer is unknown.

As for land plants, relatively few galls were reported, in the Mesozoic pre-Cretaceous, since the Great Dying at the Permian End extinguished most gall lineages. In the early Triassic only two cases were reported: a gall apparently induced by a leaf mining fly in the leaf of a specimen of the extinct *Viaznikopteris rigida*, a rare plant belonging to the group of *Pteridospermatophyta* or seed ferns (Krassilov & Karasev 2011) and a gall that occurred on the pinnate leaf of a specimen of *Dicroidim odontopteroides*, belonging to the extinct group of *corystospermales* (McLoughlin 2011).

Recovery of the moderate level of plant-insect interactions, including gall associations, that was present during the late Permian, was not matched until the middle of Triassic, 237 Mya. During the late Triassic and Jurassic periods, new groups of galling insects began to colonize Ginkgoales, Bennetitales, Conifers and other gymnosperms (plants without flowers) but cases found in the fossil record are rather sparse. In fact, only two groups (both Coleoptera) of the major modern gall-inducing insects have a pre-Cretaceous fossil record (Labandeira 2021; Alvin *et al.* 1967).

A great expansion of both plant-insect interactions and galls occurred during the 35-million-year-long interval from 125 to 90 Mya of the mid-Cretaceous, largely associated with the initial expansion of

angiosperms or flowering plants. During this period, there was a major transformation of flora from gymnosperms dominance to angiosperm dominance when the latter expanded in a wide variety of ecosystems becoming the largest and most diverse group within the kingdom Plantae. Comparison with the modern material suggests that these numerous Cretaceous galls were mainly produced in response to mites, aphides, midges and wasps.

As occurred in the Paleozoic Era, benign as well as malignant behaviors seem to have been associated with Mesozoic galls. For example, in the locality Chernovskie Kopi of Transbaikalia, Russia, two markedly different types of insect-induced galls were found in two different specimen fossils of gymnosperms of the latest Jurassic to earliest Cretaceous boundary interval, about 145 Mya (Vasilenko 2005). The first type of gall, that was described on specimens of the ginkgolean host *Ginkgoites sp.*, was small-sized, hemispheroidal with smooth surfaces and it does not appear to have been significantly harmful for its host. In contrast, the second type of gall, that was described on specimens of the pinalean host *Desmiophyllum sp.*, behaved as a canker-like lesion, producing disruptions of leaf tissue with considerable internally disrupted tissue and thin, unhardened gall walls. This gall seems to have had the power to break branches and to structurally weaken and even kill its host plant (Labandeira 2021).

3.3. Cenozoic Era (66 Million Years Ago to Present)

The end of the Mesozoic Era, associated with a massive extinction of millions of animal species, included all the dinosaurs, marks the beginning of the Cenozoic Era. This extinction—known as the Cretaceous-Paleogene (K-Pg) event—was second only to the Permian-Triassic one as the most perilous period to affect life on Earth during the past 450 million years. Cenozoic is divided in three periods, namely Paleogene [that includes Paleocene (66-56 Mya), Eocene (56-34 Mya) and Oligocene (34-23 Mya) epochs], Neogene [that includes Miocene (23-5 Mya) and Pliocene (5-2.5 Mya) epochs] and Quaternary (that includes Pleistocene, 2.5 Mya -12000 years ago) and Holocene (12,000 years ago-present). Tertiary was the old denomination for Paleocene and Neogene together and it is sometimes still used in the literature. Cenozoic Era is associated with the great diversification and spread of mammals (and birds to a lesser extent) by which this period is also known as the Age of Mammals. In addition, the continents moved into the current positions during this Era. Among animals, many cases of benign as well malignant neoplasms have been reported in the different epochs and periods of this Era.

Among benign tumors, osteomas were very frequent among different fishes of the Tertiary and Quaternary and in sirenian mammals (order *Sirenia*) from Oligocene (Capasso 2005). Osteomas have also been detected in Quaternary fossil elephants from Poland (Przyklady 1965) and multiple hereditary osteochondroma have been observed in 61% (19 of 31) of fossil remains of the North American Oligocene *Canidae Hesperocyon* (Wang & Rotschild 1992). In the same way, an osteoblastoma has been reported in a mammoth that lived about 24,000 years ago at the Late Oligocene in a locality of the actual Poland, which is known for the presence of a substantial assemblage of mammoth bones accompanied by human artifacts from the Gravettian technocomplex (Krzeminska 2008). Neoplasms of the dental tissues have also been demonstrated in many extinct Cenozoic animals such as Tertiary ungulates from Argentina, fossil horses, European mammoths, Japanese fossil elephants and in a specimen of a Holocene fossil walrus from Alaska (Capasso 2005; Cabrera 1934; Patte 1937; Hunter & Langston 1964; Kobayashi 1937). Other benign tumors were reported in Tertiary *Bovidae*, in some Tertiary and Quaternary *Canidae*, in a specimen of *Nothroterium* (an extinct ground sloth from South America) and in a specimen of *Ursusus spelaeus* or cave bear (an extinct species of bear that lived in Europe and Asia at the late Pleistocene) (Miralles & Crusafont Pairo 1952; Pales & Wernert 1953; Moodie 1929; Scott 1898; Pales 1959).

Malignant tumors have also been reported in Cenozoic Era. In effect, osteosarcoma have been demonstrated in a specimen of a Pleistocene buffalo (Conkling 1990), in a *Holocene Capra* (Capasso & Di Tota 1996) and in a right femur assigned to a specimen of the Quaternary ground sloth *Nothrotherium maquinense*, that lived about 12,000 years ago in the actual Brazil (Souza Barbosa *et al.* 2021). In addition, chondrosarcoma was reported in some species of fossil *Canidae* (Baker & Brothwell 1980, pp.110–114).

As for land plants, after the K-Pg crisis, recovery of gall and other associations, started at the middle of Paleocene, about 60 Mya. Afterwards, between 49 and 40 Mya, distinctive new gall associations, similar to extant plant-gall interactions, make their earliest appearance as fossils. During the Neogene, the expansion of galls involved a broad diversity of plant hosts and gall-inducers, especially arthropods. For example, the early Neogene (20 Mya) flora whose remains were found in a region of the actual Czech Republic, provides 16 excellently preserved gall types, some with remarkable resemblance to their modern analogues attributable to extant families or genera, suggesting prolonged evolutionary stasis (Labandeira 2021). As occurred in Paleozoic and Mesozoic Eras, most Cenozoic galls seem to exhibit benign behaviors although in some cases, a rather malignant behavior may be suspected. Both benign as well malignant behaviors may be inferred quite accurately from the study of galls induced by modern gall-inducing species showing the closest resemblance to those found in the fossil record. For example, the extinct *Taxodium dubium* (belonging to the cypress family) found in that Neogene flora, exhibits galls very similar to those induced in the present days by the midge *Taxodiomya* in cypresses. These oval shaped galls are formed on the terminal portion of the branchlets and when mature, they resemble small pineapples which do not appreciably harm the tree health (Chen & Appleby 1984) On the other hand, the extinct *Alnus julianiformis* (belonging to the family of *Betulaceae*) found in that very Neogene flora, exhibits galls almost identical to those induced today by the mite *Eriophyis inangulis* in modern alnus. These galls develop as sub-spherical distortions rising up to the upper surfaces of the leaves and may vary in color from pale yellow-green to deep red. Although few galls may be not harmful for their host, many of them may cause strong decrease of both photosynthetic activity and stomatal conductance which may affect the survival of the affected tree (Jiang *et al.* 2021).

For the last 3 million years of late Pliocene and Pleistocene, however, the fossil record of galls is relatively scarce, probably because the several cycles of glaciation and deglaciation characteristics of this period, have eroded or otherwise prevented the formation of many persistent deposits.

Lastly, the Holocene marks the beginning of the actual large collection of galls in land plants.

3.4. Pre-human and Ancient Human Populations

The earliest evidence for neoplastic disease in the hominin lineage was reported in a specimen of the extinct *Australopithecus sediba* (belonging to the family of *Hominidae*) from the fossil-bearing cave of Malapa, located about 45 km north-northwest of Johannesburg, South Africa, dated to 1.98 Mya. The affected individual was male and developmentally equivalent to a human child of 12 to 13 years of age. The specimen exhibited a penetrating lytic lesion that affected the sixth thoracic vertebra, which was diagnosed as an osteoid osteoma, a benign osteoid and bone-forming tumor (Quinney *et al.* 2016). In the genus *Homo*, the two earliest known examples are an osteosarcoma present in a metatarsal specimen probably belonging to a *Homo ergaster* who lived in South Africa 1.6-1.8 Mya (Odes *et al.* 2016) and a possible Burkitt lymphoma or an ossifying sarcoma observed in a fragment of mandibular ramous attributable to *Homo erectus* who lived in Kenya about 1.5 Mya (Capasso 2005). As for the last case, however, some researchers have suggested that, alternatively, it might have been an overabundant bone callus associated with a healed fracture, which, incidentally, would reveal the similarity between cancer and a regenerative process, just as several analogous cases have been reported since the Paleozoic.

Many years later, meningiomas were reported in the fossil bones pertaining to a *Homo steinheimensis* and to a *Homo neanderthalensis* that lived in Germany 365,000 and 35,000 years ago, respectively (Czametzki, Schwaderer, & Pusch 2003; Czametzki 1980). In addition, a fibrous dysplastic neoplasm was described in a Neanderthal rib from a specimen that lived in present-day Croatia about 120,000 years ago (Monge *et al.* 2013). In this case, the incomplete nature of the rib and the lack of associated skeletal elements, prevented the authors to speculate on the health effects the tumor had on the individual. A benign tumor called intradiploic epidermal cyst, was also described in the frontal bone of another *Homo neanderthalensis* that lived between 50,000 and 70,000 years ago in Doggerland, the prehistoric landscape now under the sea off the Dutch coast (Hublin *et al.* 2009).

Later, almost all types of modern neoplastic diseases have been documented in ancient Homo sapiens bone remains. For example, meningiomas have been

reported in skeletons from Ancient Egypt since the time of the Fifth Dynasty between 2500 and 2350 years ago, and pre-historic America. Other benign tumors such as hemangiomas, osteoclastomas, histiocytomas, osteomas, osteochondromas as well as neoplasms in other organs that affect bones—such as pituitary adenoma and fibroleiomyomas of the uterus—have been documented since prehistory in Europa, North Africa and South and North America. Malignant primary bone tumors such as osteosarcomas, chondrosarcomas, hemangiosarcomas and Ewing's sarcoma have been reported in ancient populations of Europa and Egypt and prehistoric populations of Peru, Chile and Hawaii. Paleopathological studies have also revealed the existence of bone metastases of nasopharyngeal, breast and prostatic carcinoma and lytic lesions due to multiple myeloma and melanoma in the skeleton of individuals of prehistoric populations of Europa, Iran, Egypt and Pre-Columbian America, including pre-historic sites at Peru, California, St. Lawrence island (Alaska) and the western Pampean region and northwest Argentina. Furthermore, investigations of naturally or artificially mummified human bodies, excavated in Egypt, Nubia, Peru, Chile, Alaska, China and Europa have revealed the existence of some malignant primary tumors of soft tissues including carcinomas of the prostate and rectum, naso-orbital cancer, rhabdomyosarcomas, nasopharyngeal carcinoma, melanoma and multiple myeloma among others (Capasso 2005, Odes *et al.* 2016; Shimkin 1977; Strouhal 2001; Pahl 1986; Luna *et al.* 2008; Luna *et al.* 2015; Arrieta, Mendonca, & Bordach 2018). For a more comprehensive and detailed description of the up to date 154 paleopathological studies documenting 272 archeologically recovered individuals exhibiting skeletal or soft tissue evidence of cancer (that is, including only malignant neoplasms) between 1.8 Mya and 1900 CE see (Hunt, Roberts, & Kirkpatrick 2018) and the Cancer Research in Ancient Bodies (CRAB) Database (Hunt *et al.* 2017).

4. The Incidence of Cancer over Time and Geological Ages

A conclusion derived from the record fossil from Paleozoic Era onwards, as well as from the study of skeletons and mummies from pre-human and ancient human populations, suggests that cancer or cancer-like phenomena as well as benign neoplasia are very old diseases, which have afflicted animals and land plants since long before man appeared on Earth and human beings since prehistoric times.

Until relatively recently, it was assumed that the prevalence of cancer in the remote past was quite rare in animals on the basis of the apparently very low ratio between the number of reported cases of metastatic cancer in fossil bones (it must be remember that about 95% of malignant neoplastic lesions in bones are associated with metastases of soft tissues and the remaining 5% is related to multiple myeloma and primary bone cancer) and the vast number of fossil bones that have been excavated and examined by specialists. However, this ratio may strongly underestimate the cases of cancer if the remains are represented by minimal fragments of the whole body, as it occurred in many extremely ancient fossil deposits. In effect, the probability to find a cancer in a solitary bone from a specimen with many bones is many times lower than finding cancer in a complete specimen. Therefore, for the sake of comparing properly that metastatic cancer incidence between extinct and modern animals, it is necessary that both collections contain a similar number of bones by each specimen. In addition, it is worth noting that metastatic cancer in bones may be useful for comparative purposes but not as an absolute measure of cancer incidence because there are many cancers that may not produce bone metastases.

The largest epidemiological study of tumors in dinosaurs to date, undertook by Rothschild and colleagues using computed tomography for fluoroscopically screening dinosaur vertebrae, showed that out of a total of 10,312 vertebrae from 708 individual dinosaurs of varying families, only one malignant metastatic tumor was found. This ratio 1/708 = 0,141 % is significantly lower than that obtained in humans using the Hamann-Todd Collection, that is one of the largest and best-preserved compilation of modern human skeletons for which a background demographic is known (Rothschild *et al.* 1993; Rothschild & Woods 1991). In this collection, from a total of 2906 defleshed skeletons, 33 cases of metastatic disease were identified fluoroscopically, yielding a probability of 1.136 % ($p < 0.05$ versus the ratio 0.141% observed in dinosaurs, X2 test). However, if the comparison is made with modern reptiles, based on necropsy results of captive wild animals (Effron, Griner, & Benirschke 1977; Kitsoulis, Baxevanis, & Abatzopoulos 2020), the ratio of cancer in

them is approximately 0.142 %, that is almost identical to that observed in dinosaurs (Natarajan *et al.* 2007). Further, discovery and study of tumors in dinosaurs has revealed that they are indistinguishable from tumors from modern reptiles and humans suggesting that this global disease has barely changed over 100 million years.

Similar conclusion may be achieved when comparison is made between extinct and modern avian and mammals. The relatively constant incidence of cancer within each major taxa of animals over long periods of time, is also supported for the similar cancer incidence observed among modern animals belonging to a same order, even though substantial differences in cancer incidence and mortality across major animal orders occur. For example, among mammals, all or almost all members of the order *Carnivora* (lion, tiger, hyena, bear, wolf, dog, cat, etc.) display an elevated risk to get cancer throughout their lives while, on the other hand, all or almost all members of the order *Artiodactyla* (camel, pig, cow and bull, sheep, deer, giraffe, hippo, etc.) exhibit a significant lower risk (Vincze *et al.* 2022). In the same way, among arthropods, all or almost all members of the order *Diptera* (fly, midge, jig, horsefly, etc.) exhibit a rather frequent occurrence of tumors while in contrast, all or almost all members of the order *Decapoda* (crab, lobster, crayfish, shrimp, pawn, etc.) display a low incidence (Vogts 2008). This means that the extinct ancestors of *Carnivora* and *Diptera* probably had a similar high risk of having cancer as their modern descendants. On the other hand, the extinct ancestors of *Artiodactyla* and *Decapoda* probably displayed a relatively lower one.

5. Exceptions to the rule of constancy of tumor incidence over time: examples of increased tumor incidence over time

Human beings followed the same rule of constancy up to the turn of the 20th century, after which the trend changed. In effect, comparison between ancient and modern human populations suggests that incidence of cancer remained relatively constant for many years but it started to increase progressively from 1900 onwards. In fact, Nerlich *et al.* (2006) searched for malignant growth affecting the skeleton in both, a collection of 905 individuals that have been excavated from the necropolis of Thebes-West and Abydos, Upper Egypt, covering the time period between 3200 and 500 BC, and a collection of 2547 individuals that have been buried in a Southern German ossuary dating from between AD 1400 and 1800. According to the authors, the skeletal tissue preservation of both the Egyptian and Southern German material was excellent. All available specimens were subjected to a very careful macroscopic examination and isolated findings were also radiologically investigated. In parallel, anthropological data, such as gender and age at death, were recorded. The study identified 5 cases of malignant tumors affecting the skeleton in the Egyptian material (ratio: 5/905 = 0.552 %) and 13 cases affecting the skeletal material from Southern Germany (ratio: 13/2547 = 0.510 %, p: NS). In most instances, multiple osteolytic lesions with slight osteoblastic reaction, were strongly suggestive for metastatic carcinoma. The ratios were very similar indicating that malignant tumors were present in spatially and temporarily different populations over the last 5000 years with an age-and gender-adjusted frequency not different from Western industrial populations before 1900. Afterwards, cancer incidence began to increase significantly. In effect, in the Hamann-Todd Collection that contains human skeletons from persons that passed away between 1912 and 1938, the ratio of metastatic cancer in bones had increased (33/2906 = 1.136 %) over basal values before 1900 ($p < 0.01$). Later, in the William M. Bass Forensic Skeletal Collection of the University of Tennesse, USA, which contains 868 skeletons from persons that passed away between 1970 and present time, 19 metastatic cancer in bones were reported (Fatula 2020), which represents a ratio of 19/868 = 2.19 % ($p < 0.001$ versus human populations before 1900) that is even higher ($p < 0.05$) than that reported in the Hamann-Todd collection. The increase of metastatic cancer in bone remains during the 20th century is correlated to the increased incidence of cancer reported clinically. In effect, in developed countries, mortality for cancer was only 5% in 1900 and it had climbed to 20% in 1970 and to 33% in 2018 (Capasso 2005; Khatami 2018).

Two main causes have been invoked to explain the great increase of human cancer over the last century. The first is linked to the aging of modern populations since cancer is an age-associated disease whose prevalence ranges from about 1.8 % for those with <39 years old to 27.2 % among those with 60-79 years

old. Taking into account that life expectancy increased from about 30-40 years to 70-80 years during the 20th century, age alone could be expected to reduce the incidence of malignancy in past centuries by about 90% with respect to the modern rate. The second cause is associated with the fact that ancient humans were not exposed to both chemical agents responsible for the modern environmental pollution and physical factors such as radioactivity due to nuclear assays that only began in the 1950s. In summary, in humans, the incidence of cancer remained constant for many years but the longest life expectancy and the chemical and physical contaminants associated with urban modern civilization seems to have increased the incidence of tumors.

Increased tumor incidence over time might also be associated with the fact that some organisms adopted some kind of tumors as a biologic strategy to increase their adaptability to difficult environmental conditions. For example, fossil fishes of the genus *Pachylebias* (now referred to as *Aphanius crassicaudus*) that lived about 8-5 Mya, adopted pachyostosis to facilitate immersion in the hypersaline waters of the Mediterrean Sea at the time of the Miocene desiccation period. This condition, characterized by an extraordinarily thick skeleton that occupied almost the entire body did not differ from a benign tumor originating from bone tissue. An almost identical condition occurred in the larger cyprinid fish *Hsianwenia wui* that lived in the Pliocene period (5-2.5 Mya) in the hypersaline lakes of the Qaidam Basin on the northern Tibetan Plateau. Both these unusually thick-bone fishes represented an adaptive mode to the extreme conditions resulting from continuing aridification in the two areas (Capasso 2005; Chang *et al.* 2008). In the same way, mammals of the Sirenian group that lived about 30 Mya ago during the Oligocene acquired tumor-like forms in their axial skeletons to consent browsing on the bottom in shallow waters (Capasso 2005). A similar adaptative strategy had been developed many millions of years before, by the plesiosaur *Tatenectes laramiensis* that lived in shallow marine waters during the Upper Jurassic between 164 and 157 Mya (Street & O'Keefe 2010).

In land plants, the insect-induced gall tumors have experienced a large increase in both incidence and diversification over time, since a few cases reported in Paleozoic Era up to the huge number of about 130,000 plant species that harbor 130,000 different types of insect-induced galls, in present times (Labandeira 2021; Espirito-Santo & Wilson Fernandes 2007). Galls induced by other organisms have also experienced a significant expansion although less important than the former. Sometimes, gall-inducers are plant parasites and, in such cases, they are the only ones who benefit from their inter-specific association with host plants. In consequence, the expansion of these galls over time is exclusively associated with the evolutionary expansion of their gall-inducers. In other cases, however, galls are also beneficial to plants, as in brood-site pollination mutualism where plants trade insect development sites against seed production. In these cases, the expansion of these galls over time could also be related to the fact that these plants adopted these gall tumors as a biological strategy to increase their descendants. A typical example of this mutualism is the ancient interaction between figs (*Ficus*, *Moraceae*) and their pollinating fig wasps (Borges 2021).

6. The two main evolutionary riddles of Cancer

6.1. First Riddle

Despite the major changes in the structure of animal populations, the prevalence of malignant as well benign neoplasms has remained relatively constant (and in some cases it has even increased), among the different taxa of animals for hundred million years (Capasso 2005) suggesting that malignancies as well as benign neoplasms are rooted quite deeply in the evolutionary life of organisms.

However, this seemingly unremarkably fact represents a remarkable riddle for evolutionary biologists. If natural selection, working on living organisms has been powerful enough to produce complex adaptations, from the eye to the immune system, why has it been unable to eliminate or even reduce the incidence of cancer, even though many apparently less harmful traits have been eliminated during species evolution.

For some researchers this question is neither original for cancer nor enigmatic.

They claim that it would not be original because a similar case may be stated for ancient infectious diseases and for rare genetic disorders. For example, malaria produced by Plasmodium falciparum has affected

human beings for 50,000 - 100,000 years and it may be a pathogen that accompanied the whole history of our specie; this hypothesis is further supported by the observation that close relatives of the human malaria parasites remain common in chimpanzees (Joy *et al.* 2003). However, in this as well as in other similar cases, throughout the years, foreign infectious agents may have acquired, sophisticated evolutionary strategies for attacking our bodies that may have overcome our evolutionary renewed strategies of immune defenses against them. In contrast, the tumors that affect our bodies are not foreign agents; they are made of our own cells that have evolved over millions of years to preserve the homeostasis of the organism, not to attack it. In the same way, it is true that natural selection cannot drive the spread of new defenses against rare genetic diseases because the acquisition of such new defenses would make very little difference to the average reproductive success of a population. In contrast, cancer is not some bizarre rarity: in developed countries a person has 30-40 per cent chance or more of being diagnosed with some type of cancer in its lifetime.

On the other hand, the argument that cancer should have been removed or reduced by natural selection has often been challenged on the ground of two main objections. In the first place, it is invoked that most tumors develop after reproduction has ceased and, in consequence, negative selection could not have been operative against them. In the second place, it is argued that natural selection works with hereditable traits and cancer is not, in general, a hereditable disease, taking into account that only about 5 % of cancers—the so called "familial cancers"—are transmitted by the germinal route (Ewing 1940).

These objections are highly questionable. In effect, although many species show a decline of reproductive function with age, the female menopause occurs only in humans, a few other primates and in the killer and pilot whales (Woodruffs 1982; McAuliffe & Whitehead 2005; Brent *et al.* 2015). The latter means that in most living and extinct animals over three geological eras, cancer has not been a post reproductive disease. In the second place, it is known that the "familial cancers" are associated with the hereditary transmission of a mutated allele of some genes such as RB1 and BCRA1 which confers high susceptibility to the development of retinoblastoma and breast cancer. However, even assuming that mutated RB1 and BCRA1 are the main etiological factors related to those cancers, the trait "susceptibility to cancer" could also be transmitted through deficient immunologically or biochemically-mediated anti-tumor mechanisms that would prevent the host to limit the development of the tumors much the way that, in infection diseases produced by foreign pathogens, the trait "susceptibility to the disease" may be transmitted not by vertical transmission of the main etiological agent (the foreign pathogen) but by vertical transmission of a deficient anti-pathogen host defense.

In order to explain why natural selection did not eradicate or at least ameliorate cancer from species over three geological eras, some authors have advanced the idea that cancer may play a real role within the organism (Zajicek 1996; Muller 2017), or it may be coupled to essential physiological functions that would prevent it from being removed by natural selection (Zimmer 2007). However, up to date the nature of these putative tumor roles or the normal essential functions with which it would be coupled, remain obscure.

6.2. Second Riddle

The constancy of cancer incidence over hundred million years also demands an extremely remarkable mechanistic explanation of carcinogenesis. In effect, comparison between the record fossil and present evidence of cancer reveals that, within a taxon (for example carnivorous mammals), cancer incidence is very similar regardless of the tumor host's body size and life length. Further, even considering mammals as a whole, it is clear that a higher risk of cancer does not correlate with increased body mass and lifespan (Abegglen *et al.* 1996) The prevalent somatic mutation theory (SMT) of cancer posits that the malignant cell is the physiological and anatomical unit of cancer disease (Boveri 1929; Hanahan & Weinberg 2000; Bignold 2002; Tomasetti *et al.* 2015). Implicit in this contention is the assumption that the probability of origin of an aberrant, neoplastic cell lineage may be the same per unit of both cell population and time, regardless of species or cell type concerned. However, this assumption evokes one of the most intriguing enigmas in cancer research, which remains unsolved. The riddle, currently called Peto's Paradox, asks (Dawe 1969; Peto *et al.* 1975; Peto 2015): Why do not extremely large animals with a long lifespan develop neoplasms with a much higher incidence than very small ones displaying

a short lifespan since both the cell population at risk and the exposure time at putative carcinogens are greater by several orders of magnitude? Let us consider the blue whale, the human and the mouse. If one takes the weight of a mouse as 20 g, that of a human as 60 kg and that of a blue whale as 200 ton, a blue whale and a human are equivalent to 10,000,000 and 3,000 mice, respectively. Therefore, we should expect the blue whale and the human being to develop cancer, respectively, 10,000,000 and 3,000 times more often than a mouse by unit of time (Figure 3). Furthermore, since the lifespan is 2.5 years for the mouse and about 80 years for blue whales and humans, the relative risk of cancer should be also increased in function of the ratio between both lifespans. In fact, according to the hypothesis of the multistage carcinogenesis, this increase should not be linear but exponential with the sixth power of age (Nordling 1953; Weiss 2004; Prejean *et al.* 1973; Pugh *et al.* 1999).

Some *ad hoc* hypotheses have been invoked to explain Peto's Paradox. For example, the animal fat depots might sequester fat-soluble carcinogens with an efficiency proportional to animal's size and thereby proportionately diminish the exposure of other tissues. Other putative explanations hold that faster metabolism of small animals generate more putative cancer inducing-free radicals, or that the efficiency of defenses against neoplasia, such as mechanisms of DNA repair, cellular resistance to metabolism and mutagenic activation of putative carcinogens, number of copies of the tumor suppressor gene TP53, immunological surveillance, etc. could be proportional to animal size (Wheatley & Clegg 1994; Dung 2014; Vineis *et al.* 2009; Dunn, Koebel, & Schreiber 2006; Downs *et al.* 2020; Nunney 2020). However, these invoked mechanisms remain largely unproven as general rules and in fact there is evidence that argues against them. For example, even though the African savannah elephant (*Loxodonta Africana*) genome contains 20 copies (40 alleles) of TP53 and the human genome contains only one copy; on the other hand, the mouse genome has 2 copies and whales neither exhibit extra copies of TP53 nor of any other known tumor suppressor gene (Tollis, Boddy, & Maley 2017).

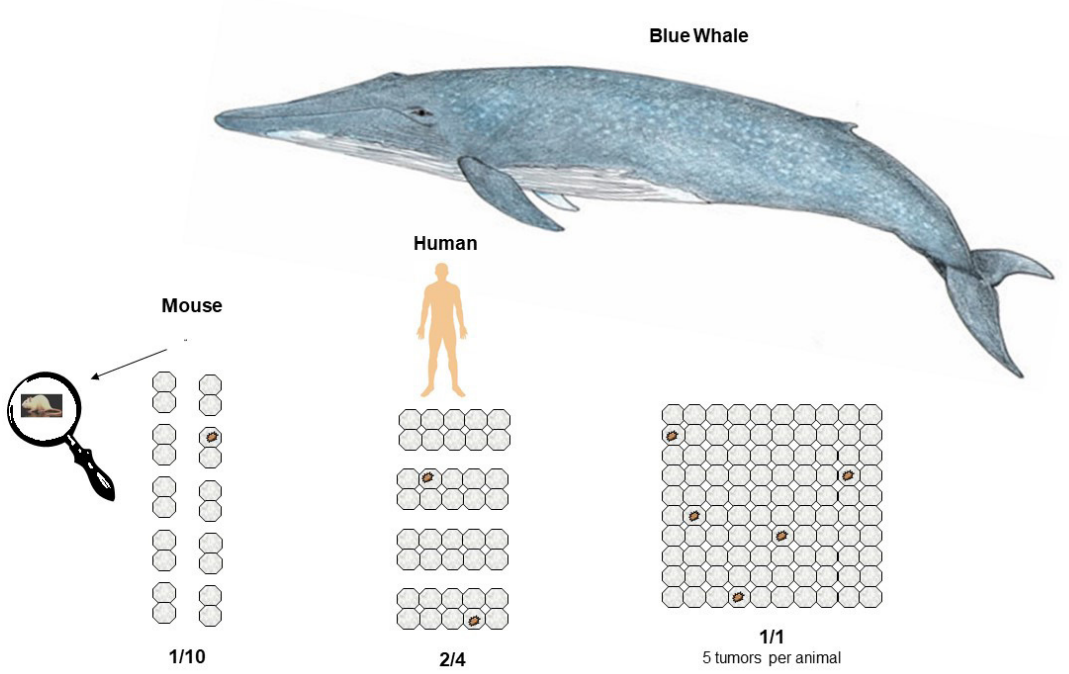

Figure 3. An illustration of Peto's Paradox: Theoretical influence that size of whole body would have on tumor incidence per unit time on the assumption that the individual cell is the unit at risk of carcinogenesis. We have arbitrarily assumed that a carcinogenic mutation occurs at a rate of 1 per 20 cell units per unit time (tumor cells are identified by an internal mark). As a consequence, animals with 2, 10 and 100 cells should develop, respectively, 1 neoplasm in every 10 animals, 2 neoplasms in every 4 animals and 5 neoplasms per animal, per unit time. The correspondence between organisms [mouse (20 g); human (60 Kg) and blue whale (200 Ton)] and number of cells (2, 10 and 100, respectively) is only illustrative. These theoretical expectations do not match reality: long-lived and large-sized animals do not have more cancer than short-lived and small-sized animals (image by the Authors).

Using a mathematical model of carcinogenesis, Nunney (2020) proposed that neither intrinsic changes in metabolic rates nor different mutation rates nor changes in immune surveillance, may resolve by themselves Peto's Paradox. Instead, he proposed that in order to compensate the sharp intrinsic increase of cancer risk associated with increased body size and longevity, large-sized and long-lived organisms (such as human beings and blue whales) may have acquired much more genetic controls of cancer (the sum of proto-oncogenes and tumor suppressor genes, that is, not only suppressor genes such as TP53) than small-sized and short-lived ones. However, although this proposal is attractive and it might theoretically explain the similar accumulated cancer incidence observed in all animals at the end of their lives, it would not explain the fact that, for all tested animals, not only the final incidence but also the shape of the curves of cancer incidence throughout their lives, are also very similar (Nordling 1953; Weiss 2004;Prejean *et al.* 1973; Pugh *et al.* 1999) (as seen above, roughly proportional to the 6th power of age). This suggests that the number of oncogenic steps (each one assumed as oncogenic genetic mutations by the hypothesis of multistage carcinogenesis) are also very similar among all animals.

A recent paper aimed to study the landscape of somatic mutation across 16 mammalian species displaying 30-fold variation in lifespan and 40,000-fold variation in body mass, has demonstrated that somatic mutation rate per year varied greatly across species and exhibited a strong inverse relationship with species lifespan (Cagan *et al.* 2023). These results suggested that the somatic—and presumably the oncogenic—mutation burden by unit of mass at the end of lifespan was roughly similar among long- and short-lived animals. However, since the mutation rate did not exhibit significant variation with tumor mass (Cagan *et al.* 2023), even if individual end-of-life cells across species have a fairly similar mutation burden, overall cancer risk should still be expected to scale with the number of cells in an organism, which we know it does not happen.

7. A Light in the Dark

Most attempts to explain the evolutionary riddles of cancer were based explicitly or tacitly on the SMT, that is the hegemonic paradigm in cancer research. The theory states that cancer is the outcome of the constitutive activation or mutation of some genes (protooncogenes) or the inactivation of others (tumor suppressor genes) allowing the cell to evade the mechanisms controlling cell proliferation. These genetic changes would define the attributes of the malignant cell, which, in turn, should be the target of specific therapies against cancer. This theory has the merit of unifying, through an immediate common cause, the numerous different mediate causes of cancer such as chemicals, radiation, viruses, etc. However, it has some theoretical difficulties that have been addressed by some authors (Sonnenschein & Soto 2021; Peto 2015; Prehn 2005) which have also emphasized that—apart from some particular advances in targeted molecular therapies against certain neoplasia (Danthala 2017)—cancer remains a major cause of morbidity and mortality, despite the explosive development of our knowledge about the molecular mechanisms associated with the control of cell cycle and survival (Bailar & Gornik 1997; Sung *et al.* 2021). Of course, these theoretical difficulties and the failure to treat malignant diseases, especially disseminated cancer, do not necessarily imply that the SMT is incorrect, but they encourage us to explore other approaches. SMT or some of its variants posit that the origin of cancer must be placed at the cellular or subcellular level of biological organization. On the other hand, some authors have raised the idea that cancer is primarily a disease of higher levels of organization, that is, an organismic, organ or tissue-based disease rather than a cellular one. This possibility has been advocated by Waddington, Smithers and others many years ago (Waddington 1935; Smithers 1962), and more recently by the group of Sonnenschein and Soto in their tissue organization field theory (TOFT) of cancer (Sonnenschein & Soto 2000; 2016; 2020). TOFT states that carcinogenesis occurs when some factors called carcinogens disrupt the flow of information between the stroma and the adjacent epithelium and unlock the constitutive proliferative capacity of the epithelial cells (Maffini *et al.* 2004). This is not to say that tumor cells do not harbor mutations, but they would not have the pivotal carcinogenic role that SMT attributes to them.

Several lines of evidence from both the record fossil and comparative oncology, seem to favor the latter interpretation.

For example, an osteosarcoma was recently diagnosed in the vertebral intercentrum of a

temnospondyl Mesozoic amphibian that lived more than 200 Mya in the current locality of Krasiejów, southern Poland (Surmik *et al.* 2022). The authors claim that the growth dynamics and development of the tumor are consistent with the postulates of TOFT which locates the cause of cancer in disorders of tissue architecture. This consistency is expressed in different ways: a) the fast growing characteristics of the newly formed bone, which mixes a slowly deposited matrix type with spatial distribution typical for rapidly growing bone; b) both the affected intercentrum and the overgrowth being subject to physiological remodeling processes, as evidenced by the numerous areas of bone tissue destruction within the tumor and the vertebra itself suggesting that the physiological processes occur in the neoplasm and the original bone alike; c) the difficulty to explain why the border between the physiological bone and the overgrowth is ordered and clearly marked taking into account that multiple lesions and a chaotic organization could be expected from an invasion of a collection of autonomous and independent mutated neoplastic cells. The existence of common physiological processes in both the normal remodeling bone and the neoplasm in this ancient fossil remain highlights the resemblance between cancer and regenerative processes and it is paralleled with the recent findings of oncogenic mutations in many normal aging tissues (Martincorena *et al.* 2018; Kakiuchi & Ogawa 2021) which, in turn, challenges the causal direct role of these mutations in the genesis of cancer.

In addition, although cancer or cancer-like phenomena have been observed in many of the largest groups of pluricellular organisms, including not only animals and land plants but also fungi and red and green algae (Aktipis *et al.* 2015), not all taxa exhibit it. Considering only the animal kingdom, cancer is rarely (if ever) produced in animals or body regions displaying regenerative abilities that remain efficient throughout life. These regenerative abilities are generally "strong" (strong meaning the capacity to regenerate complex structures such as a whole limb); and the regions that exhibit such abilities can encompass the whole body, as in sponges, ctenophores, cnidarians, echinoderms, annelids, etc. (Aktipis *et al.* 2015; Wellings 1969; Sparks 1969; Tascedda & Ottaviani 2014; Edgar *et al.* 2021) or parts of the body, as in the upper body regions of Planaria, phylum *Platyhelminthes* (Saló 2006) and limbs, tails and some other tissues of urodele amphibians (Prehn 2007; Stocum 2017). In contrast, cancer is relatively frequent in animals that display regenerative abilities that are efficient mainly during youth and wane progressively as the animals

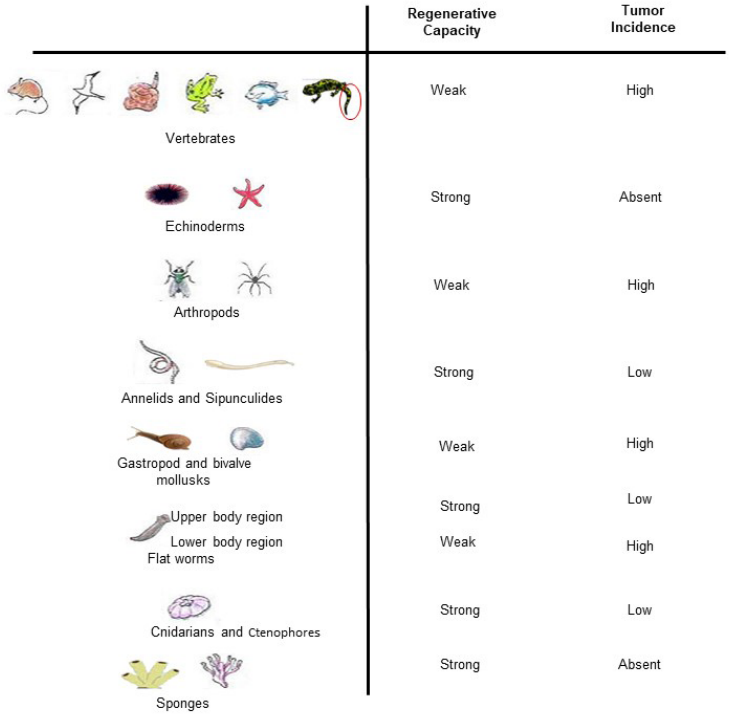

Figure 4. Comparing regenerative capacity and tumor incidence among different phyla.

age (Sharpless & DePinho 2004). These regenerative abilities are generally "weak" (by weak we mean having the capacity to repair o regenerate relatively simple structures only, as in compensatory hyperplasia of the liver, skin regeneration, etc.) and can encompass the whole body such as seen in most vertebrates others than urodele amphibians, nematodes, arachnids, insects, gastropods and bivalve mollusks (Aktipis *et al.* 2015; Kitsoulis *et al.* 2020; Gubin *et al.* 2001; Tascedda & Ottaviani 2014; Prehn 1997; Robert 2010; Ostrander *et al.* 2004; Caussinus & Gonzalez 2005; Kiriakakis, Markaki, & Tavemarakis 2015). A similar relatively high frequency of tumors has been observed in the body regions of urodele amphibians that lack a strong reparative capacity (Prehn 1997) and in the lowest body region of Planaria where the regenerative ability gradient is minimal (Hall, Morita, & Best 1986) (Figure 4). In animals in which cancer is relatively frequent, cancer incidence rises exponentially with age (Nordling 1953; Weiss 2004; Kiriakakis, Markaki, & Tavemarakis 2015; Hall, Morita, & Best 1986; Campisi 2013; Rozhok & DeGregori 2016) coincident with decreased reparative capacity. In addition, when cancer develops in young animals, it is usually associated with injured organs and tissues such as cirrhotic liver, gastric tissues exhibiting chronic atrophic gastritis, radiation-damaged skin, colon displaying ulcerative colitis, breasts of nulliparous women, non-secreting prostate alveoli, pulmonary fibrosis, etc., which may have a significant decrease of their regenerative abilities (Edgar *et al.* 2021; Karin, Lawrence, & Nizet 2006; Bustuoabad *et al.* 2021). The fossil record might also support this contention: although neoplasms have been described in fossils of many vertebrates and invertebrates groups (as trilobites) no neoplasms have been described in the abundant record of echinoderm (mainly crinoids) fossils, animals in which strong regenerative abilities—such as present in living echinoderms—have been extensively documented (Gahn & Baumiller 2010).

Strictly speaking, even animals that exhibit a strong reparative capacity, such as cnidarians, can exhibit tumors termed "calicoblastic epitheliomas", upon the action of exceptional environmental stressors that are strong enough to injure seriously their organisms and to impair their reparative capacity. This seems to have occurred, especially, but not exclusively, in some coral reefs of the genus *Acropora* in some locations of Caribbean where, during the last 40 years, water pollution and other diseases have produced rates of coral mortality without precedent in the late Holocene (Ruggiero *et al.* 2008).

In summary, throughout the animal kingdom, cancer seems to occur in organs and tissues that have experienced a decline or loss of their regenerative ability. In these organs and tissues, any injury causing loss of cells or cellular function could not be adequately compensated by cellular division or increased cellular size (Mitchell & Valk 1962; Castle & McDougal 1984; Fankhauser 1945), and in consequence the original size and function could not be restored. We suggest that this situation would induce a crisis, which might promote some degree of variability in the remaining cells of the organ bearing low ability to regenerate. The outcome of this situation would be the emergence, by chance, of a cell variant bearing mitotic ability to respond to the reparative signal. If this new variant were still functionally active, normal function might be restored and this restored organ might reproduce the regulatory fields associated with the intact functional organ, after which further mitosis would be halted. However, if the injury were persistent or more profound, later or sooner, a poorly or non-functional variant bearing mitotic ability might finally arise. This new variant would begin to divide and the organ would be numerically but not functionally restored. In consequence, it would not score the regeneration as effective and it would continue to send mitotic signals. As a result of this, the new variant would grow over and over and the outcome would be a tumor.

According to this interpretation, cancer would not be autonomous and have a profound biological sense: it would eventually be the ultimate attempt to restore organ functions and structures that have been lost or altered by aging or noxious environmental agents. However, unlike normal structures, cancer would have no physiological value, because the usually poor-functional nature of its cells would make their reparative task unattainable. The fact that animals that are resistant to cancer do not exhibit neither decline of regenerative ability nor aging (Petralia, Mattson, & Yao 2014) reinforces the proposal raised here of cancer as an attempt (even futile) to restore the regenerative ability of the affected organ and to evade the process of aging. Naturally, someone could ask why individuals with less efficient regenerative abilities have evaded natural selection. We have not a definitive answer to

this question. We only may suggest that, especially for highly complex organisms in this precise moment of their evolutionary history, the maintenance of their regenerative abilities fairly efficient throughout their lives—that would eventually prevent tumor formation—might be achieved only at the cost of reducing the efficiency of growth during youth when reproduction is more probably to occur, which would be, as a whole, selectively unfavorable. The existence of undesired traits coupled with more beneficial ones that globally represent phenotypes which have been selected during evolution is highlighted in a recent paper concerning the price of human evolution (Erenpreisa *et al.* 2023).

The interpretation stated above, encoded in the so-called hypothesis of the biological sense of cancer (Ruggiero *et al.* 2008; Ruggiero & Bustuoabad 2006; Bustuoabad & Ruggiero 2017) was built within the broad framework of TOFT by assuming that cancer is basically a problem of tissue organization. In fact, according with this hypothesis, there would not have such thing as a cancer cell if it means a cell endowed with genetic anomalies that allow it to escape from the inhibitory signals of normal cell proliferation. Instead, the problem would be the reduction or absence of such tissue signals. In this context, this hypothesis could offer a relatively easy solution of the Peto's Paradox by assuming that the true basic unit at risk of carcinogenesis is the tissue or organ as a whole rather than the individual cell. In effect, according to the hypothesis, cancer originates in organs or tissues that display a significant decline of their regenerative capacities, and this would occur when a critical proportion of their cells have partially or wholly lost that capacity. In such a case, if an organ were x times larger than another one, the probability that its regenerative capacity is critically diminished would be x times lower, because an x times greater number of cells would have to be affected to depress that capacity. This lower probability would balance the proportionally higher number of their cells that could be transformed. As a result, if the unit at risk is, for example, one liver rather than 10^9 (mouse) as opposed to 3×10^{12} (human) or 1×10^{16} (blue whale) liver cells, then the human or the whale will be at no greater risk of developing liver cancer than the mouse, or any other animal with an equally efficient defense mechanism against neoplasia.

The hypothesis advanced in this paper that the tissue or organ as a whole rather than the individual cell is the basic unit of carcinogenesis might be questioned by the fact that cancer can be transplanted into healthy individuals. In effect, this universal laboratory practice—initiated by Novinsky in 1877 (Shimkin 1955)—demonstrates that only a small fragment of a tumor or a relatively small number of tumor cells [in the limit, only one euploid or polyploid cell (Weihua *et al.* 2011; Moein *et al.* 2020)] dispersed in physiological saline will suffice to transplant that tumor from a tumor-bearing donor to a normal recipient host. This would mean that the growth of a tumor does not need to be supported by any tissue, organ or organismic pathological condition but only by the nature of the tumor cells themselves. In other words, the basic unit of carcinogenesis would be the tumor cell that, in consequence, could be deemed as "autonomous". However, the whole of this apparently fatal objection pivots on the ambiguity of the word "autonomy". We can accept that tumor cells are deemed as "autonomous" if their inoculation into an appropriate recipient host is enough to induce a new tumor growth (the first meaning of autonomy). But this does not mean that the new growth has to be accomplished by evading the rules controlling normal cell proliferation (the second meaning of autonomy). In effect, tumor cells transplanted might need to injure the recipient organ and to reduce its regenerative ability as a precondition for regenerative signals produced by the injured organ to promote tumor growth. This last possibility concerning the mechanisms underlying both tumor transplantation among different individuals and strategies used by a tumor to invade adjacent or distant organs within the same individual, has significant experimental support: a) Benign tumors, which are not invasive and commonly produce little damaged to host tissues, seldom grow when transplanted in another host (Shimosato *et al.* 1976). b) In chickens, tumors induced by Rous sarcoma virus (RSV) typically form at the viral injection site but not at distant sites; the wound associated with the injection seems to be required for local tumor growth, because additional tumors can be induced at distant sites simply by wounded the infected birds (Kennt & Bissell 2003). c) The liver of a young rat, but not of an aged rat in which regenerative ability is diminished, can normalize the morphology and growth capacity of transplanted hepatocarcinoma cells. The most successful normalization occurred when cells were transplanted into the spleen and filtered as solitary cells into the liver without disrupting

normal liver architecture. On the other hand, when this architecture was disrupted by transplanting a greater number of malignant cells directly into the liver, normalization was less likely to occur (Rubin 2006). d) Upon transplantation, tumors usually grow into anatomically correct (orthotopic) organs better than in heterotopic ones (Nathanson, Nelson, & Lee 1993). This observation can be interpreted by assuming that an invasive and transplantable tumor, even if quite different from the organ of origin, tends to be more similar to that organ than to others; in consequence, it would respond to a regenerative signal from the former better than to one from the latter, resulting in faster tumor growth.

Conclusions

The hypothesis that we have presented herein could explain the permanence of cancer for hundred million years assuming that it is coupled to the normal regenerative mechanisms of the organisms without which no pluricellular organism could survive. Furthermore, some cases of the record fossil suggest that neoplasms could also be a major component of the evolutionary machinery of pluricellular organisms, taking into account that some extant and extinct animals and plants seem have adopted some kinds of neoplasms as adaptative strategies to survive in hostile conditions. In addition, it could also explain the Peto' Paradox, as long as we assume that the true basic unit of carcinogenesis is the tissue or organ as a whole rather than the individual cell, as it is usually thought when following the SMT paradigm. Apart from its theoretical value, this proposal also might have therapeutic consequences. Namely, all conventional therapies against cancer attempt to kill all cancer cells. However, according to the hypothesis that we have advanced, the problem might not be solved even though all tumor cells were eradicated. In such a case, if the organ failure remained, new tumor cells would emerge and the tumor would reinitiate its progressive growth in response to the permanent regenerative signal of the non-restored organ. The possibility that currents cancer treatments are obsolete and must be changed has been recently suggested (Galmarini 2020).

Therefore, efficient anti-cancer therapy should combine an attack against the tumor cells themselves with the correction of the organ anomaly, which would be in the core of the cancer problem. The possibility that this anomaly, that is, the decline or loss of the organ regenerative ability, may be eventually reversed is suggested by novel experiments in which transplantation of differentiated cells derived from induced-pluripotent stem cells successfully induced functional recoveries in rodent models (Sánchez Alvarado & Yamanaka 2014; Elkashty 2021). Finally, the comparative study of cancer phenomenon and cancer-resistant animals that do not age might unveil common and still unknown routes to immortality.

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