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Outline of the natural history of tumours

JANUSZ A. MADEJ

Chair of Pathology, Department of Pathomorphology and Forensic Veterinary Medicine,
Wroclaw University of Environmental and Life Sciences, Norwida 31, 50-375 Wrocław

Madej J. A.

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Summary

The paper presents a historical outline of studies on tumours from prehistoric times (paleo-oncology) to the present, as well as explains how neoplastic processes developed and why they developed only in multicellular organisms (Metazoa). One of such explanations refers to the development of the body's defence system in the form of a cellular (inflammatory) infiltrate directed both against exopathogens, e.g. viruses, and against neoplastic cells. The paper also discusses the role of the infiltrate in the primary and secondary neoplastic progression and in regression, as well as the influence of exogenous and endogenous factors, including dissipative factors, on tumour development.

Keywords: paleo-oncology, cellular defence (inflammatory infiltrate), tumour progression and regression, exogenous and endogenous oncogenic factors

Paleo-oncology

Spontaneous tumours have accompanied both humans and animals since the dawn of time. One example are osteosarcomas (*osteosarcomata*) discovered in the bones of fossil dinosaurs, for instance, those of the herbivorous *Cretaceous hadrosaurus* from the late Cretaceous period (250-65 million years ago), as well as in Indian mummies in Peru over 5000 years old (12-14). Tumours were diagnosed and even treated in ancient Mesopotamia, Egypt and India. Hipokrates of Kos (c. 460-377 BC), the founding father of modern medicine, divided tumours into benign and malignant, calling the latter *karkinos* – a word denoting a crab or crayfish – because they resembled livid crabs with limbs, especially in the female nipple. The name may also have referred to the similarity between the difficulty of detaching a crab from the ground and problems involved in eradicating a neoplastic tumour (16). Also in the antiquity, the Roman physician Celsus (53 BC-AD 7) first used the word *cancer*, still current today, and Galen (c. AD 130-200) attributed neoplastic changes to the accumulation of „black bile" at the site of inflammation (the bodily humours theory of inflammatory diseases). In a later work titled *Tumores praeter naturam* Fabricius ab Aquapendente (1533-1619) writes that „a tumour is called cancer because of its resemblance to a crayfish [in Latin „cancer" – translator's note] living in water, which has a trunk and limbs growing out of it and which holds very tight whatever it grabs ... it most often tortures the sick to death" (8).

The first evidence for the existence of osteosarcomas of the skull in humans was provided by excavations in Peru dating back to 3000 BC. (1). In a human burying ground in Viessenhauser Hof near Stuttgart various tumours were found is as many as 10% of the remains, which is now explained by the theory that the site had been used for burying victims of unusual diseases (8). Even more evidence for the existence of tumours comes from sculptures and drawings made by a human hand. And so, for instance, a Mayan sculpture from Campeche depicts a man with a neoplastic tumour in his left eye socket, and a sculpted head of the Peruvian Mochica culture has a tumour on the right zygomatic bone corresponding to an osteosarcoma. Such pathologic changes have always intrigued people, especially physicians, and it is therefore not surprising that the ancient Indian *Rigveda* contains the following statement: „a carpenter needs wood, a priest needs sacrifices, and a doctor needs diseases" (18).

The Indian medical textbook *Sushruta Samhita* includes a report on a human autopsy – obviously conducted in secret – as well as descriptions of 14 different abdominal tumours. Obstacles to the performance of post-mortem examinations explain why a description of the first autopsy of a captured enemy in China dates from AD 1145, since the veneration of the dead in that country prohibited the dissection of human corpses. Nevertheless, the Chinese at the time already had detailed knowledge of disturbed balance between „Yin" and „Yang", which is now explained by the fact that

Chinese physicians understood very well the function of the sympathetic nervous system and of its antagonist, the parasymphatetic nervous system.

Paleopathology based on the studies of skeletons or mummies did not exist in Mesopotamia because of the climate (high humidity), which was completely different from the Egyptian one (21). The cuneiform script, however, attests to the high excellence of medical practice in the „land between two rivers". Written on a diorite stele, the Code of Hammurabi (1728-1686 BC), the main principle of which was that „the strong should not harm the weak", mentions in its article 224 „a doctor of animals, who should be rewarded with one sixth of a measure of silver by the owner of an ox or donkey that the doctor has treated for a severe injury and saved". Further, in article 278, the Code describes a one-month warranty for a purchased slave if he is found to suffer from leprosy, which is the first evidence for the existence of what would be described today as forensic medicine.

In Giza (Egypt), near pyramids dating from 2723--2563 BC, Hermann Junker unearthed in 1926 a door--shaped stele covered in hieroglyphics describing a physician named Iry, a supervisor of other specialist doctors, including ophthalmologists, laryngologists, and „doctors of the stomach and anus". The existence of medical specialisation in ancient Egypt was also confirmed by the Greek historian Herodotus of Halicarnassus, who travelled in the country in the fifth century BC. We are indebted to him for a description of the masterly art of embalming human and animal corpses, in which, however, he fails to identify the originator of this practice in the land of the Nile. It is believed that the corpses were originally dried in the hot desert sun or in artificially heated chambers, and later a 70-day embalming process was developed, in which lye and table salt were used. Lye dissolved all tissues except for the skin and bones, whereas internal organs were previously removed and kept in separate urns (canopic jars), which can be seen today, for example, in the Egyptian National Museum in Cairo or in the British Museum in London.

The first X-rays of the mummies provided a clear picture of diseases afflicting ancient Egyptians (tuberculosis, smallpox, leprosy, malaria, schistosomiasis, rheumatism, atherosclerosis, periodontitis, kidney stones, gout, poliomyelitis, osteodystrophy). In three mummies, osteosarcomas of the femur and humerus were found. It is thought that the absence of soft tissues in mummies prevented the diagnosis of other neoplastic diseases, e.g. cancer. The only documented case of colorectal cancer was described in a man who died c. 3000 BC in the Dahleb oasis, and a probable case of breast cancer in a woman was reported in Egypt at the same time (3). The above analysis referred to young people (life expectancy in ancient Egypt was about 35 years). Today we know that 90% of tumours occur in people older than 50. Nor have any tumours been found in the mummies of children, which is not surprising, since, according to estimations, it would be necessary to examine as many as 10 thousand mummy skeletons to find a single case of osteosarcoma. Nevertheless, Egyptians were the first anatomists and anatomopathologists in history, although they probably had no particular need for the scientific autopsy, as their lives were dominated by the idea of an afterlife, which made them concentrate on the embalming technique (21). There is no absolute proof, but autopsies and vivisections of criminals may also have been performed in Alexandria during the time of Alexander the Great (8).

Empirical observations were sometimes recorded on papyri, e.g. the Kahun papyrus (2000-1800 BC), including a description of tumours of the female generative organ, or the Ebers papyrus (1600 BC), containing a prescription list of 900 medications. In the latter, among other things, an unknown physician, recommends yeast as a medicine for tumours. In a five--volume work titled *Drugs* (Hyle iatrike), written during the time of Nero, the Greek Pedanius Dioscorides describes 1000 medicines and 600 medicinal herbs used in the treatment of tumours. They include, among others, autumn crocus, which is known today to contain a powerful antimitotic: colchicine. On the other hand, the Roman Plinius Secundus (first century AD) recommends an extract from mistletoe as an anti-neoplastic agent.

The modern era

The first book on pathologic anatomy in the modern period is considered to be a work by Antonio Benivieni of Florence written in 1507, which marks the beginning of a rapid development of this scientific field (8). Here are some of the milestones in the development of oncology. In 1545, Dr. Walter H. Ryff wrote that „black bile, or melancholic humidity" causes lumps (*scirrhi*), that is, hardened protuberances. In 1775 in London, Percivall Pott suggested a causal relationship between chimney soot and testicular cancer among chimney sweeps. In 1867 in Wrocław, Wilhelm von Waldeyr-Hartz wrote a book titled *Carcinogenesis*, in which he stated that „cancer originates from the epithelium and forms connective tissue, rather than arising from connective tissue, as Virchow believed" (18). The first description of a biopsy (1887) comes from Morell Mackenzie, who used tweezers to collect a sample of a tumour of the larynx from the Prussian Frederick III and sent it for examination to the world famous pathologist Virchow. Georg Mathe, in his work titled *Dossier Cancer*, writes that, in oncology, surgical treatment is „cold steel", radiotherapy is „firearms", and chemotherapy is „poison gas" (8). As early as 1899 Tage Sjogren cured the first case of basal-cell carcinoma of the nose using X-rays, and in

1905 Robert Abbe successfully treated cancer of the uterus with radium (1). In Poland, the Warsaw Committee for Cancer Research and Treatment was established in 1906, and in 1932 the Radium Institute was opened in Poland's capital.

Viral etiology was proved in the case of leukemia in poultry by Ellerman and Bang in 1908, in the case of sarcoma in poultry by Rous in 1911, in the case of papilloma in rabbits by Shape in 1932, and in the case of breast cancer in mice by Bittner in 1936. Gross (1951) was the first to isolate the leukemia virus in mice (20).

The neoplastic process emerged only at a certain stage of evolutionary development, that is, in *Metazoa*, and analogically in *Metaphyta*. In the kingdom of *Protozoa*, neoplasia does not exist, or at least it has not been diagnosed as yet. Hence the conclusion that neoplasia occurs only in multicellular organisms, which had to develop an effective defence system against it (9). It is therefore supposed that the development of the immune control of the body's own cells was rendered necessary by infections, especially viral ones, and neoplastic processes. Aside from this fact, warm-bloodedness probably favoured the growth of pathogens in mammals, since most micro-organisms, contrary to popular belief, multiply more readily in high temperatures, e.g. fever, than in low temperatures (18). One exception are gonococci, which die at a temperature of about 41°C. In this way a more precise immune system, e.g. an integrated humoral and cellular response, and lymphatic organs, especially lymph nodes, were developed. It should be noted, however, that the immune control is markedly more effective against viruses than against neoplastic cells, which have a number of specific mechanisms for avoiding detection and destruction by the immune system.

Pathogenic invasion triggers a defence mechanism in the form of an inflammatory infiltrate that destroys dead cells by dissolving them with lysosomes (heterolysis) but spares healthy cells, except in few special cases, such as autoimmune inflammations. It is also possible to draw analogies with the above-mentioned evolutionary development of the immune system in organisms, because inflammation – that is, the organism's defence mechanism – does not develop until early or late fetopathy (in humans, 76th-180th day and 181st day after birth, respectively), and therefore it does not occur during embryopathy or blastopathy. Mature plasmatic cells, capable of producing cytokines, are found in children older than 3 months, and so there is no reaction from these cells, as well as from lymphocytes, immediately after birth. It is possible, however, to note reactions on the composition of the fetal haematopoietic centres in the liver and spleen (16). In contrast, infiltration by neoplastic cells damages healthy cells of the organism, destroying them completely (e.g. by necrosis or, indirectly, by the degradation of the basement membrane and stroma of the organ) or partially, e.g. by exerting pressure that causes them to atrophy. The latter phenomenon may stimulate the hyperplasia of connective tissue (fibroplasia), which together with the connective tissue of the tumour stroma forms a capsule around the tumour. It is only rarely that neoplastic cells do not damage the

Tab. 1. Comparison of inflammatory and neoplastic infiltrates

INFLAMMATORY INFILTRATE	dead cells are destroyed by dissolution (no damage to healthy cells)	autoaggression (exception)
	cytokine production (e.g. TNFα, IL-1, IL-6, IL-8)	neoplastic cells are damaged
		healthy cells are damaged
NEOPLASTIC INFILTRATE	healthy cells are damaged	partially (e.g. atrophy as a result of pressure*)
		completely (e.g. necrosis)
	no cells are damaged	infiltration between cells (e.g. along myelin sheaths, through the fluids of serous cavities)
	the production of vessels and (normal) stroma	harmonious
		excessive (desmoplastic cancer)
	metastasis (the acquisition of invasive and migratory abilities)	• autocrine activation of the autocrine motility factor receptor and loss of E-cadherin • adhesion to fibronectin and laminin, and migration in ECM ** • degradation of the stroma and basement membrane *** • invasion beyond the basement membrane of the epithelium (type IV collagen, laminin, proteoglycan) • invasion beyond the basement membrane of vascular endothelial cells • formation of the site of metastases (e.g. the absence of protease inhibitors, the presence of growth factors)

Explanations: * this may stimulate connective tissue, which together with the connective tissue of the tumour stroma forms a capsule around the tumour; ** a different composition substance (proteoglican, triple helix of collagen stabilised by crosslinks, adhesive glycoproteins, elastin, fibrillin, hyaluronian, syndicans), which bind to e.g. ECM fibroblasts through integrins). Integrins interact with both epithelial cells and mesenchymal cells; *** metalloproteinases (gelatinase, collagenase, stromelysins) and protease proteines, e.g. katepsine D

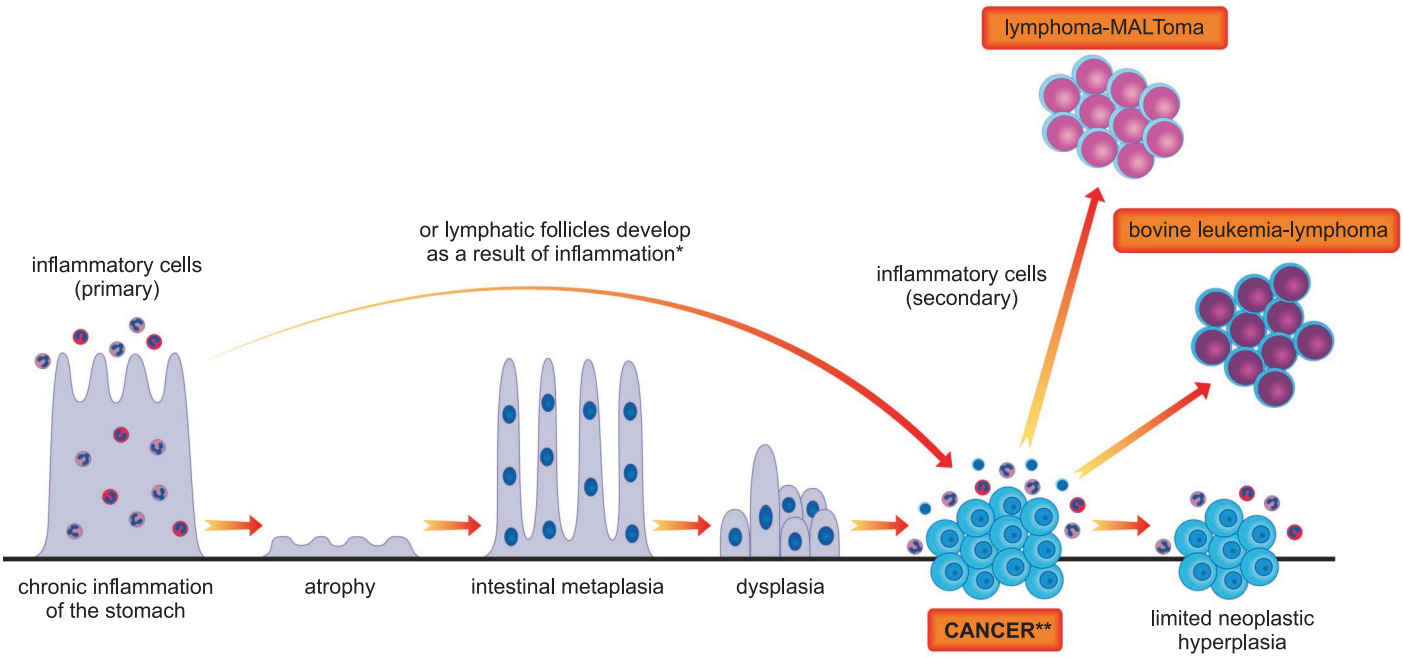

Fig. 1. Primary and secondary involvement of inflammatory infiltrate cells in tumour progression or regression
Explanations: * lymphatic follicles do not normally occur in the mammalian stomach; ** the involvement of *Helicobacter pylori*, *H. felis*, *H. heilmani* (in animals)

cells of the macro-organism as, for example, when they infiltrate between myelin sheaths or spread into fluids of serous cavities in the process of metastasis (tab. 1). Finally, it is worth mentioning that the role of the inflammatory infiltrate can be ambivalent. On the one hand it can locally restrain or even completely stop neoplastic hyperplasia, as in the treatment of the bladder cancer in humans with the use of attenuated *Mycobacterium tuberculosis*. On the other hand, the infiltrate can be a source of the hyperplasia of its own cells and the creation of another type of tumour of mesenchymal character (e.g. gastrointestinal stromal tumour) (10, 15, 17). Other examples of an excessive proliferation of the cells of the inflammatory reaction are certain types of eosinophilic, mastocytic, lymphocytic and basocytic leukemia. Metaphorically speaking, in these conditions the body's defence cells become its enemies. In exceptional cases, an inflammatory infiltrate may also facilitate the migration of neoplastic cells by causing oedemal changes in the stroma and by penetrating into intercellular tissue spaces through this route.

Chronic inflammation of the stomach can lead to the atrophy of the mucous membrane, a consequent intestinal metaplasia, dysplasia, and eventually cancer. Alternatively, inflammation may lead to the creation of lymphatic follicles, which do not normally occur in the mammalian stomach. This is an example of the primary involvement of inflammatory infiltrate cells in neoplastic progression or regression (fig. 1). However, cancer that has developed in this way can be secondarily infiltrated by inflammatory cells that locally inhibit its proliferation. Similarly, a lymphoma can develop secondarily from B-type lymphocytes ($CD5^-$, $CD10^-$, $CD23^-$ – *lymphoma – MALToma*), from the cells of mucosa-associated lymphoid tissue (MALT) undergoing a neoplastic transformation, which frequently accompanies cancer of the stomach. This process begins with a polyclonal inflammatory lesion (*pseudolymphoma*) and progresses to the development of a monoclonal tumour of greater or lesser malignity (16). This is a very important diagnostic sign differentiating a lymphoma as a monoclonal growth from a polyclonal inflammatory infiltrate of lymphoid cells. The presence of *Helicobacter pylori* in the stomach is considered as an important factor in the neoplastic transformation of cells. After the removal of these bacteria, both cancer and the lymphoma may regress (16). A similar phenomenon occurs following an infection with the spirochete *Borrelia burgdorferi* (borreliosis or Lyme disease), in the course of which, after many months, a lymphoma may appear on the skin of the sick person. Another example of the atypical behaviour of inflammatory infiltrate cells is the neoplastic transformation of B lymphocytes into lymphoma cells, which occurs in the course of the inflammation of the thyroid gland known as Hashimoto's disease (16).

A different explanation why tumours appeared only in higher animals refers to the amount of phylogenetic time that was necessary for the development of the tumour-host relationship, that is, for the mutual adjustment of the two biological systems. A similar phenomenon has been observed in the relationship between tapeworms (parasites) and fish (hosts). In phylogenetic terms, fish are the oldest vertebrates, and so they

had time to become hosts to the first tapeworms before other vertebrates did. Hence the low pathogenicity of these parasites to fish is considered as evidence that this parasite-host relationship is a long-standing one. Perhaps a similar mechanism was in play in the relationship between tumours and lower vertebrates, whereas in the case of mammals the mutual coexistence was considerably shorter in evolutionary terms (9).

Another unresolved question is whether the development of cellular immunity was necessary as a mechanism of preventing tumours, or vice versa: the absence of tumours in invertebrates has resulted in the absence of this kind of immunity in these animals. In any case, the fact is that tumours occurred only in vertebrates – that is, in animals with a developed cellular response – which has been established by research on the ontogenesis and phylogenesis of immunity.

The growth of tumours is, anthropomorphically speaking, „revolutionary" and „anarchical". Its underlying causes are molecular changes that damage genetic material non-lethally and in many stages: a tumour is therefore a „disease" of DNA. For example, the *MYC* gene from chromosome 8 and the *IGM* gene from chromosome 14 may combine with each other after the rupture of DNA, which results in a carcinogenic translocation, e.g. in Burkitt's lymphoma (16). The closer the proximity of chromosomes in the nucleus, the more frequently they combine, e.g. in the B lymphocyte, chromosomes 8 and 14 are adjacent. According to other researchers, however, tumours are a mitochondrial disease, as evidenced by changes in their shape, size and metabolism (ATP production level, oxidoreductive potential, TP53 protein location), as well as by their molecular status, e.g. mtDNA mutation (4). At present it is estimated that one person in three will develop a malignant tumour, and one in five will die of it. Despite enormous financial investment, to say nothing of intellectual effort, the outcome of the fight against cancer is still far from satisfactory, and there has been no therapeutic breakthrough as yet, nor is there any in sight. Notwithstanding some brilliant molecular discoveries concerning protooncogenes and oncogenes, there has been scarcely any progress in therapy.

It is assumed that approximately 80% of tumours are caused by endogenous and exogenous oncogenic factors. The risk of neoplasia may be related to workplace conditions (contact with benzene or asbestos), diet (ingestion of the B_1 aflatoxin produced by the fungus *Aspergillus flavus*), lifestyle (smoking) or other factors, such as treatment with certain drugs (e.g. cyclophosphamide) (9). Tumours are therefore a result of destructive human activities and are sometimes described as man-made diseases. Thus, if it were possible to remove all carcinogenic factors from the environment, the incidence of tumours could theoretically be reduced by the above-mentioned 80%. Some researchers, such as Rosaline David and Michael Zimmerman, go as far as to claim that man himself has created tumours by polluting the environment, smoking tobacco and adopting unhealthy eating habits. They published this (not entirely new) theory in *Nature Reviews Cancer* in 2010 (3).

Out of 4000 chemical substances created by cigarette smoking, as many as 60 are carcinogenic compounds (including polonium-210) causing about 30% of cancer-related deaths. Smoking leads to a 10-fold increase in the risk of developing lung cancer, and smoking 40 cigarettes a day makes this risk up to 60 times greater. There were countries where tobacco smoking used to be punished by impaling the smoker or at least cutting off his hands, as in the Ottoman Empire under Murad IV, or where smokers were exiled, as in Russia under Tsar Nicholas (16). Nowadays, this addiction is regarded as a disease of choice, that is, a self-inflicted disease. Objectively, however, one cannot ignore the role of genes in the neoplastic process. Cigarette smokers who have the alleles of the *CYP1A1* gene (10% of the human population), which encodes highly active enzymes (e.g. P450 cytochrome monooxygenases), develop lung cancer more frequently than smokers without this gene (2). On the other hand, deletion of the gene encoding glutathione transferase, which detoxifies polycyclic aromatic carbohydrates present in cigarette smoke, (a feature found in 50% of the white population) is associated with a many times greater incidence of lung and bladder cancers.

The role of genes cannot be overestimated: Mutations in the *BRCA1* gene located on chromosome 17 at locus q21.3 is found in about 50% of women suffering from breast cancer, and mutations in the *BRCA2* gene (on chromosome 13 at locus q 12-13) occurs additionally in about 30% of breast cancer patients, which means that as many as 70% of women with these two mutations develop breast cancer by the age of 80 (2, 5). They are suppressor genes, and when both alleles become inactive or defective (e.g. because of an embryonic mutation in one and a later somatic mutation in the other), breast cancer is induced. In 50% of cancer cases, one also observes an increased expression of cycline D_1, which can stimulate neoplastic transformation in two ways: as an activator of CDK4/9, which are involved in passage through the G1 phase restriction point, as well as by operating together with the estrogen receptor and enhancing transcriptional activities of estrogens (10). Moreover, one observes overexpression of the *HER2/NEU* protooncogene, which is amplified in about 30% of cancers, amplification of the *RAS* and *MYC* genes, and mutations in the *RB1* and *TP53* suppressor genes, which are almost always associated with gene amplification. For example, the risk of *retinoblastoma* in people with the *RB1*gene mutation is 10,000 times greater than in the population as a whole (11). The *TP53* gene is the „guardian angel" of the organism's genome, since the

TP53 protein encoded by this gene prevents cells with damaged DNA from entering the cell cycle. Otherwise, such cells enter the cycle and may undergo neoplastic transformation.

According to other theories the only sufficient cause of tumours is an internal dissipathogenic state of cells, which may result from a great number of various but unnecessary factors (6, 7). In order for a neoplastic cell to develop within a multicellular organism, the cell must find itself in a dissipative state, which causes it to self-organise into a new dissipative structure. Otherwise, the cell dies. An example of this are cervical cancer cells, in which the conversion of matter into energy during self-organisation manifests itself as a reduction in the dry mass of the cytoplasm and cell nucleus, and as changes in their surface area. This is a so-called bifurcation point, situated in a range of unstable states far removed from the equilibrium of any, not only biological, system. Thus the tumour has its own thermodynamic branch, characterised by the dissipation of matter and energy around the tumour and the consequently increasing entropy. Hence the conclusion that such dissipative states in unicellular organisms lead to cellular mutations and, in multicellular organisms, to neoplasia. Thus, according to this theory, carcinogenic factors are not necessary for the induction of tumours, since the latter can develop spontaneously as a thermodynamic necessity (the second law of thermodynamics): entropy. It is therefore impossible to be fully protected from the development of neoplastic cells, even if all oncogenic factors are completely eliminated. This is the price paid by the organism for evolutionary development. It must be emphasised, however, that the role of oncogenic factors is very important, especially in speeding up neoplastic processes or in increasing their incidence, even if oncogenic factors are not necessary to induce them (7).

Finally, it should be mentioned that warm-blooded organisms are characterised by substantial bioenergetic instability related to the continuous fight against entropy, as well as by increasing molecular inertia and considerable dissipation of energy. This results in an increased likelihood of damage to genetic information and the danger of the development of neoplastic structures. Cold-blooded organisms, by contrast, are characterised by a high degree of bioenergetic stability, caused by the body warmth becoming even with the outside temperature, which may explain a considerably lower oncogenicity in these animals (7, 9). Hence the self-organisation of cells is probably related to a disturbed relationship between entropy and temperature.

An indirect confirmation of this theory comes from observations of metabolism in warm-blooded animals, which show that, contrary to what might be expected, the intensity of metabolism is fractal, rather than exactly proportional to the body weight and surface area (19). For, according to Mandelbrot (cyt. for 19), a living organism is a collection (a tangle) of fractal objects (the word „fractal" derives from the Latin „*fractus*" for „broken"), that is, irregularly undulating surfaces of body organs, their parts and molecular structure. Examples of fractal objects are the bronchial tree with its many branches, the dendritic tree of neurons, renal glomeruli and microcirculatory blood vessels.

The complicated pathological process of neoplasia, encompassing about 500 types of tumours, is a formidable challenge to contemporary biochemistry and molecular biology: a challenge requiring an urgent response. It is to be hoped that the definitive answer to questions about the molecular mechanism of carcinogenesis – a discovery that will have enormous therapeutic and theoretical consequences – is not far away in the future. The key to answering these questions lies in interdisciplinary research and international cooperation. Apart from proven facts, there are also hypotheses, which may sometimes be controversial. Rejecting them *a priori*, however, without verification, is scientific defeatism, which obstructs any genuine progress in science. We should bear in mind that man's setting foot on the Moon did not come easily, either.

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Corresponding author: prof. dr hab. Janusz A. Madej, ul. Norwida 31, 50-375 Wrocław; e-mail: janusz.madej@up.wroc.pl