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REVIEW

Spontaneous and Experimentally Induced Pathologies in the Naked Mole Rat (*Heterocephalus glaber*)

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Abstract—The naked mole rat (*Heterocephalus glaber*, Rüppell, 1842) is a unique eusocial rodent with unusually long lifespan. Therefore, the study of spontaneous and experimentally induced pathologies in these animals is one of the most important tasks of gerontology. Various infections, noninfectious pathologies (including age-dependent changes), and tumors have been described in the naked mole rat. The most frequent pathologies are traumas (bite wounds), purulent and septic complications of traumatic injuries, renal tubular calcinosis, chronic progressive nephropathy, hepatic hemosiderosis, testicular interstitial cell hyperplasia, calcinosis cutis, cardiomyopathy, and dysbiosis-related infectious lesions of the digestive system. However, the summarized data on pathology (including tumor incidence) and on the causes of mortality are insufficient. There are only few publications about the results of experiments where pathologies were induced in the naked mole rat. All these problems could be subjects for promising future studies without which adequate studies on mechanisms providing the long lifespan of the naked mole rat are impossible, as well as the elucidation of causes of tumor resistance of this species.

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The naked mole rat (*Heterocephalus glaber*, Rüppell, 1842) is a unique eusocial rodent with the unusually long lifespan (an order of magnitude longer than the lifespan of laboratory mice and rats), and this is the reason for increasing interest in this animal of biologists with different specialties [1-8]. Sometimes these animals are referred to as an ageless species (more accurately, to species with negligibly small aging) [1-4] or considered an example of neoteny among mammals [5-8]. Studies on spontaneous and experimentally induced pathologic changes in the naked mole rat are among the most interesting aspects of its biology, especially on the age-related and neoplastic changes and on the possible causes of its natural mortality. Although in all these aspects there are still more questions than answers, some definite findings were obtained recently, and we think that a review of them would be useful as a jumping-off place for further studies. We think that studies not only in pathologic anatomy of this unusual animal could be useful, but also in the fields where the naked mole rat is an important model animal in gerontology and biology of eusocial animals. According to the tradition adopted in pathology of laboratory animals, all lesions known in the naked mole rat will be subdivided into infectious and noninfectious pathologies. Problems of tumor growth, age-related changes of organs and tissues, and causes of spontaneous death of this rodent will be considered separately.

INFECTIOUS LESIONS

Infectious diseases of the naked mole rat are known the least. It is supposed that this animal is more resistant to pathogens usual for laboratory rodents [4], but up to now no accurate experimental data about this have been published. In this connection, it seems interesting to mention here that infecting (by scarification of the extremity skin) with recombinant herpes simplex first type virus apathogenic for mice caused 100% death of naked mole rats [9]. They are also very sensitive to experimental infection caused by *Leishmania donovani* [10].

Abbreviations: CPN, chronic progressive nephropathy; hTERT, human telomerase reverse transcriptase; *ras*, (rat sarcoma) oncogene; SV40 TAg, simian virus 40 tumor antigen.

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Hill et al. [11] found six cases of bilateral pneumonia in 25 spontaneously deceased animals in a colony of naked mole rats in their laboratory. The etiology of this pneumonia remained unknown. In the same colony, five animals died with a pathomorphological picture of septicemia accompanied by typhlitis and typhlocolitis (sometimes of hemorrhagic type); moreover, from the lungs and blood pneumococcus cultures were isolated, although pneumococcus is not a usual causative agent of spontaneous respiratory infections in laboratory rodents [12]. Moreover, in the animals with clinical signs of the disease (which ones is not specified in the work), bacteria from the groups *Haemophilus* and spirilla were found in the blood.

Nonspecific differently located purulent lesions are not rare in naked mole rats [13]. Many of them seem to be associated with infecting traumas caused by other animals (bite wounds) that lead to development of ulcerative dermatitis. Sometimes a severe purulent inflammation was caused by infecting of the wound on implanting a chip for labeling the animal. Especially severe are purulent lesions of the muzzle leading to its total necrosis, mutilation, and impossibility of food consumption by the animal. The further spreading of the purulent inflammation often leads to development of phlegmon, myositis, arthritis, osteomyelitis; in some cases – to sepsis, peritonitis, and even (on lesion of the muzzle) to purulent encephalitis and encephalomyelitis (our observations). Bacteria causing these lesions have been identified as *Pasteurella*, *Pseudomonas*, *Staphylococcus* [4].

Hill et al. [11] also described a disease of the gastrointestinal tract morphologically manifesting as ulcerative colitis that they called "dysentery". They connected the etiology of these lesions with *Balantidium* and *Trichomonas* found in the large intestine. However, today these protozoa are thought to be components of the intestinal contents of healthy animals [4]; therefore, the etiological role of these organisms needs to be proved (sometimes we observed *Balantidium* in the intestinal wall of naked mole rats, and this was always associated with signs of pronounced tissue autolysis, but inflammatory reaction was absent). Similar inflammatory epizootic-like lesions were also described by other authors [4, 13]. In these cases, diarrhea was observed, as well as overfilling of all parts of the intestine with gas and liquid contents, hemorrhages, and areas with mucosal ulcers (with mixed leukocytic infiltration, rare basophilic intranuclear inclusions in enterocytes, and hyperplasia of crypts), signs of intoxication, exicosis, and death of animals. However, the etiology of these lesions was explained differently than in the work by Hill et al. [11]: based on all the cytological, histological, and microbiological data (including tests on rotavirus, clostridial enterotoxin, and mycotoxin), it was hypothesized that these changes could be caused by intestinal dysbiosis, but not by a single specific causative agent [4, 13]. However, the role of an agent with unknown biological (cultural) properties cannot be excluded [4]. A high lethality (44.1%) epizooty outburst was described of a disease accompanied by diarrhea, exicosis, and intestinal hemorrhages caused by coronavirus [14]. Males and the younger animals were more sensitive to this infection than females and old animals; the inbreeding degree also decreased the resistance to the coronavirus. Hill et al. [11] mentioned a case of stomach ulcer but did not discuss its etiology. Later ulcerative lesions of the stomach were described among the other changes during dysbiosis of the gastrointestinal tract [13]. Up to now, *Helicobacter* genus bacteria affecting many laboratory rodents have not been detected in the naked mole rats [4].

It is difficult to determine the summarized incidence of spontaneous infectious lesions in deceased naked mole rats based on the literature data, because, even on excluding infections obviously associated with wounds, this incidence will vary over very broad limits: from 9.42% [13] to 64% [11].

TUMORS

The problem of tumor development in the naked mole rat is widely known and most intriguing. The initial reports published by zoologists stated that tumors were absent in 800 and even in 2000 dead bodies of the animals [2, 15]. These reports led to a steady conviction about the extraordinary resistance of the naked more rat to carcinogenesis and even to attempts to find the reason for such resistance [16, 17]. This conviction was partially confirmed by results of the first pathological study of a significant series (138 animals) of naked mole rats [13]. However, it should be noted that animals that died of natural causes were only a part of this series (45 animals), whereas 93 animals were killed by euthanasia. The authors did not ascribe to tumors two cases of proliferative lesions with atypical cells but denoted them as preneoplasias. One case presented a focal expansion of atypical cell structures in the kidney (a tubular papillary hyperplasia with atypia), and the other case presented limited alterations in the spleen characteristic for follicular lymphoma. The summarized incidence of such changes was 1.5%. However, the limitation of this work (besides the investigation was mainly of euthanized animals) is the absence of precise data on the age structure of the material studied. Since the risk of tumor development is clearly age-dependent [18], this is important for comparing with data on other animal species and on colonies of naked mole rats, as well as for answering the question about the incidence of spontaneous neoplasms in this species.

Recently, two works were published that clearly indicated the possibility of development of malignant tumors in naked mole rats and even presented an approximate idea about their incidence [15, 19]. By now, separate cases

have been described of the following neoplasms: adenocarcinoma of axillary region (mammary or salivary gland), neuroendocrine carcinoma of stomach [19], skin hemangioma, nephroblastoma (Wilms' tumor), adenocarcinoma of esophagus, hepatocellular carcinoma with lung metastases and disseminated lymphoma (lymphosarcoma) [15]. Histopathology and clinical behavior of these tumors (invasiveness, metastasizing) were similar to those of the corresponding neoplasms in the other laboratory rodents [20-23]. Unfortunately, only one work [15] reported the age characteristics of the animals studied, although very generalized (all animals were of age above one year) and the size of the sample (37 animals) was given. According to this publication, the incidence of tumor arising in naked mole rats is 8.1% (3/37).

Comparison of these data with the results of studies on tumor incidence in other animals gives the following picture. Routine comparison of naked mole rats with inbred strains (BALB/c or C57BL/6) and hybrid laboratory mice (among which tumors were found at necropsy in 50-95% of the animals that died of natural causes [24-26]) results in the conclusion about incomparably lower tumor incidence in the naked mole rats [15]. The same result is obtained if we compare the data on necropsy in naked mole rats with modern data on the risk of tumors in humans during their entire lives, which is ~40% [27]. However, it should be taken into consideration that comparison of the modern data on the incidence of clinically detected neoplasms in the human population with the results of necropsies in animals is somewhat incorrect, because in humans most tumors are revealed during their lifetimes, and many patients die without subsequent autopsy or are cured. Moreover, the latter circumstance makes possible appearance of another tumor, which significantly influences the evaluation of the total oncological risk [28, 29]. Unfortunately, modern data from autopsy are virtually absent from the literature, because patients who died from tumors are relatively seldom subjected to autopsy. Therefore, it seems reasonable to compare the incidence of neoplasms in the naked mole rat with the data obtained on wild animals and with the results of autopsy of patients obtained when there were no approaches for the efficient treatment and vital diagnosis of malignant tumors. Then the autopsy and histological examination were an obligatory procedure very similar to the algorithm used now for studies on tumor incidence in laboratory animals. According to results of such studies, the total incidence of tumor-damaged animals in the adult population of wild mice (*Mus musculus*) having lived to natural death was 9.5% [30], in the population of wild rats (*Rattus norvegicus*) it was 10% [31, 32], and in Northern mole voles (*Ellobius talpinus*) it was 9% [33]. Autopsy results of cats and dogs give similar values [32]. As to humans, autopsy results fitting the above-presented requirements give tumor incidence of 8% (Moscow, data of all autopsies made in hospitals during 1929-1932) [34], or 8-10% of the total mortality in different countries during the period from 1930 to 1960 [35]. Thus, it appears that the total incidence of tumors arising during the whole life is quite comparable (about 8-10%) in all the mentioned mammals. It is likely that in this case the situation is the same as with Guinea pig (*Cavia porcellus*), which for a long time was thought resistant to carcinogenesis [22, 31, 32], although analysis of the literature revealed the absence of valid studies favoring this viewpoint [36].

According to the literature, the comparable incidence of tumors in naked mole rats and in mice does not mean that the naked mole rat has no relative resistance to carcinogenesis. However, this means that its resistance is manifested by the longer latent period of tumor appearance or by the prolonged life period free of tumors that is indirectly confirmed by the different lifespans of these animals. A comparative study on this problem can be performed only in models of tumors induced by chemical or physical factors, which has not yet been done on the naked mole rat. Meanwhile, it is *a priori* unlikely to expect that the antitumor resistance of cells and tissues of the naked mole rat will be higher than such resistance of human cells and tissues, since the human lifespan (and hence the duration of the tumor-free life period) is more than twofold longer and the body weight and total cellularity (stochastically determining the risk of the mutant clone appearance [37, 38]) are three orders higher than that of the naked mole rat.

Attempts to experimentally induce tumors in naked mole rat are extremely important. Unfortunately, the results published by now were obtained in very strange and unusual models, whereas classical methods of inducing tumors by chemical carcinogens or by ionizing radiation have not been reproduced on naked mole rats. Nevertheless, in some works the results obtained in such ersatz-models are taken as reliable data. This may be exemplified by a publication [16] where data are discussed of a work [39] about the tumorigenic potential of induced pluripotent stem cells of the naked mole rat and mechanisms of their resistance to tumorigenesis. However, in the original work [39], the authors studied the ability of the naked mole rat's stem cells transplanted to nude mice to form teratomas. Having in mind that teratomas are benign lesions with a very specific position in oncology [35, 40], it is obvious that these results have only an indirect connection with studies on carcinogenesis in the naked mole rat. Another work declared as being the first study on the resistance of the naked mole rat's cells to experimental carcinogenesis [41] really contained only data that the naked mole rat's fibroblasts transfected with three genes – virus SV40 TAg antigen, oncogene Ras, and the gene of one of hTERT telomerase subunits – could grow after subcutaneous transplantation into immunodeficient mice. The key event needed by the naked mole rat's cells to acquire this ability was the transfection with the telom-

erase catalytic subunit gene that was not necessary for the cells of rats and mice. From the viewpoint of experimental oncology, this work is only a variant of the experiments by Seluanov et al. [42] on induction of the naked mole rat's immortalized cells, different only by the cultivation of these cells in immunodeficient mice instead of nutrient medium. The need to introduce the gene of the human catalytic telomerase into the naked mole rat's cells seems paradoxic, because in both mice and naked mole rats (as discriminated from humans) this enzyme retains high activity in somatic cells [37, 38]. In general, we think that none these works allow us even to speak about attempts of experimental reproduction in naked mole rats of real malignant tumors as has been for long the routine practice for many other laboratory rodents [32].

Even in the absence of reliable data on spontaneous neoplasms and of attempts to reproduce real experimental malignant tumors, many investigations have been done, and some hypotheses have been proposed about possible mechanisms of the naked mole rat's resistance to carcinogenesis. These works were summarized recently in a review [16]. It should be noted that any specific feature found in the naked mole rat in comparison with mouse, if it could have any (even a hypothetical) relation to tumorigenesis, was automatically ascribed to mechanisms responsible for this animal's resistance to tumor growth. Such mechanisms are suspected to exist in genome features, level of general metabolism, redox and protein homeostasis, cell resistance to stress, telomerase activity, and early contact inhibition. It is necessary to note that data about the unusual expression of contact inhibition [42] and the role in it of high molecular weight hyaluronan [43] seem doubtful and in any case not universal. Such mechanism is unreal for so frequent tumors of rodents as lymphomas and leukemias, because their cells, unlike fibroblasts and epitheliocytes, can proliferate in the suspension state, and in this case contact inhibition cannot act as a regulatory mechanism preventing carcinogenesis.

OTHER NONINFECTIOUS DISEASES

The list of nontumorous lesions in the naked mole rats is rather large. According to the work of Delaney et al. [13], in the naked mole rats studied (61 male, 77 females; 45 deceased spontaneously, 93 euthanized) the following lesions were found: renal tubular calcinosis (80% in males, 84% in females), wounds inflicted on animals by each other (56% in males, 70% in females), wounds inflicted upon moving animals (10% in males, 5% in females), CPN (57% in males, 49% in females), liver hemosiderosis (59% in males, 69% in females), megalocytosis of hepatocytes (20% in males, 34% in females), extramedullary hemopoiesis in the spleen (39% in males, 43% in females), hyperplasia of the testicular interstitial cells (31% in males), calcification of the skin (18% in males and 4% in females), adrenal cortical hyperplasia (16% in males, 25% in females), generalized calcification (23% in females, 8% in males), myocardial megalocytosis (8% in males, 14% in females), pulmonary edema (15% in males, 10% in females), myocarditis (5% in males, 10% in females), myocardial fibrosis (0% in males, 8% in females), generalized lipofuscinosis (8% in males, 4% in females), dystrophic changes in intervertebral disks (5% in males, 1% in females), pancreatic fibrosis (5% in males, 1% in females), arteriosclerosis (2% in males, 3% in females), and atypical hyperplasia of the thymus and lympholysis (0% in males, 1% in females).

Virtually all the above-listed pathological changes were described earlier in other laboratory animals and, being different in the incidence, they are similar in macro- and microscopic morphology [20-23, 44]. The only exception was calcinosis cutis caused in naked mole rats by vitamin D excess and leading to formation of very large tumor-like deposits of calcium salts [13].

The most frequent type of histological changes in naked mole rats is calcium phosphate deposits in renal tubules of animals of both sexes. Similar deposits with the same high frequency are found in intact rat Wistar females of different age, but not in the males [20]. The development of these changes in the naked mole rats is thought to be contributed to by both metastatic (i.e., associated with decrease in calcium level in blood and urine) and dystrophic mechanisms (i.e., caused by biochemical changes in areas of massive death of cells) [13].

In the second place, there are various wounds and their complications. This is difficult to compare with other animals because, although traumas are significant mortality causes in laboratory rodents, such animals are usually rejected and are not considered in the summarized statistics of pathologic alterations and the corresponding data are not published. The complications caused by these traumas, such as ulcerative dermatitis, are usually described in other rubrics. Severity of the traumas in naked mole rats varies very strongly – from almost invisible scratches on the skin to giant subcutaneous hematomas and fractures of bone structures of the chest.

Special attention is given to chronic progressive nephropathy (CPN), the frequency of which is higher than in the other laboratory animals [20-23]. This pathology with still enigmatic origin [45] is considered in a separate study [46]. In this work, the morphology is described in detail and the incidence of individual CPN manifestations (different variants of lesions of glomeruli, interstitium, and tubular component of kidneys) is characterized. However, the authors also ascribed to these manifestations kidney infarction and post-infarction changes that are not usual components of CPN in laboratory rodents [20-23, 45]. It is interesting that in that work no cases were described of amyloidosis or nonamyloid glomerulopathy (although changes similar to membra-

nous glomerulonephritis were observed and described also as CPN manifestations), which are not rare in laboratory mice [21-23]. The primary role of the tubulo-interstitial component in the development of CPN in naked mole rats occurred to be much more pronounced than in rats and even in mice [46]. This can be significant because the primary role of the tubulo-interstitial component is a necessary condition for realizing the scenario of the clonal–mutational pathogenesis of this disease [45]. It is also interesting that in the naked mole rat there are foci of pronounced renal hemopoiesis described earlier in an ecologically similar species, the Northern mole vole [33]. It is also worth attention that in some of the naked mole rats there were kidneys with the classic picture of terminal renal disease [46] usually leading to death [35, 40].

Hepatic hemosiderosis, or more precisely even hemochromatosis (because many deposits of iron-containing pigment are found in the hepatocytes and not only in the Kupffer cells) occurs frequently in the naked mole rat, but not in the other laboratory rodents. The hemosiderin deposits in the naked mole rat most frequently are detected in the periportal zones and are associated with megalocytosis of the hepatocytes [13]. The cause of the disease must be elucidated, and this requires complex studies of the iron metabolism, of the system of protein iron carriers, and of the activity of erythrocyte destruction and utilization (hemolysis). As to megalocytosis, it is supposed to arise, in particular, because of the entrance into the naked mole rat's organism of xenobiotics with the plant food [13].

Diffuse hyperplasia of testicular interstitial cells (Leydig cells) with atrophy of the spermatogenic epithelium occurs in naked mole rats with extremely high frequency and causes sterility of the males [13]. It is thought to be associated with the low blood levels of gonadotropins and testosterone and decreased reproductive activity [47].

Myocardial fibrosis, productive myocarditis, and megalocytosis of cardiomyocytes together are fully corresponding to the histological picture of a disease known as spontaneous cardiomyopathy [20-23]. The frequency of these lesions in naked mole rats is the same as in laboratory mice [48]. The cause of development of this disease is not established [23], but its incidence decreases on application of mitochondria-targeted antioxidants [48]. This is associated with a little diastolic dysfunction arising with age in females but not in males [49]. In some animals, pulmonary edema is observed (which is often associated with pulmonary congestion), but it is not a self-inflicted disease but a complication of traumas, severe pathologies of the heart and kidneys, or a manifestation of agony at euthanasia [13, 35, 40]. It is important to note that the naked mole rat lung morphology (neotenic) is not characteristic for rodents, and the large respiratory pathways sometimes induced an erroneous diagnosis of bronchiectasis [13].

Cortical hyperplasia of adrenals in the naked mole rat has a typical morphology and can be focal or diffuse. The focal hyperplasia is an age-dependent pathology, whereas the diffuse hyperplasia can be associated with both age-related changes and stress [13]. Both variants of this hyperplasia are observed in the naked mole rat.

Other alterations described in the naked mole rat can be considered minor and therefore do not require special commentaries, which can be found in guidebooks on pathology of laboratory animals [20-23]. We have also observed two leukemia-like cases with the peripheral blood of the animals characterized by the presence of many immature myeloid elements, including blasts, but without leukemic infiltrates in organs (unpublished data). We ascribed these observations to leukemoid reactions like those that were earlier described in the Northern mole vole [33]. Hill et al. [11] mentioned "avitaminosis" and other lesions of the tail skin caused by placing the animals into quite dry sand. It is more likely that these lesions are similar to lesions arising in laboratory mice maintained under conditions of insufficient humidity (tail dry gangrene, *ringtail*) [22] and which have been described in the naked mole rat by other authors [4]. Hill et al. [11] also presented two cases of death, one of which they thought to be caused by cardiac arrest caused by the expanded stomach, and the other to be caused by "renal–cardiac failure" (with subcutaneous edemas and ascites) because of the "acute nephritis". The absence of histological data and the insufficient documentation of the investigation results of the deceased animals prevents us from determining the correctness of these diagnoses.

Experimental reproduction in the naked mole rat of diseases not belonging to infections or tumors are virtually absent. We can mention only works that revealed the unusual resistance of these animals to hypoxia [50] and the resistance of their neurons to the toxic action of beta-amyloid related with development of Alzheimer's disease [51].

AGE-DEPENDENT PATHOLOGICAL CHANGES

Although the naked mole rat is an animal with unusually long for rodents lifespan, even the first professionally executed pathological studies revealed in it diseases and tissue alterations characteristic for senescent short-living rodents, including lipofuscinosis, sarcopenia, cortical hyperplasia of adrenals, megalocytosis of cardiomyocytes and hepatocytes, dystrophic changes of intervertebral disks, heart changes of age-related type, and also renal changes represented by CPN [3, 13, 46]. It is interesting to note that, as differentiated from short-living mice and rats, in the naked mole rat thymus there are true Hassall's bodies (resembling such bodies in humans), whereas the spleen of animals at the age of several years has signs specific for stress-induced or the age-related

atrophy (our observation). Age-related changes also include preneoplasias and true neoplasms, which are inevitably present in the naked mole rat [13, 15, 19]. The common age-related pathology and the unusual for rodents long lifespan do not contradict each other, but such animals cannot be considered ageless (in any case, if we understand aging as stepwise accumulation of changes in tissues and associated decrease in physiological functions). Nevertheless, to elucidate the cause of such anomalous lifespan remains a very real problem. Thus, the question comes to the fore of spontaneous diseases limiting the lifespan, or otherwise, about causes of the natural mortality of the naked mole rat.

MORTALITY CAUSES

The causes of mortality of naked mole rats is the first question that the scientific community expects to be answered by pathologists. However, unfortunately, the approach adopted in pathology of laboratory animals can answer this question only in probabilistic form. This problem has already been posed in a work [52] and then discussed in a series of publications [53-55], which allows us to not present it in this article. Note only that difficulties of studying the causes of death of laboratory animals are amplified if the individual maintenance and monitoring of physiological and biochemical parameters of animals are impossible, as in the case of naked mole rat colonies [46].

Unfortunately, it must be said that up to now there are no works with correct data on causes of the naked mole rats' natural mortality. In a work by Delaney et al. [13], only about one third of the animals died of natural causes, and these data are combined with data obtained on euthanized animals. The conclusion of the authors of this work that the euthanasia was the most frequent cause of the death of the traumatized animals cannot be adopted as a sufficient answer to the general question about the mortality causes of naked mole rats. However, based on the available data, let us try to outline the range of diseases and pathological conditions that can significantly contribute to the natural mortality of these animals.

There is no doubt that fatal injuries of animals caused by each other must be mentioned as first. Such injuries directly cause the death of at least half of all naked mole rats (our own observations). Some other animals die as a result of fatal purulent and septic complications, but its incidence cannot be determined based available data.

The second place is for that of CPN-type renal damage, which occur in more than half of the animals. Although the incidence of such damage in naked mole rats is known, it remains unclear how often this disease leads to death, because it is impossible to perform regularly individual analyses of blood and urine of the animals in the colony [46]. Terminal renal disease is the CPN stage that, in the absence of other pronounced lesions, can be established as the cause of death, but it was recorded only in 9.4% of the animals investigated in the work of Delaney et al. [46]. However, this investigation was conducted on the same animals as described earlier in the work [13]; therefore, the presented value characterizes the totality of spontaneously deceased and euthanized animals, and the deceased animals represent only one third of the total material. Consequently, this work does not allow us to conclude about the contribution of kidney lesions to the total spontaneous mortality of naked mole rats.

Just the same notes can be referred to such comparatively frequent pathologies of naked mole rats as hepatic hemosiderosis and those damages of the myocardium that can be combined as cardiomyopathies. In the last case, the role of this disease as the cause of death can be established not only by regular monitoring of clinical and biochemical parameters, but also by investigation of the functional state of the animals' hearts.

The real role of tumors as a mortality cause of the naked mole rats needs to be elucidated; however, as judged by the available data, their contribution cannot be more than 10% of the general mortality of the animals. Data concerning infections are rather contradictory. It seems that under laboratory conditions, excluding the cases of epizootics and complications of traumas, infections also can cause the death of no more than 10% of the animals. First, this refers to a strange form of the gastrointestinal tract infectious damage whose etiology is thought to be associated with dysbiosis.

Such states as dermal or generalized calcinosis, dystrophic changes in intervertebral disks (if they lead to neurological damages), and possibly generalized lipofuscinosis can have minor significance as causes of death of individual animals of the total population. Based on general pathology concepts [35, 40], other damages described in the naked mole rats cannot themselves cause the death of the animals.

Thus, although the available data allow us to outline the spectrum and even rank the significance of possible mortality causes of naked mole rats, the contribution of different causes to the general mortality of these animals cannot be accurately determined until a sufficient number (some hundreds) of spontaneously deceased animals have been studied. For such studies a rather complex algorithm should be developed and used for individual clinical, physiological, and biochemical monitoring of their health state [52].

As one can see from the data presented here, the naked mole rat suffers from many diseases described earlier in laboratory rodents, and overall the spectrum of its diseases, despite some peculiarities, does not seem abnormal on the background of the interspecies differences of the other rodents [22]. For the naked mole rat, high fre-

quencies of injuries caused by the animals to each other, CPN, liver hemosiderosis, calcinosis cutis, and diffuse interstitial hyperplasia of the testicle are relatively specific [13]. The presence of age-dependent pathological changes of tissues and organs, including malignant tumors, can be considered firmly established. However, the number of animals studied, especially of those who died from natural causes, is still insufficient. Expansion of pathological studies, especially the search for spontaneous tumors with careful characteristics of the material studied, is a very urgent task, the solution of which will allow us to establish the true frequency of malignant tumors in this species.

Another important task is experimental reproduction on the naked mole rats of pathological processes and general pathological reactions, because such data are very scarce. This especially refers to induction of tumor growth with chemical carcinogens or by ionizing radiation, without which it is impossible to study the features and mechanisms of carcinogenesis and antitumor resistance. However, we think that one should not have great expectations on discovery of new approaches for the prevention and treatment of human tumors, because human cells and tissues are probably more resistant to carcinogenesis than the cells and tissues of the naked mole rat. The real state of the question about the possible mechanisms of the naked mole rat resistance to carcinogenesis appears very vague. A great variety of hypotheses and the absence of precise data about the contribution to this resistance of each of the mechanisms under discussion do not allow us to adopt the viewpoint [16] that this resistance is provided by the whole complex of the known factors. In general, the study on the antitumor resistance mechanism before obtaining reliable data on the spontaneous and experimental carcinogenesis (tumor frequencies, their spectrum, latent period, etc.) does not seem to us the right approach.

The assumption that the naked mole rat, like humans, is an example of neoteny and that the seemingly abnormal lifespan of this animal is connected just with it [5-8], in general does not contradict the available data on the age-related pathology of this rodent: there is no reason to think that neoteny completely excludes the development of age-related changes. Thus, various spontaneous malignant tumors have been described in animals with classical neoteny – axolotls [31, 56-58] that, as mentioned above, are considered a typical manifestation of age-related pathology [18]. Another thing is that now it is unknown how exactly neoteny can influence the spectrum and development of spontaneous and experimental pathological processes, and here the naked mole rat, like the axolotl, can prove itself as a remarkable model object. It is quite possible that during aging neoteny can prevent only the "fast" component of phenoptosis and only modify the "slow" component [59] – at least this conclusion does not contradict the data discussed in this report. Perhaps in the case of neoteny, when the phenoptosis program is canceled or its execution is strongly modified and slowed, aging occurs mainly by accumulation of errors.

Finally, it is extremely urgent to develop an algorithm for a complex individual clinical, biochemical, and physiological study and its application for monitoring the health status of a sufficient laboratory population of naked mole rats with the aim to accurately determine the mortality causes of these animals.

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