Size Limits of Very Small Microorganisms

Proceedings of a Workshop

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Summarized by Kenneth Nealson, Panel Moderator

Goals of the Session

Panel 2 focused in general discussions on the issue of whether any given kind of environment appeared to favor very small microbes. Experts with experience in a wide variety of intracellular and extracellular niches, including host .cells (Van Etten and Kajander), aquatic environments (Button and DeLong), hydrothermal environments (Stetter and Adams), and soils and sediments (Staley) presented their views (Table 1). Insofar as it was possible, the discussion was focused on questions relating to the size ranges of organisms found in each environment, and the question of whether some properties of the environment (nutritional, physical, or chemical) might lead to the favoring of very small, nanometer-sized cells. In essence, this discussion sought to use the natural experiences of field and laboratory microbiologists to reach consensus on questions such as the following:

1. What are the smallest sizes of viable organisms actually seen in the environment?
2. What are the environmental issues that impose or relieve restrictions on cell size?
3. What strategies are used to attain and maintain small size in nature?

Organisms Encountered in Natural Environments

What are the smallest viable organisms actually encountered in the various environments? In pursuit of the answer to this question, the speakers focused on their environments of interest (see Table 1) and the sizes of organisms encountered there. Included were organisms such as obligate parasites and symbionts, as well as free-living organisms, both rapidly growing and in various types of resting stages. For the sake of completeness, mitochondria and chloroplasts were included, although no presentations were specifically made in these areas. The size ranges shown in Table 2 represent the consensus values reached in the presentations and in ensuing discussions by the assembled group. In many cases it was hard to reach consensus on firm estimates for the smallest organisms or organelles encountered, and the reader is referred to specific arguments in the individual papers. For example, there was considerable debate with regard to the nanobacteria, as summarized by Dr. Kajander. While such nanobacteria have been reported to be smaller than 100 nm in diameter, Dr. Kajander was of the opinion that the only organisms for which growth could be established with certainty were those of 100-nm diameter or larger. This represents an area of considerable importance in terms of being able to search for and recognize very small organisms (e.g./Are there organismal fragments that appear to have similar morphologies, but are not actually viable, growing entities?).

Table 1 Organisms, Environments, and Presenters -

Organism	Environment	Speaker
Viruses	Animal or plant cells	Van Etten
Nanobacteria	Animal serum	Kajander
Attached bacteria	Soils, sediments, rocks	Staley
Hyperthermophiles	Hot springs and vents	Stetter
Hyperthermophiles	Hot springs and vents	Adams
Aquatic bacteria	Lakes and oceans	Button; DeLong

Table 2 Size Ranges of Organisms or Organelles, and Niches Where They Are Found

Organism	Diameter Range (nm)	Life Style
Virus	30 to 200	Host-dependent
Nanobacteria	100 to 200	Host-dependent
Marine bacteria	100 and larger	Free-living
Attached forms	100 and larger	Free-living
Hyperthermophiles	200 and larger	Free-living
Mitochondria	200 and larger	Host-dependent
Chloroplasts	200 and larger	Host-dependent

A point of interest with regard to this area is that virtually all of the microbiologists present had encountered structures resembling cells in the size range of 100 to 200 nm, but whether or not these could be demonstrated to be viable or cultivable microbes had usually not been established. The timewom method of filtration through a 200-nm (0.2 micrometer) pore-size filter was still very dependable in terms of delineating cultivable bacteria.

Environmental Parameters and Size

What are the environmental issues that may impose or relieve restrictions on the smallest sizes that can be achieved by organisms? In pursuit of this question, the speakers considered a variety of different environmental factors that might lead to organisms adopting a smaller size. These included:

1. Nutrient-rich environments, which allow evolution to small cells with less biosynthetic capacity, such as obligate parasites or symbionts;
2. Nutrient-poor environments, which lead to adaptation of small, starved cells;
3. High or low temperature; and
4. Attachment to surfaces.

Of the issues discussed, that of nutrient availability was repeatedly noted as one of potential importance. Two major issues were emphasized: (1) the effect of nutrient limitation and starvation, which leads to adaptation of normally large cells to resting stages that are considerably smaller; and (2) the effect of nutrient richness, which leads to evolution of cells that are host dependent, and often considerably smaller.

In nutrient-poor environments, organisms were deemed to be small in the starved state, although the lower size limit of this starvation state appears to be on the order of 200 nm. The mechanisms for achieving such small size (or for returning to a state of larger, rapidly growing cells) are not well understood. However, such organisms are not regarded as true nanobacteria, because under nominal growth conditions, they are considerably larger than the diminutive forms discussed here. These larger forms are thought to represent a true evolutionary lower size limit for DNA-based life.

In the case of intracellular symbiosis or parasitism in nutrient-rich environments, considerable discussion occurred as to whether or not such organisms could eliminate enough functions to evolve to a very small size. Dr. Adams presented a general discussion of the theoretical limits of life, based on organisms with the same basic biochemistry as those we are familiar with. At the theoretical extreme are the viruses, which are obligate intracellular parasites and which have no need for their own transport systems, translation machinery, or transcription apparatus. These organisms can be quite small, as they consist of a protein coat surrounding the genetic material. The lower size limits are seen in some RNA viruses like the Qp virus (which contains only three genes), and in certain animal viruses (e.g., poliovirus) that are in the range of 25 to 50 nm in diameter, while most others are in the range of 100 to 200 nm or even larger. Symbiotic organelles or bacteria are also commonly found in the 200-nm range and are sometimes smaller. These include non-cultivable bacteria from a wide variety

of organisms, intracellular organelles (e.g., mitochondria or chloroplasts), and the enigmatic nanobacteria discussed by Dr. Kajander.

It should be clear, however, that the strategies used for attaining and maintaining small size will be very different for the oligotrophic organisms, which become small as a matter of optimizing their surface-to-volume ratio under diffusion-limited growth conditions, and the eutrophic organisms, which are allowed to become small because of the richness of their environment. In the latter case, these organisms are not faced with the maintenance of the genetic or physiological capacity for either extensive biosynthesis or diverse catabolism. While it is often possible to maintain such "obligate" symbionts or parasites in a host-free growth phase using a very rich medium, discussion of their role(s) as very small bacteria may be relevant only in the context of their existence as parasites or symbionts.

Perhaps the liveliest discussion in Panel 2 centered on the specification of the smallest sizes actually seen in the environment and the criteria that one accepts for a living cell. To this end. Dr. Kajander proposed that nanobacteria may fragment into non-growing entities that appear considerably smaller than the true, viable organisms, and that these fragments may come together at a later time to form a viable organism. In terms of this possibility. Dr. Van Etten pointed out that some plant viruses exhibit just such a pattern. Each particle packages separate RNA, and sometimes three separate particles are needed to establish an infection. It was also noted that many estimates of the smallest sizes for viable organisms come from filtration studies, and that bacteria with non-rigid cell walls may pass through filters of pore size smaller than their actual diameter.

As a final point, one would like to have an indication of the minimum cell volume needed to sustain life. Dr. de Duve emphasized that diameter alone is not a sufficient parameter, pointing out the practical difficulty of estimating true diameter from random thin sections To this end, the discussion by Dr. Adams focused almost entirely on the intracellular volumes of variously sized and shaped organisms, and the possibility that such volumes could accommodate the machinery of life.

Strategies for Attaining and Maintaining Small Cell Size

Are there strategies that can allow the minimum size of an organism to be smaller than might be anticipated through studies of extant organisms? With regard to this question, several strategies were considered by Panel 2 speakers. The first, discussed briefly above, was that of Kajander and Van Etten, in which organisms actually fragment so that each very small organism is incapable of growth, but the population is capable of achieving success. While this strategy is known for some RNA viruses, there are as yet no examples among the prokaryotes.

A second strategy considered was that employed by parasites and symbionts, which simply discard a sizable fraction of their genetic information and adopt a host-dependent life style. Such organisms, while achieving a very small size, sacrifice the freedom of being host-free.

Other approaches that might allow attainment and maintenance of a smaller cell size are (1) reduction of the average size of proteins; (2) an RNA-world approach in which a single type of molecule accomplishes both catalytic and genetic functions; and (3) the use of overlapping genes and genes on complementary strands. In no case has a systematic analysis of any of these approaches been done.

Consensus?

In terms of reaching a consensus, Panel 2 members, with the exception of Dr. Kajander, who described nanobacteria in the size range of 100 nm, considered that the lower size limit of bacteria-like particles believed to be cultivable corresponded to spherical'organisms with a diameter in the size range of 200 to 250 nm. The nanobacteria of Kajander are "obligate" parasites (e.g., they require very rich media to achieve host-free growth) and so may fall into the category of organisms adopting a host-dependent life style. Thus, despite a very large amount of discussion, a general consensus was reached that was in agreement with the theoretical arguments put forward during the workshop, that the lower limit of size for a free-living, DNA-based organism corresponds to a spherical organism with a diameter in the size range of 200 to 250 nm. For host-dependent organisms the size may be smaller, and the extent of the smallness will certainly depend on the extent to which genetic and physiological functions have been discarded.

For an organism that used one type of molecule for both catalysis and replication, the size could be considerably smaller, as discussed by Dr. Benner and others.

SUGGESTIONS FROM OBSERVATIONS ON NANOBACTERIA ISOLATED FROM BLOOD

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ABSTRACT

Nanobacteria are the smallest cell-walled bacteria, only recently discovered in human and cow blood and in commercial cell culture serum. The environment causes drastic changes in their unit size: under unfavorable conditions they form very large multi-cellular units. Yet, they can release elementary particles, some of which are only 50 nm in size, smaller than many viruses. Although metabolic rates of nanobacteria are very slow, they can produce carbonate apatite on their cell envelope mineralizing rapidly most of the available Calcium and phosphate. Nanobacteria belong to, or may be ancestors of, the alpha-2 subgroup of Proteobacteria. They may still partially rely on primordial life-strategies, in which minerals and metal atoms associated with membranes played catalytic and structural roles reducing the number of enzymes and structural proteins needed for life. Simple metabolic pathways and lack of energy-consuming pumps, apparently only compatible with life in very small cells, may support the 10,000-fold slower growth rate (absolute rate of mass gain) of nanobacteria, as compared to the usual bacteria. Simplistic life strategy may also explain the endurability of this life-form in extreme environmental conditions. Nanobacteria may have evolved in environmental sources, e.g., in primordial soups or later as scavengers in hot springs, to take advantage of the steady-state calcium-phosphate and nutrient supply of the mammalian blood. Their elementary particles or units do appear and may function much like viruses, but can support autonomous replication under suitable conditions, e.g., after union of several units, thus opening a new survival strategy for smallest life-forms.

Is There a Relationship Between Minimum* Size and Environment?

Nanobacteria and Minimum Size of a Living Cell

Nanobacteria grow under mammalian cell culture conditions. They pass through sterile filters and endure g-irradiation like a virus (1 megarad not effective). Their size is between that of a virus and cell-walled bacteria. They are stained with DNA fluorochromes such as mitochondria. Nanobacteria produce a slimy biomatrix that forms carbonate apatite mineral around them in culture (Kajander et al., 1997; Cift9ioglu et al., 1997, 1998). This bizarre new form of life seems to have adapted to living inside the mammalian body, an ecologically free but hostile niche. The suggested name Nanobacterium sanguineum refers to their small size and their habitat, which is blood. Nanobacteria are one of the most distinct organisms ever found in humans. Their poor culturability and long doubling time, and cyto-toxicity (Cift9ioglu and Kajander, 1998), can be compared only to some Mycobacteria, such as M. leprae. The average diameter of nanobacteria measured with electron microscopic techniques, about 0.2 jjm, is smaller than that of large viruses. The smallest units of nanobacteria capable for starting replication in culture, possibly as aggregates of several, have sizes approaching 0.05 i-un, based upon filtration and electron microscopic results (Kajander et al., 1997; Ciftcioglu et al., 1997). The theoretical. minimum diameter of a cell, based on the size of those macromolecules now considered to be necessary for a living cell, has been calculated to be about 0.14 pm (Himmelreich et al., 1996; Mushegian and Koonin, 1996). Some nanobacterial cells appear smaller than that. Do nanobacteria really exist?

Nanobacteria Do Exist

1. Nanobacteria can be cultured, have a doubling time of about 3 days, and can be passaged apparently forever. Now they have been passaged for over 6 years monthly.
2. They produce biomass at a rate of about 0.0001 times that of £'. coli.
3. Their biomass contains novel proteins and "tough" polysaccharides.
4. SDS-PAGE of nanobacterial samples shows over 30 protein bands. Amino terminal sequences are available from 6 different proteins One of them is a functional porin protein (unpublished work in collaboration with Dr. James Coulton, McGill University). Porins are a hallmark for gram-negative bacteria located in their outer membrane and make trafficking through it possible for relatively small molecules. Porins seem to be located in the mineral layers in nanobacteria. Muramic acid, a major component of peptidoglycan, has also been detected. So, nanobacterial cell walls do have typical gram-negative components, although their ultrastructure is unique and varies during their growth phases.
5. Nanobacteria contain modified nucleic acids detectable specifically with stainings and spectros-copy, and their components can be detected with mass spectroscopy (Kajander et al., 1997).
6. Nanobacterial growth can be prevented with small concentrations of tetracycline antibiotics, or with high concentrations of aminoglycoside antibiotics. Both stop bacterial protein synthesis at the ribosomal level.

7. Nanobacterial growth can be prevented with small concentrations of cytosine arabinoside or fluoro-uracil, both of which are antimetabolites preventing nucleic acid synthesis in all types of cells.

8. Nanobacteria can be detected with metabolic labeling using methionine or uridine.

9. Nanobacteria have unique strategies for social behavior and for multiplication, including communities, budding, and fragmentation.

Nanobacterial Mineral Is Biogenic

All carbonate apatite in the human body is biogenic. Nanobacterial mineral formation is a specific biogenic process, for these reasons:/ .

1. Mineral grows directly on the nanobacteria, forming parts of the cell envelope. Without nanobacteria there is no mineralization in the medium. Mineral growth is dependent on a biomatrix made by the nanobacteria (Kajander and (y:ift9ioglu, 1998).

2. Mineral layer is under active remodeling of its size and shape, and it is budding.

3. No significant mineralization takes place if nanobacteria are killed with y-irradiation.

4. Mineralization is an active process that does not imply super saturation. It brings phosphate levels to zero in the culture medium (Kajander et al., 1998).

5. Mineral grows as layers in a biomatrix, comparable to that in pearls.

6. Mineral crystallization is under biocontrol with serum factors, much as bone is.

Nanobacteria Are Distinct Bacteria and Not "Contaminants" of Biological Samples

We have found nanobacteria belonging to, or being an ancestor of, a group of bacteria, the alpha-2 subgroup of Proteobacteria, that contain both environmental bacteria and bacteria inhabiting mammalian blood and tissues. The nearest relatives are Phyllobacteria found in soil and causing tropical plant diseases. These bacteria do not produce apatite and differ much from nanobacteria (Table 1).

Table 1 Nanobacteria Compared to Phyllobacteria, Their Closest Relatives in 16S rRNA Gene Comparison

Nanobacteria	Phyllobacteria
Culturable only in cell culture medium	Culturable in most bacterial media
Thermophile, gamma-irradiation resistant	Maximum growth temperature 32° C, gamma sensitive?
Present in blood, very slow grower	Present in soil and plants, fast grower
Mineralizing, ultrastructure is unique	No minerals, ultrastructure is gram negative
No polyamines, but cadaverine-like compound	Normal polyamines present
Modified nucleic acid bases present	Normal nucleic acid components
Specific protein pattern, sequences, epitopes	Specific protein pattern, sequences, epitopes
Porin protein only weakly cross-reactive	Porin protein only weakly cross-reactive
Polymerase chain reaction (PCR) needs special protocol	PCR. works with standard protocols

Nanobacteria and the Other Small Bacterial Forms

Bacteria do exist in sedimentary rocks. Much of this bacterial metabolism and function is unlike that of previously known organisms, and is related to the slow mineralization of inorganic and organic compounds available. From such biota, particles resembling our tiniest nanobacteria were discovered by Dr. Folk, who named them as "nannobacteria" (Polk, 1993). They may contribute to the formation of carbonate minerals and remain uncharacterized. Ultramicrobacteria, passing through sterile filters, have been found in soil and natural water sources. They are difficult to culture and their nature is largely unknown (Roszak and Colwell, 1987), as is their possible connection to nanobacteria. Normal bacteria may acquire a dormant state and do not even multiply on subsequent culture (Roszak and Colwell, 1987). The size of such starved cells can be only a fraction of the size obtained when multiplication is reached again. Nanobacteria are not in a dormant state.

Cell-wall-deficient bacteria, L-forms, show small and lajrge forms. Conventional culture methods do not support the growth of L-form microbes. L-forms can pass through sterile filters but can be easily lysed and their nucleic acids and proteins extracted (Darwish et al., 1987). Mycoplasma, Chlamydia, and Rickettsia are the smallest "classically known" bacteria, and they can be cultured in cell culture conditions with mammalian cells. Only mycoplasma can grow autonomously. All can pass through sterile filters: filtering through 0.2 um pore-size results in over 100-fold reduction in their numbers, whereas with nanobacteria the reduction is typically less than 10-fold (Kajander et al., 1997), and bacterial L-forms are reduced by lO^fold (Darwish et al., 1987).

"Pseudoorganisms" forming "pseudocolonies" have been detected in mycoplasma culture media. These were regarded as non-living artifacts, e.g., calcified fatty acids, owing to resistance to disinfectants and unsuccessful attempts at

DNA detection (Hijmans et al., 1969). Some of their properties were similar to those of nanobacteria: presence in serum, difficulties in fixation or in disruption, inability to stain with common dyes, resistance to antibiotics and disinfectants, and high calcium-phosphate content. Buchanan (1982) found similar "pseudocolonies" in several horse sera but considered them as atypical bacterial L-forms.

Size is considered to be typical for a certain bacterial species. The alternative is that size, shape, and morphology change according to the environmental and social status of the organism. Examples of such organisms are known. Myxococcus xanthus has a life cycle, carefully controlled by cell density and nutrient levels, and consisting of tiny forms, actively moving large forms, and huge social formations producing mushroom-like fruiting bodies. Nanobacteria do show several growth forms, sizes, and social formations depending on culture conditions. Fastly growing mycoplasma "forget" cell division, forming very long multicellular forms. Thus, bacterial size is dependent on growth phase. Small size is not directly linked to the genomic size: Myxococcus xanthus genome size 9.4 Mb (Chen et al., 1990) is among the largest, whereas mycoplasmas have the smallest genome sizes, 0.58-1.6 Mb (Barlev and Borchsenius, 1991). Chlamydia and Rickettsia have genomes of 1 Mb. Nanobacterial genome size is unknown, but quantitative Hoechst staining suggests it may be smaller than that of mycoplasmas.

Is There a Continuum of Size and Complexity That Links Conventional Bacteria to Viruses?

Nanobacteria, Mycoplasma, Chlamydia, and *Rickettsia* are structurally only a little more complex than large viruses. They all use environmental supplies appropriately to minimize the need for their own synthetic pathways. Nanobacterial cultures do indicate virus-sized elementary particles and'large nanobacteria acting like mother cells in a life cycle involving nonreplicative and replicative forms. This is analogous to modem gene technology: viruses, helper viruses, and competent bacteria are used to replicate new viral particles.

Simplistic Strategies by Nanobacteria

Nanobacterial function is simple: be ready for nutrients when they come, replicate; make protective mineral to "hibernate," and wait for a new cycle of nutrients. The main features are these-:

1. Nanobacteria use ready amino acids from medium/environment.
2. They use large amounts of Gin, Asn, and Arg from medium for structural components, or energy production or mineralization process (amino groups could bind phosphate).
3. They use ready fatty acids from their medium. When fatty acids are scarce, they are "saved" by replacing membrane lipids partly with apatite.
4. They react to stress by becoming social and forming communities. Communities may help to overcome mutations, etc. They can "hibernate" for extensive periods waiting for suitable conditions permitting growth.
5. Because of their small size, nutrients can be obtained by diffusion and brownian movements.
6. Nanobacteria may have low internal pressure. Normal bacteria concentrate metabolites inside them so that their internal pressures can be 3-5 bars. Such a system provides fast metabolism, but consumes energy and requires complex pumps and their controls. In unfavorable conditions cell death can result from inability to keep up the ion gradients. Nanobacteria may lack these systems; That might explain partially their high resistance to near-boiling temperatures (Bjorklund et al., 1998) known to explode bacteria mainly owing to an imbalance in intracellular ions. Their endurance is similar to that of some viruses.
7. Nanobacteria may form and shed units resembling viruses that could spread even via tiny pores or cracks, e.g., in rocks.

The survival strategy of nanobacteria indicates that small is efficient in these ways: minimize synthetic systems, energy consumption, pumps; scavenge nutrients when they are available; endure deadly attacks but eat up nutrients from dead bystanders; and have a strategy for surviving in very hostile places that kill normal bacteria (hot springs) or places providing all nutrients (primordial soup, blood).

What Is the Phylogenetic Distribution of Very Small Bacteria?

The most powerful comparison can now be based upon genomic sequences of organisms. Myco-plasmas are among the smallest bacteria, with a diameter of about 0.2-0.5 urn, and their genomic size is the smallest so far known. The M. genitalium genome is 0,58 Mb compared to 4.6 Mb for E. coli. The small genome seems to be an indicator of life strategy, the parasitic life style. Such organisms do not need to manufacture all their building blocks themselves. Could this apply for environmental simplistics? What type of metabolic simplifications could be possible?

Polyamines and Life Strategy

Polyamines are now considered essential for cell proliferation. Bacteria contain putrescine and spermidine, but may contain some 30 other di- and polyamines. Their patterns have been used as a • phylogenetic tool (Hamana and Matsuzaki, 1992). What can be learned on the enzymes ofpolyamine synthesis from the genomic sequences? Genes for enzymes producing putrescine and spermidine are absent in M. genitalium, Borrelia burgdorferi, and Treponema pallidum. Haemophilus influenzas can produce putrescine, and Helicobacter pylori, Mycobacterium tuberculosis, and E. coli can produce both putrescine and spermidine. Some Archaea, Methannococcus (M. jannaschii) and Halococcus, lack synthesis of polyamines and lack them in direct analysis (Hamana and Matsuzaki, 1992). Nanobacteria do not have putrescine or spermidine, but contain a compound having similar mobility with cadaverine in high pressure liquid chromatography. Cadaverine, a special polyamine used by several eubacteria as a covalently linked component in peptidoglycan, absence of normal eubacterial polyamines, and lack of putrescine/spennidine transporter genes make nanobacteria unique. The parasitic bacteria acquire their polyamines from their hosts, and can thus afford losing the synthetic enzymes of importance to their freely living relatives. The environment provides compensation for the loss. What is the smallest genetic size for life? Obviously it depends on the generosity of the environment and the life strategy.

Smaller Is More Practical

Organisms must have been very small in primordial soups! And slow growers. Large cells would have to have complex systems including active transporters and moving apparatus. Small cells can rely on diffusion and Brownian movements for obtaining nutrients. Very slow metabolic rates would allow for use of minimal numbers of enzymes, since many of the reactions could be uncatalyzed, or catalyzed by metals and minerals or be contributed by nonspecificity of the existing enzymes. Such a system may well do the observed 10,000-fold slower biomass production than that of common bacteria. Nanobacteria have apparently small genomes. Hoescht 33258 staining indicated that nanobacteria should have DNA amounts between that of mycoplasmas and mitochondria. Can bacteria have novel nucleic acids contributing to smallness? One potential example could be use of single stranded nucleic acid genome, maybe resembling the multi-copy single stranded DNA found in bacteria.

Further simplification would be obtained by omitting the need for a closed compartment needed to keep homeostatic conditions intracellularly. We are suggesting an elementary system of tiny units performing special tasks. Only when united and surrounded by membrane, closing the compartment, would they resemble present forms of bacteria.

Mitochondria in *Saccharomyces cerevisiae* have 35 genes, and about 290 more are in the nuclear genome (Hodges et aL, 1998). So mitochondria are operating probably with a smaller number of genes—but with a full operational capability—than any modem bacteria. Mitochondria would fall into the alpha-2 subgroup of Proteobacteria, if classified as bacteria, and thus be near-relatives of nanobacteria. They may have lost many genes in the process of domestication as a eukaryotic cell organelle. This also points out that metabolic collaboration between various bacteria, or bacteria and other organisms, can significantly reduce necessary genomic sizes. This is understood from the fact that none of the bacteria with genomic sizes 1.6 Mb or smaller can synthesize polyamines necessary for their growth. The suggested minimum number of genes, 256 genes (Mushegian and Koonin, 1996), may be still too high a number for the simplest genome for the reasons discussed above. Another conclusion is that it is possible to evolute into miniature life-forms from several bacteria groups, since the smallest organisms fall into several classes. The main factor for thriving is the environment and stability of its conditions: primordial soup may have provided nutrients for supporting organisms with many fewer genes than are necessary to survive in present-day environments. Why do we think that nanobacteria may serve as a model for primordial life? Because they may well be just that! The modern-day primordial soup is blood.

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