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On the origin of genomes and cells within inorganic compartments

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Building on the model of Russell and Hall for the emergence of life at a warm submarine hydrothermal vent, we suggest that, within a hydrothermally formed system of contiguous iron-sulfide (FeS) compartments, populations of virus-like RNA molecules, which eventually encoded one or a few proteins each, became the agents of both variation and selection. The initial darwinian selection was for molecular self-replication. Combinatorial sorting of genetic elements among compartments would have resulted in preferred proliferation and selection of increasingly complex molecular ensembles – those compartment contents that achieved replication advantages. The last universal common ancestor (LUCA) we propose was not free-living but an inorganically housed assemblage of expressed and replicable genetic elements. The evolution of the enzymatic systems for (i) DNA replication; and (ii) membrane and cell wall biosynthesis, enabled independent escape of the first archaeabacterial and eubacterial cells from their hydrothermal hatchery, within which the LUCA itself remained confined.

Introduction
Because all cells synthesize their proteins with the help of similar mechanisms on homologous ribosomes using the same genetic code, the same L-amino acids and the same D-sugars, biologists generally agree that all known life shares a common ancestor. However, the nature of that last universal common ancestor (LUCA) is a matter of conjecture and debate [1–13]. The traditional approach to inferring the nature of any common ancestor, including the LUCA, is to identify features that are shared by all of its descendants (or most of them, allowing for degenerative evolution), thereby pinning attributes to the ancestor. But that approach runs into problems with the LUCA because, beyond the code, the cores of the translation and transcription systems, and the homochirality of sugars and amino acids (i.e. the exclusive use of one stereoisomer of each, namely L-amino acids and D-sugars), few attributes are truly universal to all cells, as genome comparisons attest [14–16]. Today, all known cells, including those of highly reduced parasites, are surrounded by membranes and their genomes encode >500 proteins [12]. However, the onset of life could not have been a leap from disorganized chemical compounds to fully fledged cells. It must have been a stepwise process, albeit, perhaps, rapid in terms of geological time [17]. Along the path from inanimate chemicals to the first free-living cells (ignoring all dead-ends), molecular complexity inevitably increased, and each transitional stage must have had means of heritable variation in a setting that permittedselection [18]. Scenarios to account for these crucial early stages of the evolution life strive for an uninterrupted sequence of steps that are logically linked to one another [13].

Modern biochemistry and information processing could have hardly evolved in free solution [19]. Without pre-existing and hence necessarily abiogenic compartments to restrain the building blocks of life from free diffusion into the ocean, the monomeric constituents of biopolymers would never have reached sufficient concentrations to react with one another [17,19,20]. Today, the barriers that organisms have against diffusion to the environment are lipid bilayer membranes and cell walls. However, archaeabacteria (archaea) and eubacteria (bacteria), the two divisions of prokaryotes, have membranes consisting of unrelated lipids (isoprene ethers and fatty acid esters, respectively), and the enzymatic pathways involved in archaeabacterial and eubacterial membrane biogenesis are non-homologous [21]; the cell walls of archaeabacteria and eubacteria share even less chemical similarity [21,22].

The case for a LUCA confined within a network of inorganic compartments
Perhaps the simplest interpretation of the disparity of prokaryotic membranes is that the LUCA was not a free-living cell and did not have a biogenic membrane but, instead, arose and existed within geologically formed, inorganic, abiogenic compartments [17,19,20,23,24] that fulfilled the imperative compartmentalizing function of lipid bilayers and cell walls before the latter arose. Alternative views of the origin of cellular organization either suggest that life somehow emerged on two-dimensional surfaces and that cells bubbled off when the process had been completed [10,25] or merely postulate the transition from some form of uncontaminated prebiotic soup to cellular organization [6,26], without providing any plausible reasoning for how the complex chemistry and genetics of living systems could have arisen in free solution.
Among the plethora of ideas about the origin of life, the hypothesis that living systems arose within naturally formed three-dimensional compartments is, in our view, currently the only one that can satisfy the demands imposed by the inordinate level of complexity that a biochemical and genetic system must attain before it can approximate life as we know it. From the geochemical standpoint, it seems most plausible that these compartments consisted of iron sulfide (FeS) deposited at a warm (<90 °C) submarine hydrothermal spring [17,24]. Such naturally formed, inorganic compartments ranging in size from <1 μm to ~100 μm, have been discovered at ancient hydrothermal sites [23], and their formation has been simulated in the laboratory [20,27,28]. Moreover, intricate, small-scale networks of hydrothermally formed microcompartments (although not consisting of FeS owing to the paucity of Fe²⁺ in modern oceans) occur today at the warm (~40–90 °C) Lost City vent [29,30], which has been continuously active for >30,000 years [31]. Iron sulfide compartments at a hydrothermal vent are conceptually satisfying ‘hatcheries’ for the emergence of life because they simultaneously provide a concentrating mechanism – physical restraint from free diffusion into the ocean – for biochemical building blocks, a catalyst for a wide variety of biochemical reactions in the form of Fe-S and Fe-Ni-S centers [17,32–34] and a continuous source of chemical energy (the H₂-O₂ redox couple) that the origin of life inexorably requires [17,32] (Figure 1). In the present context, and consistent with prior formulations of hydrothermal origin of life [17,19,24], we demand only two reasonable attributes of the compartment-system: (i) porosity, enabling movement of molecules of different sizes among compartments (with example in evidence at the active Lost City vents [30]); and (ii) sustained formation of new compartments through continuous metal-sulfide precipitation at the ocean interface (with example in evidence at more ancient vents [17]) such that organic molecules could invade new territories, thereby generating discrete units on which selection could act. Discrete units are essential, because in a homogeneous system selection is unattainable, whereas in a physically differentiated system it becomes possible [18].

According to the hydrothermal origin hypothesis, the first organisms were chemolithoautotrophs whose metabolism centered around thioester formation reactions [17,19] similar to the modern acetyl-CoA (Wood-Ljungdahl) pathway [32]. These reactions would have been fuelled by the exergonic reaction between hydrothermal H₂ and marine CO₂ to produce reduced carbon compounds [32,35]. The model combines the plausibility of the FeS-based primordial biochemistry [34], in which carbonyl sulfide (COS; a catalyst of peptide bond formation [36,37]) might have played a crucial role, with a physical basis for compartmentalization rooted in geological observations [17,27]. Based on those considerations, we outline here how darwinian selection and evolution of genetic organization could have proceeded within the confines of such a warm hydrothermal vent. We stress ‘warm’ [24] (but not ‘pond’, as in Darwin’s famous passage) because hot vents like the familiar ‘black smokers’ are typically 350–400°C [38], a temperature that is much too hot for the chemistry of life, at its origins or otherwise. Our proposal also draws on competition and selection among self-replicating molecules [39–42], the retrovirus-like model of the genetic system of LUCA [43,44] and the selfish operon hypothesis [45,46].

Replication of a confined LUCA

Archaeabacteria and eubacteria sharply differ not only by virtue of their unrelated membranes and cell walls but also by the equally dramatic disparity of their DNA replication machineries [47,48]. Surprisingly, the central components of these systems (DNA polymerases, primases and replicative helicases) are either unrelated or, at least, not orthologous in archaeabacteria and eubacteria [44,49–52]. This contrasts the basic unity and conservatism among the major proteins of the translation and transcription systems [53]. Thus, LUCA is inferred to have had an advanced translation system that resembled modern ones in its principal features, but lacked a double-stranded, replicating DNA genome, possessing an RNA-based replication system instead [44,47,53].

However, several other components of the DNA replication machinery, such as the sliding clamp plus the clamp loader ATPase and the DNA ligase, as well as enzymes of DNA precursor biosynthesis – ribonucleotide reductase and thymidylate kinase – are homologous in all prokaryotes, which led to the proposal that LUCA had a retrovirus-like replication cycle [44] (Figure 1). Because RNA molecules are fragile compared with DNA, and no RNA virus with a monopartite genome >30 kb has been described [54], it has been suggested that the genome of LUCA consisted of a set of co-inherited RNA segments, each coding for one or a few proteins [44]. The retrovirus-like genetic cycle of LUCA would account for a set of multiplying, competing, functionally diversifying and recombining molecules without demanding the complexity of a fully fledged prokaryotic genome. For longer RNA molecules to unfold for replication, short-term temperature cycles (analogous to PCR reactions) would be extremely helpful in such a system. This does not require specially fluctuating environmental conditions because, in

Figure 1. A scenario of evolution from the origin of RNA molecules to the independent escape of archaeabacterial and eubacterial cells within naturally forming inorganic compartments consisting primarily of FeS at a Hadean (>3.8 Ga old) hydrothermal vent. The left hand side of the figure shows the proposed sequence of events (from the bottom to the top) described in the main text; the right portion is a highly schematic drawing illustrating increasingly complex levels of molecular organization within the compartments along the path from inorganic carbon to LUCA and from LUCA to free-living chemoaototrophic prokaryotes (modified from Ref. [24]). The enlarged compartment shows the proposed retrovirus-like genetic cycle of LUCA [44]. The synthesis of the RNA–DNA hybrid and the dsDNA is thought to have been catalysed by reverse transcriptase, with RNase H (a ubiquitous, probably, ancestral enzyme) involved in RNA strand removal during the latter step. The transcription of RNA from dsDNA would have been catalysed by DNA-dependent RNA polymerase (another universal enzyme). The parts of the replication system that are shared by archaeabacteria and eubacteria (sliding clamp, clamp loader ATPase and DNA ligase) might have been involved in the dsDNA synthesis and/or transcription steps. The figure is schematic, and not drawn to scale. The compartments could be from <1–100 μm in diameter, as in fossil [24] and modern [30] vents (see main text for details).

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the presence of a temperature gradient, as exists at vent–ocean interfaces [17,30], laminar convection within compartments under isothermic conditions produces the required melting and annealing effect, an efficient process in the laboratory known as ‘convective PCR’ [55]. The utility of convective PCR at the origin of life has been noted [55], and it offers efficient replication in chambers of 10–500 μm thickness, in line with the size of modern [30] and ancient [17,27] vent compartments (<1–100 μm), thus underpinning the hydrothermal origin model.

Constrained within a primordial network of FeS compartments, virus-like genetic elements would have been, at this stage of evolution, the agents both of natural variation (mutation and recombination) and of natural selection, initially, for self-replication only. The life histories of these elements would have involved diffusion between compartments, colonization of newly formed compartments, unavoidable RNA recombination [56] and replication in those compartments where appropriate combinations of genetic entities and monomeric precursors had accumulated. Competition for substrates available within a compartment is analogous to the classical in vitro darwinian experiments of Mills et al. [39] and Biebricher et al. [57] and would necessarily have entailed the emergence of autocatalytic, self-sustaining ensembles of molecules (Figure 1). The latest mathematical modeling results indicate that the emergence of such autocatalytic networks could be more probable than is often assumed [42,58].

Selfish cooperatives
One class of winners in the struggle for replication would consist of truly selfish elements, non-coding parasites exploiting the resources provided by other elements, as modern viroids and virusoids do [59,60]. However, ‘altruistic’ elements, such as those coding for translation system components or products promoting nucleic-acid-precursor synthesis also would be selected for the ability to enhance their own replication potential, as well as that of others, through a ‘cell-type strategy’ [61]. Additional survivors would include elements coding for a RNA replicase and/or a nucleic-acid-binding protein. These can be seen as virus-like agents that depend on other elements for everything but replication, yet might promote replication of other genetic elements unable to do so on their own. In this regard, we note that an origin of viral-like genetic systems (although not fully fledged viruses) concomitant with the origin of the first genomes is a salient feature of the present model. At the first stages of evolution of replicating molecule ensembles, the viral-like and would-be prokaryotic genomes are indistinguishable in as much as selection operates solely at the level of self-replication. However, the formation of selfish cooperatives would mark the emergence of larger ‘protogenomic’ ensembles from viral-sized genetic systems and birth of viruses as genetic elements employing parasitic strategies; these elements could have had various replication cycles, some of which conceivably have persisted into the modern viral world, including RNA viruses, retrovirus and, later, DNA viruses.

The sorting of individual genetic elements between compartments would result in new combinations leading to preferred proliferation of the genetic compartment contents that attained effective replication – selfish cooperatives. With increasing probability, the most successful compartments would infect their neighbors via diffusion of rapidly replicating combinations of genetic elements. Propagation of such ensembles would also involve molecular seeding of newly formed compartments at the continuously growing (enlarging through continuous FeS precipitation) surface of the vent. Replicative success would correspond to fitness in the classical sense, by virtue of seeding ability. Thus, the genetic complements of successful compartments would be the fittest, spreading such that these gene ensembles (fragmented ‘genomes’ of the compartments) would proliferate effectively, but with a much lower fidelity than modern genetic systems. Importantly, the genetic contents of the compartments would emerge as discrete agents of selection within a continuously expanding system of inorganically formed territories. Under this model, the geological formation of new compartments can be viewed as the abiogenic predecessor of cell division, whereas diffusion of coding molecules between compartments would be analogous to horizontal gene transfer (HGT) before the origin of free-living cells, as others have suggested previously, albeit in a context lacking physicochemical mechanisms to demark recipients from donors [6,62]. In contrast to earlier views, the present model operates via selection acting on discrete individual units (compartment contents) as is required for darwinian lineage differentiation [18] rather than via (essentially, unattainable) selection in a freely mixing gene pool.

In this scenario, there will be genetic parasites that avidly compete for resources. But just as today, parasites that eradiate their host eradicate themselves. Hence our selfish cooperators, although unable to outcompete their most aggressive parasites, could also potentially benefit from assimilating some of the greedy properties of the more attenuated parasites (e.g. high-fidelity replicases). Persistence of ensembles of selfish cooperators, particularly those with a weak autocatalytic feedback into resource synthesis [42,58], would be favored for long-term survival, albeit facing the constant threat of takeover by parasites. This aspect of the present model is similar to the switch from individual to group selection (selection for proto-cell gene packages) in the stochastic corrector model described by Szathmary [63–65].

Selfish superoperons
At this point, all routes to further complexity and sustenance of novelty would require co-distribution of a growing ensemble of genetic elements with a replicable translation system, a prototype of the ribosome, which LUCA unquestionably possessed. Originally, this proto-ribosome might have functioned as a triplet replicator (a triplex), its function in translation arising later [13,66, 67]; however, genome comparisons clearly indicate that LUCA already had a translation system similar in its basic features to the modern one [53].
The spread of advantageous combinations would be greatly facilitated if (some of) the genes for proteins that are, directly and indirectly, required for replication were located on the same genomic segment, along the lines of the selfish operon concept [45,46]. Multigenic elements roaming the LUCA network would be quintessential selfish operons, free of mobility constraints imposed by the large, typically, monopartite genomes of modern prokaryotes. The few operons that are shared by archaeabacteria and eubacteria and do not show signs of extensive HGT could have descended from such primordial genetic elements. The primary winner in this primordial darwinian competition might have been an element encoding the principal ribosomal proteins and RNA polymerase subunits, a probable ancestor of the largest superoperon which is, to a varying extent, conserved in all contemporary archaeabacteria and eubacteria [68,69].

Transition to the next complexity level would require longer, more stable information storage and transmission molecules, perhaps approaching large contemporary plasmids in size and coding volume, to counter the deleterious effects of reassortment disrupting beneficial combinations of genetic elements. But how big could such RNA genomes get? Poole and Logan [70] and, independently, Forterre [71] have recently suggested that LUCA could have had a highly complex RNA genome by virtue of RNA repair, which seems to be rather widely distributed among modern cell lineages, and which would improve the replication fidelity of an RNA genome. RNA-repair activities are congruent with the idea that LUCA, in principle, could have had a relatively large RNA genome. However, even with the benefit of several enzymes implicated in the repair of viral RNA [72], the largest known RNA genomes, those of coronaviruses, do not exceed ~30 kb [54], a size compatible with the formation of a complex superoperon but obviously insufficient to encode the entire repertoire of cellular functions on one or a few genomic segments. Ultimately, switching to DNA-based information storage and the accompanying functional specialization of DNA and RNA into the information-storing and information-expressing components of the genetic system, respectively, would have been a necessity en route to life as we know it.

**DNA genomes and cellular escape**

The synthesis of double stranded DNA (dsDNA) is an intrinsic feature of the retrovirus-like replication cycle postulated for the inorganically confined LUCA discussed above (Figure 1) and, obviously, would be inherited by the still inorganically confined ancestors of archaeabacteria and eubacteria. However, it appears from genome comparisons that LUCA did not have the ability to replicate these small dsDNA molecules [44] and, because of this, the retrovirus-like cycle was not conducive to transmission of large numbers of linked genes. Genome comparisons suggest instead that the enzymatic systems for dsDNA replication, and hence the ability to use DNA as the main information storage device, evolved separately in the two primary prokaryotic lineages [44,70]. The first DNA-replication systems, possibly of virus-like nature [73], would have stored information in compartments that provided hospitable conditions. In such compartments, the DNA elements would have become sinks accreting other genetic elements, perhaps, including the ribosomal superoperon, via reverse transcription into growing DNA molecules. Agglomeration of the numerous proteins and cofactors required for the formation of lipids and semipermeable membranes (and the even larger number of subordinate proteins needed to provide amino acids, coenzymes and other metabolites efficiently) was probably unattainable before the emergence of large DNA genomes. Hence, we find it unlikely that cells with largely or solely RNA-based genetic storage were capable of existing outside a network of inorganic compartments, particularly because precise cell-division machinery is a prerequisite for successful escape.

The two distinct systems for membrane lipid biosynthesis might have evolved on small, mobile entities that colonized distinct populations of FeS compartments and joined the growing DNA genomes. Once membranes and turgor-resistant cell walls evolved, there must have been numerous escape attempts, most of them failing as the ocean was increasingly nutrient-poor and inhospitable with increasing distance from the vent. The successful, independent escape of proto-cells with archaeabacterial and eubacterial membranes had to await the assembly, on a single (or a few) chromosome(s), of a collection of genes encoding the full complement of functions necessary and sufficient to support the free-living lifestyle.

We only considered the two prokaryotic domains of life and disregarded the eukaryotes. This is because, in contrast to suggestions that eukaryotes are direct descendants of the first cells [8,74], we find the available evidence to indicate that eukaryotes emerged much later, through symbiosis between fully fledged archaeabacteria and eubacteria [75–77] (further specification of the possible partners involved being irrelevant here). Such a symbiosis could only have occurred after the escape of both forms of prokaryotic life from the primordial system of inorganic compartments.

**Inorganic compartments versus membrane-bounded cells as the means for confining the LUCA**

It has been repeatedly argued that the complex molecular composition inferred for LUCA could not have been attained without prior evolution of biogenic-membrane-bounded cells [18,26,71,78], mainly because (i) compartmentalization is a prerequisite for the evolution of any complex system; and (ii) certain key membrane-associated enzymes, such as the signal recognition particle (SRP) and the proton ATPase, are conserved in eubacteria and archaeabacteria. The model of a compartmentalized, but inorganically confined LUCA obviates the first problem. However, the second problem – the conservation of certain membrane-associated functions in all modern forms of life – is more challenging. The ubiquity of the SRP (with its notable RNA component) and the proton ATPase across genomes, together with the clear split between archaeabacterial–eukaryotic and eubacterial versions, suggests that these complexes were present in LUCA as opposed to spread subsequently via HGT (notwithstanding some...
HGT for the proton ATPase [79]). Because the SRP inserts proteins into hydrophobic layers and ATPase requires a hydrophobic layer to function, this would seem to imply the existence of membranes in LUCA, apparently in contradiction to our arguments above concerning the late and independent emergence of lipid biosynthetic pathways. The essential distinction to be made is between a ‘hydrophobic layer’ and a ‘biogenic membrane’. The latter requires elaborate suites of lineage-specific enzymes (given the unrelated isoprene ether versus fatty acid ester chemistries of the membrane lipids in archaea and eubacteria, respectively). The former could consist preferentially of C8–C12 aliphatic acids, which are expected to arise from H2 and CO2 geochemically in studies of thermodynamic equilibria under warm (∼50–100 °C) hydrothermal vent conditions [35]. Furthermore, in experiments simulating vent conditions, de novo synthesis of aliphatic acids up to C5 [80], their elongation by up to three carbons atoms [81,82] and their condensation [81,82] through inorganic catalysis only have been reported. Thus, the SRP and proton ATPase could have operated within hydrophobic layers provided naturally at the compartment surfaces of a hydrothermal vent, without the demand for genetically encoded mechanisms of lipid synthesis.

Some biologists might object to this very specific aspect of our current formulation. However, it finds support from theory [35] and experiments [34,80–82], whereas the two current alternatives are more problematic. In one, Cavalier-Smith [10] argued that archaea arose from actinobacteria (high-GC Gram-positive bacteria) ∼850 million years ago (Mya) and evolved an entirely new lipid membrane and cell wall biochemistry in response to thermophilic adaptation; independently, Gupta proposed that archaea derive from low-GC Gram-positive bacteria [83]. The problems we see with these scenarios are that: (i) no known prokaryotes have demonstrably undergone any vaguely similar catalycmic lipid transition; and (ii) to our knowledge, no genome-wide data implicate either actinobacteria or low-GC Gram-positive bacteria as ancestors of archaea. The other hypothesis, developed by Wächtershäuser [25], suggests that the LUCA was a form of life that existed in two dimensions only and that could synthesize both lipid (and, implicitly, cell wall) types, followed by differential loss. Differential loss explains all of the differences between archaea and eubacteria, but makes the (primitive?) LUCA the biochemically most-potent organism that ever lived, with functionally redundant parallel pathways for a plethora of essential functions (lipids, cell walls, DNA replication). Our proposal avoids arguably the most challenging conundrum faced by all models entailing a free-living LUCA – replacement of one ancestral membrane type by another in either eubacteria or archaea – and furthermore avoids the need for two-dimensional life, while keeping the LUCA metabolically simple and simultaneously accounting for the observations from genomes.

We cannot summarily dismiss models entailing a free-living LUCA, but the model of an abiogenically confined LUCA outlined here seems to require less imagination with respect to membrane evolution, and is also satisfying in other respects. In particular, it explicitly permits evolution of considerable complexity without requiring prior emergence of a complete cell division mechanism (such a mechanism, even a primitive one, is prerequisite to the free-living state) or mechanisms for intercellular DNA exchange that are required for HGT, and are central to some competing views. On the contrary, this model allows locally restrained transfer of coding material within a system of physically juxtaposed, interconnected compartments – a suitable setting for the emergence of genetic complexity.

Concluding remarks

This formulation of hydrothermal origins builds on previous models [17,19,20,23,24,27] and specifically addresses the emergence and early evolution of genetic systems. It does not tackle the origin of the genetic code, although it seems to be compatible with the recent, intriguing suggestion that the code evolved through a two-letter intermediate entailing the RNA-catalyzed synthesis of biogenic amino acids on RNA [84]. The model does, however, offer conceptual inroads towards structuring severe problems – limiting steps – en route to evolving genomes. What would keep genes from diffusing into the ocean? What was the source of energy supporting their synthesis? How could the transition from selection for self-replication to selection for versatile functions have occurred? A continuously expanding set of naturally formed compartments (with real examples in nature) would enable early (geobio)chemistry and self-replicating systems to attain a level of complexity approaching that of the simplest extant life forms. The transition from non-living to living systems in pre-existing compartments that have a continuous energy and carbon source, in which combinations of self-replicating molecular cooperatives can arise and undergo bona fide darwinian selection, implies a LUCA that was complex but dramatically different from modern cells, most notably in that it was not free-living. We believe that this version of LUCA – physically contained, possessing ribosomes and translation but lacking membranes and large DNA genomes – could be a crucial and not implausible intermediate in the early evolutionary sequence.

How can these ideas be tested? More work needs to be performed with chemistry simulating hydrothermal vent conditions (reviewed in Ref. [34]), in particular, to investigate synthesis of cofactors and bases in the presence of suitable nitrogenous compounds [24] (the synthesis of peptides via carbonyl sulfide seems to work efficiently [36,37]). If microbiology and genomics were to uncover a dense spectrum of continuous variation spanning the archaeobacterial–eubacterial divide, such that their deep distinctness should disappear (e.g. prokaryotic groups with archaeobacterial DNA replication but eubacterial membranes or vice versa), the abiogenically confined LUCA aspect would become unnecessary. Our prediction is clearly that, despite much HGT between archaea and eubacteria, genuine intermediates will never be found, because they never existed as free-living cells.
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The WHO and six medical journal publishers have launched the Access to Research Initiative, which enables nearly 70 of the world’s leading medical journals to be made available free of charge, for the benefit of developing countries. The initiative was launched in 2001, initially covering more than 1000 biomedical journals and subsequently extended to more than 5000 journals in 2005, to enable developing countries to gain free access to biomedical literature through the Internet.

The science publishers, Blackwell, Elsevier, the Harcourt Worldwide STM group, Wolters Kluwer International Health and Science, Springer-Verlag and John Wiley, were approached by the WHO and the British Medical Journal in 2001. Initially, more than 1000 journals will be available for free or at significantly reduced prices to universities, medical schools, research and public institutions in developing countries. The second stage involves extending this initiative to institutions in other countries.

Gro Harlem Brundtland, director-general for the WHO, said that this initiative was ‘perhaps the biggest step ever taken towards reducing the health information gap between rich and poor countries’.

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