Indeed, any DNA molecule of any length could be assembled from oligonucleotides; thus, a virus might be resurrected from pure genomic information. We were probably among the first to realize the potential dangers associated with this technology—the possible misuse of viral synthesis in bioterrorism. The US Defense Advanced Research Project Agency (Arlington, VA USA) took the same stand and provided funding for our project, an endeavour we considered as a wake-up call. Indeed, the widespread attention generated by our publication raised the overall awareness of the new reality of synthetic viruses and its possible consequences

…news of the poliovirus synthesis reached a highly irritated public, particularly in the USA, which was ready to link it with bioterrorism

The different reactions to the poliovirus synthesis were astounding and perplexing. In general they fell into one of the following categories: positive reactions, ethical concerns, questions about the scientific value of the experiment, concerns about jeopardizing the global eradicatio of poliovirus, issues of national security, and issues of freedom and censorship of biological research. Thankfully, the majority of responses were positive.

When I am asked whether poliovirus is a non-living or a living entity, my answer is yes. I rega viruses as entities that alternate between non-living and living phases. Outside the host cell, poliovirus is as dead as a ping-pong ball. It is a chemical that has been purified to homogene and crystallized (

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Destroy user interface controlSchaffer & Schwerdt, 1955), with its physical and chemical properties largely determined (

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Destroy user interface controlWimmer et al, 1993), and its three-dimensional structure solved Just like a common chemical, poliovirus has been synthesized in the test tube.

Once poliovirus, the chemical, has entered the cell, however, it has a plan for survival. Its proliferation is then subject to evolutionary laws: heredity, genetic variation, selection towards fitness, evolution into different species and so forth—that is, poliovirus obeys the same rules that apply to living entities. One could even argue that poliovirus undergoes sexual reproduction in the infected cell, as it readily recombines with sibling progeny or with other related viruses (P. Jiang, J.A.J. Faase, H. Toyoda, A.E. Gorbalenya and E. Wimmer, unpublished data) to exchange genetic information (

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Destroy user interface controlWimmer et al, 1993).

Barring religious beliefs, scientific wisdom holds that living entities will irreversibly die. I suggest that viruses do not follow this destiny, but rather switch between non-living and living phases. These seemingly incompatible qualities of viruses might be difficult to comprehend, but think of the electron: it took physicists decades to accept that it is both a wave and a

particle.

In 1978, Charles Weissmann and colleagues revolutionized RNA virology by inventing revers genetics (

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Destroy user interface controlTaniguchi et al, 1978). To use the methods developed for DNA molecular biology, the researchers converted the purified genomic RNA of phage Qβ, a virus of bacteria, into full-length cDNA with the enzyme reverse transcriptase. This virus-specific cDNA yielded authentic RNA Qβ phages after transfection into bacteria (Fig 4A). After 3 year

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Destroy user interface controlRacaniello & Baltimore (1981b) repeated this experiment using purified poliovirus RNA and human cancer cells as hosts (Fig 4A). They too obtained authent virus. After our publication of synthetic poliovirus in 2002, the question was asked: why bothe to chemically synthesize cDNA (Fig 4B) when this can be done faster and much more cheapl with the help of enzymes? In relation to this, a perplexing view was aired in the journal *Science*, claiming that the chemical synthesis of poliovirus cDNA was just a publicity stunt (

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Destroy user interface controlBlock, 2002)

Critics in this frame of mind ignore the fact that generating poliovirus cDNA *per se* was not the message of our 2002 paper. A major point was that viruses can be looked at as chemicals and, accordingly, can be synthesized from publicly available information with off-the-shelf chemicals. Notably, the entire process of recreating the virus can happen outside living cells. should also be mentioned that we predicted in 2002 that, given the rapid progress in biotechnology, it would soon be possible to synthesize poliovirus in a few days. As I will discuss later, the future has already begun.

In addition, immune-deficient persons receiving the OPV can develop persistent infections, shedding highly neurovirulent poliovirus for years (

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Destroy user interface controlMacLennan et al, 2004). The known number of persistently infected persons is small and the actual number of poliovirus shedders cannot be determined at the present time. But persistently infected individuals pose a serious health threat once vaccination has been terminated. These complications have led a panel of experts to recommend the development of novel anti-polio drugs for the control of poliomyelitis (

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Destroy user interface controlNational Research Council, 2006).

Herd immunity against poliomyelitis will rapidly decline as new children are born who have no been infected with wild-type viruses or were not vaccinated, a condition that has never existe in human history. Thus, any outbreak of poliomyelitis will be disastrous, whether it is caused by residual samples of virus stored in laboratories, by vaccine-derived polioviruses or by poliovirus that is chemically synthesized with malignant intent. The emerging scientific and logistic difficulties of poliovirus eradication, combined with the new reality of rapid *de novo* synthesis of viruses, force us to ask whether the polio campaign has been rendered a dream. Our resources are perhaps better spent on controlling poliomyelitis rather than eliminating its cause. It has been suggested that vaccination against poliomyelitis, based on newly develope vaccines, might have to continue indefinitely (

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Destroy user interface controlAgol et al, 2005

Within days of the online publication of the synthesis of poliovirus in *Science* in July 2002, harsh comments from some scientists and politicians suggested that, for reasons of national security, the work was irresponsible and the manuscript should never have been published. C course, it was certain then, and still is today, that the chemical synthesis of poliovirus does no pose a threat to the general population. Yet the question persists as to

whether the poliovirus synthesis was a blueprint for bioterrorists.

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Eighteen months after the poliovirus synthesis was published, a paper appeared describing the *de novo* synthesis, in just 2 weeks, of the 5,386 base-pair DNA genome of bacteriophage X174 (

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Destroy user interface controlSmith et al, 2003). The unedited DNA was transfected into bacteria, which sorted the good from the bad and produced viable phages. This rapid assembly of DNA was a technical feat that could be applied without modification to any virus, including those on the select bioterrorist agents list from the US Centers of Disease Control and Prevention (Atlanta, GA, USA).

Thus, the strategy could be used to synthesize poliovirus or Ebola virus within weeks. Surprisingly, this fact was lost on the American public in December 2003; the great uproar after the poliovirus synthesis in 2002, which had been largely fuelled by Craig Venter, senior author of the 2003 φX174 paper, had been mostly forgotten.

Another landmark publication in virology was the resurrection of the Spanish influenza virus b

chemical synthesis (

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Destroy user interface controlTumpey et al, 2005). This virus, with the genetic signature H1N caused the horrific influenza pandemic of 1918/1919, which killed an estimated 20–50 million people worldwide. Given the constant danger of new influenza pandemics, including the uncertain threat of the highly pathogenic avian influenza H5N1 strain, it was deemed importa to resurrect the Spanish influenza virus and to decipher the molecular mechanisms by which it expressed its deadly instincts.

A tentative genome sequence of the Spanish influenza virus was deciphered from specimens uncovered eight decades after the pandemic. This sequence guided the *de novo* synthesis of the deadly virus, which, in turn, permitted the study of its pathogenesis (

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Destroy user interface controlTumpey et al, 2005). The publication of the resurrected killer influenza, which caused much public concern, was carefully embedded in multiple layers of commentaries, all eventually supporting its synthesis and publication. It was argued that the benefit of the scientific endeavour, which yielded numerous important new insights into influenza pathogenesis, outweighed the risks of misuse. I share this view. Evidently, in late 2005, the general public was much better prepared, and perhaps better educated, to accept the rewards of rapidly advancing medical technologies without emotional outbursts.

Just over a year earlier, another paper exemplified how fast the technology in DNA synthesis

was progressing (

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Destroy user interface controlTian et al, 2004). The authors described a new method by whic they claimed that any DNA molecule of 20,000 base pairs could be synthesized at a price of US$1. If so, the dreaded hepatitis B virus or poliovirus could be synthesized for a few cents and Ebola virus for a few dollars. This new reality in synthetic biology was not unexpected, bu the speed with which it arrived was astounding. Thus, it is even more urgent to develop new strategies in order to protect us from misuse by fostering open research in the broadest sense, not by restricting it.

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