In the valley of the shadow of death

Roger Brent

Director and President
The Molecular Sciences Institute
Director
Center for Quantitative Genome Function
Berkeley, California 94704
USA

1) Summary

During the 20th century, advances in biological understanding sparked a global revolution in biological capability, or RBC. Since that time, the revolution has proceeded in a Moore's-law-like fashion for many decades. One negative consequence of the RBC is that the US now faces a large and growing threat of catastrophic biological attack. To deal with the threat, this article advocates a two-part strategy. First, during the current period of high and growing risk, Period 1, "the Valley of the Shadow of Death", the US should bring into being a patchwork of agile technical capabilities to detect and respond to attacks, and social and normative policies to diminish their risk of occurrence. Second and simultaneously, the US should initiate research whose fruits will eventually deter biological attacks by rendering them "impotent and obsolete". Creation of effective, responsive, and agile Period 1 capabilities will buy time, by lowering the probability of attacks and blunting their impact, until strong technical defenses enabled by longer-term research can become operational in Period 2. Executing the two components of this strategy will be far more costly and complex than is generally contemplated, albeit probably less expensive and difficult than execution of the containment strategy during the Cold War. However, the increased security, human health and felicity, and economic growth that this activity will engender will repay the effort and cost many times over. Entry into Period 2, defense so strong as to deter attack by making it unlikely to have any effect, coincides with the effective elimination of most naturally occurring infectious diseases as a factor in human affairs. But at the moment, the best names for Period 2 seem to be "Partial Victory" or "Basin and Range", in that later trends may shift once again to favor attack.

2) The existing strategic landscape and how it came to be

"*Military action, whatever its form, consists in the first place of the study of the elements of the problem, and this requires a discipline of mind which excludes fantasy. In addition, the means at disposal have fixed properties, respect for which in their case is an inflexible condition" (Charles de Gaulle, "Vérs l'armée de métier", 1934)*

a) The revolution in biological capability (RBC)

The history of the use of biological weapons in war and of the 20th century germ war programs is largely irrelevant to the current strategic situation, and I will not review it here. Rather, I will arbitrarily date the start of the events defining the strategic picture to the elucidation of the double helical structure of DNA (Watson and Crick, 1953). This finding immediately suggested how genetic information was stored and transmitted, and led within 20 years to an understanding of how it was read out into messenger RNA and protein, and to the beginnings of an understanding of how its expression was controlled. The ensuing decades of more or less pure "scientific" development, of increasing biological *knowledge*, also eventually sparked a self-propelling increase in biological *capability*. I refer to this development as the *revolution in biological capability,* or RBC. A good analogy might be how another advance in human knowledge, the understanding of electricity and magnetism (codified in Maxwell, 1873) to a threshold theoretical level deep enough to use to build technologies, enabled the development of a self-sustaining increase in electronic capability. Examples of the consequences and progress of the technologies enabled by theoretical understanding of electromagnetism include long range wireless transmissions in the 1900s, deployment of radio onto ships at sea in the 1910s, mass production of radio receivers in the 1920s, the spread of radio networks and the emergence of radio broadcasts as a factor in US and European politics in the 1930s, integration of radio and microwave technology into the tactics of air forces, and the beginnings of television, in the 1940s, the widespread use of vacuum tubes in digital computers in the 1950s, commercial deployment of solid state logic circuitry in the 1960s...

By this analogy, understanding of the basics of DNA, RNA, and protein molecular biology enabled key developments in the RBC including:

- Recombinant DNA methods (Jackson et al. 1972, Carbon et al., 1973),
- DNA sequencing (Sanger, 1977, Maxam and Gilbert, 1977) and sequencing machines (see Hunkapiller et al., 1991),
- Expression of human proteins encoded by synthetic DNA in bacteria by recombinant DNA methods (Goeddel et al., 1979)
- Machines to facilitate production of synthetic DNA (see Horvath et al. 1987),
- PCR, the Polymerase chain reaction (Mullis et al., 1986, Saichi et al., 1988)
- Determination of the genome sequences of numerous organisms (1980s-present) and their distribution via the Internet (1992-present), making it easy for any researcher to obtain any stretch of DNA by PCR.

These examples concern sequencing, isolating, constructing, synthesizing, and producing in bacteria defined sequences of DNA, RNA, and protein. One can lay out similar timelines for other protein manipulations, for the ability to introduce DNA into cells and organisms and direct the synthesis of new RNAs and proteins, and for the ability to produce directed point mutations and directed genomic rearrangements via site specific recombination. Table 1 lists particularly important technical capabilities that have grown greatly during the last ten years.

One consequence of the RBC is that information embodied in DNA sequence and the actual molecules of DNA, RNA, and protein, are at this point completely fungible. Every day, in thousands of labs worldwide, genes, mRNAs and proteins, isolated from cells or organisms, are conveyed as bits (via the internet) or as self replicating molecules (via Federal Express), and reintroduced into other cells or used to engineer new organisms. Information as to how to perform these manipulations is widely available from cloning manuals and the Internet (figure 1). It is thus in biology that one goal of nanotechnology (Drexler, 1986), the ability to operate upon strings of bits via "molecular assemblers" to produce precisely defined objects, has already been realized.

The capital costs needed to equip a lab for synthetic and recombinant DNA work are low and dropping (figure 2), and there are probably >10,000 labs worldwide that are capable of performing manipulations of this type. Obviously, this synthetic engineering capability confined to sequences now found in nature. Novel DNA sequences are now designed and built *de novo* for introduction into living cells or incorporation into new organisms by undergraduate students in technical universities (Ferber, 2004).

Rob Carlson has attempted to quantify the pace at which some biological capabilities are developing (Carlson, 2003, redrawn in figure 3). In his sketch, some indices of capability relating to DNA synthesis, on a semi-log plot, have a steeper slope than the Moore's law line showing the increase in the density of semiconductors in integrated circuits (Moore, 1975).

b) Impact of the Revolution in Biological Capability

The extent to which the RBC has already impacted the economy is not widely realized. Here, briefly, the largest 20 pharmaceutical companies (aka "pharma") had worldwide sales of >$370B in 2001. The pharmaceutical industry is now utterly dependent on gene cloning, DNA sequencing, protein expression, recombinant construction of cell lines, and other recombinant DNA techniques to identify, isolate, and "validate" the protein targets against which its small molecule drugs are developed, to develop the high throughput assays, and to solve the protein structures that are used to identify the chemicals that become the drugs. It has begun to use these methods to make animal model systems to test the putative drugs and to use genomic techniques to select and monitor human subjects during clinical trials. More than half the 2003-2005 top 100 selling drugs would not exist without these methods.

Second, molecular biological capabilities have also had an enormous impact on agriculture. By 2003, in the US, more than 1/3 of the corn, 2/3 of the cotton, and 3/4 of the soybean crop was genetically engineered. This decade will see application of recombinant DNA methods to animals and plants to produce drugs, and to engineer animals with desired traits such as less fatty meat or inability to contract mad cow disease. It may also see the engineering of food crops to meet needs in the developing world.

Third, the RBC is directly responsible for the "biotech" industry. Here I use "biotech" to refer to two types of firms, those that use recombinant DNA techniques to make protein drugs, and those that use molecular biological or genomic techniques to generate proprietary capabilities that they sell to pharma. This industrial sector is sometimes held to be disappointing (stock prices are volatile, most investors lose money, an industry with $220B total investment had only $220B market cap in 2003, the industry is still recovering from a deep recession, etc., etc). However, for more than 20 years, until the 2002-2003 downturn, revenues increased steadily at 10-20%/ year, to $38B for 2002. And these figures not count the large number of biotech companies that are absorbed each year into pharma by acquisition.

Biotech, the third (and smallest) sector, attracts the majority of the business reporting in biology. The biotech press is relatively unsophisticated about the science, extremely vulnerable to spin, and possessed of a notoriously short attention span. Perhaps because of this press focus on biotech, and particularly its focus on "news" defined by events that move share prices, the steadily increasing contribution of the RBC to the US economy is not widely appreciated and is even sometimes discounted. As well might Englishmen in 1845 have complained that economic and social impact of railways had been oversold. That is, even though, during the period 1830-1860, most individual investors and most railroad companies lost money, the fortunes of individual investors and individual firms were utterly irrelevant to a larger economic picture. The capital had to come from somewhere, and, in Britain, it came from investors. By 1845, it was clear that the steady growth in miles of track, increase in amount of rolling stock, decreases in cost of transport, etc. made possible by these large capital investments were enabling new kinds of economic activity and increasing the wealth of the country (Landes, 1969).

The RBC progresses because its current and likely consequences, including but not limited to new medicines, food for the starving, new materials, new industries, and new economic growth, are strongly positive. Numerous, powerful, economic drivers favor a continuation of this high rate of change. In general, every increment in biological capability pays back the researcher and the researcher's sponsors in short order. Payback comes in the esteem of peers, in promotions, and in increases in the academic or corporate salaries of the researchers whose work generates knowledge and new therapies. Payback comes in the form of profits for the manufacturers of kits to perform the manipulations, royalties for the writers of the methods manuals profits for the drug industry. Payback comes for the public in the form of new drugs and therapies.

In addition to the fact that strongly established trends suggest that the rate of increase in biological capability will remain high, it is important to note that by contrast with other kinds of highly technical human activities undergoing progressive change, including for example aerospace, semiconductor production, and advances toward hydrogen fusion, the RBC is extremely widely distributed. It advances every day, at tens of thousands of research sites scattered throughout the affluent and developing world. These sites are neither controlled nor well-understood by the US government (see for example Boutin, 2005). Capital costs are low. The level of skill needed to carry out the work is typically

medium-high and is steadily decreasing, and the ability to perform the work is well-supported by methods manuals, reagent kits and information available online.

It thus appears inevitable that, during this century, the impact of the RBC will expand from pharma, agriculture, and existing biotech to other economic domains. Molecular biological techniques will transform the synthesis of chemicals, fuels, and materiel (see for example the industrial use of directed evolution or "DNA shuffling" methods to engineer *Trichoderma reesei* to allow industrial production, from cellulose, of glucose for feedstocks for microbial chemical synthesis, and, from the glucose, ethanol for transportation (www.iogen.ca, and Wald, 2005)). They will be applied to environmental remediation (arguably the greatest legacy of the 20th century is cleanup) and environmental management (for example, the possible construction of organisms that fix carbon more efficiently to mitigate climate change caused by greenhouse gases). They will also impact medical care, enabling monitoring and detection methods that allow better preventive care and diagnosis (see below). By mid century they may well impact other activities, such as the construction of buildings, bridges and roads. In about a 20-year time frame, many serious observers (Stock, 2002) believe that capabilities that RBC has already generated (see figure 8) will be used to engineer humans. Taken together, It thus seems likely that by mid 21st century or earlier, the ability to manipulate DNA will be as important to the economy, and to human affairs, as the ability to manipulate electrons and bits was to 20th century (Brent, 2000, Carlson, 2005).

c) Unknowable threats and fixed defenses

"Dynamite makes all men equal, and therefore makes them free". (Albert Parsons, 1887)

"I do not wish to see the coffins of my family, my children, and my grandchildren created as a consequence of the utter naivetée, arrogance, and hubris of people who cannot see that there is a problem". (George Poste, 2004)

At the same time, the RBC has also enabled the current grave and increasing threat of biological attack. Over the next two decades, trends now firmly in place mean that the US faces a continually increasing probability of a catastrophic strike, here, arbitrarily defined as an attack that kills >3M Americans or leaves them so disabled as to require permanent care (figure 4). The RBC has also greatly increased the number of different kinds of attacks that might occur. In fact, because it is enabled by rapidly developing technologies that are practiced by increasingly large numbers of people, it is impossible to enumerate the "most probable" or in fact to do more than group then into classes (for example, vaccine and antibiotic resistant bacterial pathogens, or viruses with increased virulence, resistance to antiviral drugs, and expanded host range)For policy writing that begins to grasp this fluid aspect of the biological threat, see Cordesman, 2001). The democratization of technical capability and the increase in the number of people who can practice the technologies lengthens the list of actors that might mount such attacks (Table 2). Together, these developments constitute the most important characteristic of the near-term biological security environment.

These facts also have an important corollary. The current defense strategy is to enumerate knowable likely pathogens, and to build and stockpile countermeasures against each one, The RBC has given to tens of thousands of individuals worldwide the knowledge and power to circumvent these countermeasures. Vaccines and antibiotics stockpiled against known or knowable pathogens constitute fixed defenses. In a century when elements from both nature and artifice can be used modify existing organisms and to create new ones, fixed defenses can be no more effective for the defense of the US than the Maginot line was for the defense of France in 1940.

3) A strategy for defense and partial victory

"It is a love of comfort, not to say sluggishness, that characterizes those who protest against revolutionary innovations that happen to demand fresh efforts in the way of intellect, physical striving, and resolution" (Heinz Guderian, in "Achtung-- Panzer!", 1937)

To imagine how to move beyond the existing strategy, it may be helpful to divide the first half of the 21st century into two different periods (figure 4). We are now in Period 1. In this period, "the Valley of the Shadow of Death", trends in place increasingly favor attack over defense. The strategic approach during Period 1, particularly its technical elements, is essentially reactive, characterized by rapid detection and rapid reaction to attacks. Period 1 can be brought to an end with the implementation of measures that provide defense against biological attack so general and so effective as to render attack irrelevant, and thus deter it. In previous versions of this article, I referred to Period 2 as "Safe haven" or "Victory", but now refer to it as "Partial Victory" or "Basin and Range" (see notes on publication of the 2005 article).

The remainder of this essay details the technical and institutional steps that the US should initiate this decade to minimize the risk during Period 1 and to speed the transition to Period 2.

During Period 1, the set of capabilities that increase the probability of survival comprise a patchwork. Some are technical, and require either directed and focused engineering efforts or directed and focused scientific research efforts. Some are social, such as the passage of laws and the promulgation of ethical norms. Taken together, even the sum of all the elements in this patchwork is not likely to guarantee the US as much security during Period 1 as the US enjoyed during the late Cold War (1970-1990).

By contrast, the capabilities needed to bring about Period 2 are largely technical. Insofar as one can now envision them, some Period 2 capabilities can only be realized by prosecution of a broad array of undirected basic scientific research projects in the context of a specific goal-- rendering attack by pathogens ineffective. The need for undirected research that (or, more properly, research that is directed only that it occurs in the context of a goal) arises from the fact that one cannot now predict which lines of investigation and sets of technical capabilities will be most useful (Table 7 shows examples of the

types of capabilities that would be useful), so that, initially, the US will need to confront the problem in many ways. These constraints make it likely that attaining most Period 2 capabilities will take a good deal of time (~20 years).

Attaining the operational capabilities needed to survive Period 1 and to bring about Period 2 will be difficult and costly but will repay the investment via improved security, scientific understanding, human health, and by the creation of entirely new nexuses of economic activity. Moreover, entry into Period 2 will enable the effective elimination of naturally occurring infectious disease as a factor in human affairs.

During both periods, all technical capabilities for defense and partial victory are enabled by the RBC. Attaining them will require input from commercial entities: pharmaceutical companies, ag-bio companies, biotech companies, diagnostic companies, and from the skilled scientists and executives who work within them. Existing commercial actors will be vital during the formulation of the strategy, and will be utterly required for its execution. However, just as the Air Force needed to take the lead in articulating requirements and technical needs to existing aircraft companies and newly created aerospace companies when the nation required ICBMs (Hughes, 1998), the government must assume that the needed leadership on biological defense cannot come from executives associated with the existing commercial sector. This situation should be familiar to policymakers, as it closely matches current challenges in energy policy: if we wish to bring about a future in which our economy is less dependent on energy imported from abroad, where most of the energy comes from the sun, and our vehicles run on hydrogen, the executives and lobbyists for energy companies do not have an existing plan to get us there, and do not by themselves possess the expertise to articulate one. Rather, in biology as well as energy, the detailed plan to implement a strategy will come from a complex created and orchestrated by the government, while execution of the strategy (and of course realization of the profits to be made from executing it), will more likely be effected by a combination of existing companies and new ones born in response to the national need (see again Hughes, 1998, in particular the second chapter, on the Atlas missile program).

4) Strategy for defense against catastrophic attack during Period 1, the "Valley of the Shadow of Death"

"*It is therefore by maneuvering that France is protected*" *(Charles de Gaulle, 1934, ibid.)*

a) General observations on Period 1

The first observation on capabilities needed during Period 1 is the current efforts now contemplated by the political, medical, and public health establishment (and embodied in the US "Bioshield" legislation) consist of procuring and stockpiling assets (diagnostic tests, vaccines, antibiotics, and antiviral drugs) against known or knowable threats. As already stated, this approach is tantamount to building a Maginot line. Although such a defensive line may be of some good against technically unsophisticated attackers, a

realistic defense needs to assume that motivated nation states, terrorist groups, and even individuals will bypass fixed defenses, designing, building, and evolving (see Stemmer, 1994) pathogenic organisms that resist existing antibiotics, ignore existing vaccines, escape detection by existing diagnostic tests, etc. This fact means that a large fraction of the national detection capability, and the bulk of the national response capability, will need to be general and agile, able to detect and respond to pathogens whose nature is currently unknown and usually will not be knowable until they are used in an attack. Because of the need to respond to the unknown, and because an attack will often be able to cause considerable damage before an effective reaction can counter it, the totality the capabilities the US could marshal during Period 1 cannot provide Americans the level of security they enjoyed during 1970-1990.

The second observation is that the competencies needed for Period 1 defense are now greatly fragmented among people in numerous different institutional compartments divided by disciplinary, historical, and political distinctions that no longer seem relevant. Any attack with a contagious disease will likely be international rather than national or regional in impact. An attack could come on people, or cows, or on the bacteria responsible for the ecology of the soil in the US Midwest. The people who respond to an attack might well include military officers, public health officials, biotech executives, physicians in clinical practice, physician-researchers, and university professors of molecular biology. In each case the more "old-fashioned" skills have not become obsolete, but the list of required skills has grown, as has the need for those skills to be aligned within a "modern" overarching intellectual and organizational framework that overcomes disciplinary boundaries and allows the right people to work together.

The third observation is that the Period 1 tactical and operational capabilities are comprised both of technical capabilities and normative or "social" capabilities. The technical capabilities spring mainly from directed engineering research, and to a lesser extent from directed scientific research. The fact that these technical capabilities can be achieved without a great deal of undirected research is good news. However, with the significant exception of the paths pursued by the pharma and biotech industries, biology does not at the present have a tradition of directed engineering or scientific research. It has no historical equivalent to the programs that successfully developed the Atlas missile or the Internet (Hughes, 1998). For Period 1 defenses to come on line, US will need to create a culture that supports such efforts. Even achieving the most conceptually simple Period 1 technical capabilities (table 4) will be far more costly than most people have dared contemplate, and will require overcoming significant institutional and structural barriers. By contrast, attainment of many useful "social" or "normative" capabilities will be inexpensive and could happen quickly, and many are proactive rather than reaction. However, attaining these social and normative capabilities will require that the US persuade other countries to adopt them as well, which in turn will require the US to be well-liked and capable of conducting effective diplomatic efforts to achieve its ends (table 5).

The fourth observation is the achievement of these capabilities both requires the RBC and feeds it. Efforts to build Period 1 technical defenses will pay for themselves in new

industrial and economic activity and will increase the pace and help channel the development of the RBC. And it is only the continued increase in biological capability guided by some measure of government input that can bring Period 1 to an end.

b) Technical elements of Period 1 strategy

1) Flexible detection

a) General means to monitor the microbial environment and detect changes and emergent organisms within it.

One component of the strategic problem for Period 1 defense is the need to devise systems to achieve near-real-time situational awareness and detection, and patient diagnosis and assessment, for known and unknown pathogens. One small part of this problem is the need to get a handle on the microorganisms that are now present in various niches in the environment, so that deviations from the baseline can be detected. Fortunately, the technology to do this now exists. At the level of nucleic acids, technical means to conduct such surveillance (PCR amplification of random sequences present in a sample, followed by characterization of the sequences by hybridization to known sequences or even by direct DNA sequencing) have been developed within the past decade (see for example Handlesman et al., 2002). Their cost is dropping and their power increasing in pure Moore's law fashion.

Scientifically, the results of such surveys have been breathtaking. Wherever one looks, conventional wisdom about microbial ecosystems turns out to have been grossly incomplete. Each ecosystem contains previously unknown microbes and the population structure differs from what was thought (Handlesman et al., 2002). These scientific explorations now become relevant to national security. During this decade, the US will need to get a handle on microbial population baselines, in the air: above cities, at ground level, in bus stations and airports, in day care centers and office buildings, in water, soil, sewers, and feedlots, so it can detect deviations from them (figure 5). Establishing such baselines will pay immediate dividends in new knowledge relevant to health and the environment, as well as laying the technical foundation for a surveillance system that can detect anomalous events against a background of baselines and trends.

Technical means for detecting biological attack now deployed or contemplated for deployment in the US do not address the above issues. None give information about organisms with RNA genomes (eg influenza virus, SARS virus, HIV, measles virus, mumps virus, etc.), none give information about organisms transmitted by coughing at ground level (or any route other than attack by releasing an aerosol), none give data about the population and deviations from the natural baseline of micorogranisms, and none detect organisms that are now unknown. Perhaps as importantly, the US does not have data integration and analytical tools that would permit a national or international command to use information from "modern' detectors to recognize outbreaks of existing organisms, or new organisms, against the natural baseline.

Since 2003, there have been two significant lines of technical development affecting the detection problem. First, the practice of bulk sequencing of nucleic acids extracted from a sample, now usually called "metagenomics" has become widely accepted (see for example Schloss and Handlesman, 2005, and Mongodin et al., 2005). It is important to note that in this context there is no effective difference between a sample coming from the environment and one that comes ultimately from other sources such as patient isolates, so that any separation of the technology development issues into "environmental monitoring" and "patient diagnosis" tracks is not justified by the engineering problems that need to be solved. Second, technical improvements in mass spectrometry and development of ultrasensitive assays for non-nucleic-acid molecules such as "tadpole" based assays (Burbulis et al., 2005, Nolan, 2005), have defined a clear path for future technical development of means to survey non-nucleic acid based molecules in a sample to tell what organisms are present.

b) General means to detect and diagnose disease, and to assess disease progress, in people and other organisms

The second arm of the flexible detection network detects organisms and their effects in people. As mentioned above, one part of it, the part that detects the organisms, benefits from the same technologies that will detect the organisms in the environment. For example, Ghedin et al. (2005) published a study of the sequence of the genomes of 209 different influenza viruses, which required development of more facile pipelines to sequence large stretches of RNA genomes; the same developments that made sequencing of RNA genomes even cheaper will benefit environmental monitoring and patient diagnosis, whether those RNA genomes were obtained from air samples or clinical isolates from throat swabs. Such "genomic" assessments should become cheap enough (~$10-$100) so that they are performed routinely during patient visits to physician's office and emergency rooms.

Another component is the accelerated development and deployment of methods that rely on "signatures" to provide knowledge of clinical public health baselines, early warnings for new disease, and to assess and triage people after an attack. The method closest to deployment is the ability to divine information about human disease states by monitoring patterns of gene expression (mRNA expression) from a small sample of white cells in blood (see figure 6 and Whitney et al., 2003, Rubins et al. 2005, Griffiths et al., 2005). At this point there is every reason to believe that deviations of white cell mRNA expression patterns from the norm will allow assessment of infection, provide some information to help identify the infecting pathogen, and also identify numerous other disease states. Capability to conduct such monitoring, perhaps first deployed to determine the clinical baseline for a "sentinel corps" of healthy volunteer individuals, should be, as mentioned, be extended to conduct patient assessment and early warning in emergency rooms, and for triage of possibly infected people after biological attack. The demand for such broad based assessment will be extremely elastic and would expand greatly as the cost was reduced. Such capabilities would find large markets, and be integrated into 21st century schemes for health maintenance and health care delivery. Technically (ignoring institutional and commercial barriers), devices allowing

establishment of population baseline data could be in use by 2007, and large production runs allowing assessment during an infection could be stockpiled and ready for use by 2007-2008 (Table 3).

Further from deployment are technical means to monitor proteins and other signature molecules in blood and saliva. However, at this point a number of studies demonstrate the diagnostic utility of signature patterns of proteins in blood (see Wulfkuhle et. al., 2003, and Mor et al. 2005). In 2003, may of these methods depended on a technique called protein mass spectrometry, which was reasonably expensive. Since that time, cheaper wet methods for detecting signatures such ELISAs (Mor et al., 2005) have demonstrated their utility and the ultrasensitive methods mentioned above (Burbulis et al. 2005, and Nolan, 2005) have become available, while, as in most things biological, the cost of mass spectrometry has continued dropping at Moore's law rates. Devices based on any of these methods could be deployed well before 2010.

As these broad based methods become cheaper, their use can be extended to economically important animals and plants and, and perhaps eventually to sentinel organisms selected by the biological community to monitor ecosystems. Information from these methods, as well as more "classical" epidemeological and public health data (eg., the number of visitors to hospital emergency rooms with flulike symptoms) would flow to the same entity that handles data integration and analysis in figure 5.

c) Agile specific detection of pathogens in the environment and upon infection of the host

In addition to requiring general detection, Period 1 requires technical capabilities that enable agile generation of simpler, cheaper tests to detect new pathogens in the environment and detect, diagnose, and assess infections by the new pathogens. In diagnosis, development of the polymerase chain reaction (Mullis, 1986, Saiki, 1988) opened up new ways to identify and diagnose infectious disease. PCR based tests for specific pathogens are widely deployed and there is an effective national mechanism to devise and promulgate new tests. This is a bright spot, but it is the only aspect of the use of molecular methods to diagnose disease in which practice in medicine and public health matches the state of the possible. By contrast to the PCR methods, the technology used to detect non-nucleic acid pathogen molecules and the host response to them is 20-30 years behind the state of the possible. The reasons for this are complex, but mainly arise from institutional barriers mentioned below. From a technical standpoint, the US could field a rapid, agile ability to make specific, very low cost (<$100) non-PCR-based diagnostic and assessment assays for pathogens and host responses, based on antibodies and other affinity molecules, by 2007-2008.

2) Agile response

"Military art finds itself placed in an equivocal position.... to renew the ancient processes of maneuver, thanks to all that modern engines possess in the way of power, of precision, and of speed, is the task of the tacticians of our day." (de Gaulle, 1934, ibid.)

The key word to describe the needed response capability during Period 1 is that it must be *agile*.

a) Agile ability to generate new vaccines.

One component of the Period 1 strategy is to develop means to deploy vaccines against new pathogens within weeks of their identification. Here, it is easy to identify components of a directed R&D effort that would allow experimental vaccines to be fielded within weeks of identification of a new pathogen. In this view, the US should accelerate the development of computational techniques to identify candidate protective B cell and T-cell epitopes (with the T-cell epitopes even tailored to match individual HLA genotype) on given proteins, and, in complementary experiments, speed the development of combinatorial pooling approaches to select epitopes that confer protective immunity to mice. In a first line emergency system, identified epitopes could be delivered on synthetic DNA with genes encoding adjuvant cytokines by gene gun, while, at the same time, the epitopes would be expressed by recombinant DNA methods to make recombinant protein subunit vaccines. Working merely from a technical standpoint (ie, ignoring institutional and regulatory barriers), if work began in 2006, the US could deploy a capability to generate [untested] emergency DNA vaccines within a week by 2008, and a recombinant capacity to generate [untested] emergency protein subunit vaccines within 8 weeks, in 2 years, by 2008.

The non-emergency testing of vaccines is slowed by the fact that the immune systems of mice and humans differ significantly, while human-like primates are scarce, so that testing for efficacy depends directly on human experimentation, through that expensive and highly regulated medium of the "clinical trial". Over a 5-7 year time frame, a longer term response to these deficiencies would include heavy investments in improved functional genomic approaches to understand how and when the generation of immunity by vaccines succeeds or fails, in further development of improved computational approaches to predict B and T cell epitopes, and in the creation of freely available "massively humanized" mice that contain the entire B-cell and T-cell system from humans as well as the full complement of human cytokines and cytokine receptors. Those capabilities could become available by 2010 or shortly thereafter and significantly improve the first order Period 1 emergency DNA and recombinant subunit vaccine infrastructure

b) Agile ability to generate new small molecule drugs.

For small molecule drugs, there have been continued increases in knowledge of protein structure, in the ability to manipulate protein structures and small molecules *in silico*, in combinatorial chemistry and in high throughput directed chemistry. Taken together, these advances now make it possible to imagine technical paths that would allow identification of reasonably potent small molecules rapidly, perhaps within weeks of isolation of a new pathogen and identification of protein targets encoded by the pathogen's genome. Similarly, it may well be possible to establish surrogate markers for

side effects that arise during preclinical testing (animal tests) and clinical trials (human tests) of these small molecules. Such surrogate markers could provide quick but crude information about safety and efficacy. At this point it seems quite possible that there are patterns of gene expression in white cells of mice and people that provide early warnings of drug induced toxicity such as kidney damage. It would be reasonable to imagine that a directed research program could result in the ability to go from a new pathogen to millions of doses of an experimental small-molecule drug in 6 months by 2012, and in 1 month by 2020 (table 3). Periodic monitoring using the technologies developed for Period 1 detection would provide real time warning of side effects.

c) Agile ability to generate new protein drugs, other therapies, and prophylaxes.

For protein drugs, from this same high-altitude viewpoint, there are essentially no technical impediments now to the rapid development of receptor-, ligand-, and antibody-type protein drugs. In particular, given an accelerated testing regime, it should be possible-- using existing technology-- to field neutralizing humanized soluble monoclonal antibody derivatives directed against a new toxin, or that confer passive immunity to a new pathogen within weeks of its isolation. The same ability to isolate and rapidly produce new antibodies for an agile specific diagnostic capability could be used to generate antibodies for use as experimental drugs and to confer passive immunity (figure 7), and it could be available in the same time frame, circa 2008-2009 (table 3).

c) Social and normative elements of Period 1 strategy

There is a gamut of non-technical steps that the US can undertake during Period 1 to increase safety. As with technical means, non-technical means can supply capabilities that can contribute to the overall Period 1 patchwork, even if they are only partly effective. To give examples of steps of this kind, it might be possible for the US to lead in creating an international ethical environment where it is expected that biological engineers embed hallmarks and signatures in the DNA code they write, and in which the design and deliberate release of a biological organism that causes harm is both a criminal act and regarded with near universal loathing, on a par with slavery or child molestation today. Even if these cultural controls sometimes fail (as, in the case of terrorist groups, they often will), they can help bring about a normative and ethical climate (Kwik et al, 2003) in which aberrant behavior is more likely to come to the attention of government and international agencies that handle intelligence, enforcement, and preemption. Table 5 lists a number of possible "social" and "normative" steps that might be of some value in this sphere. By contrast, Table 6 lists other possible tactics that may not be of much use for biological defense in the world of the RBC. Most of these come from the cold war era controls on materials and knowledge for nuclear weapons.

d) Barriers to attaining technical and non-technical elements needed for Period 1 defense

A full exposition of the barriers to achieving the Period 1 technical capabilities is well beyond the scope of this article, but the main ones deserve to be listed. Many of the

technical goals are expensive; attaining them probably will require continued expenditures that exceed $10B/ year. Achieving them will require directed effort now scattered throughout numerous disconnected executive branch agencies, mission statements, and constituencies. Achieving them will require learning how to perform directed biological engineering and directed scientific research in biology, and how to orchestrate the activity of complex combinations of public and private entities. Achieving them will require reconfiguring of the current industrial, investment/ capital, and intellectual property structure to facilitate creation of an industry that has appropriate incentives to combine existing capabilities into working devices and systems and whose profit margins and investor expectations are lower than they now are in biology, more in line with those now found in aerospace than in pharma (for a taste of how complex the creation of a new industrial structure to support needed technical development can be, see the description of the Atlas missile program in Hughes, 1998).

By comparison with these barriers to attaining technical capability, the barriers to achieving social/normative capabilities largely consist of configuring US diplomatic efforts so that other countries and international organizations will support our objectives. Achieving these "social" objectives may be difficult but will be cheap compared to the costs of building an adequate national detection network, an agile vaccine development capability, and the like.

5) Strategy for entry into Period 2, "Partial Victory" or "Basin and Range"

Period 2 is defined by capabilities that might allow defense so strong at to constitute deter attack, even by individual attackers and terrorist groups. Most of these capabilities have at least one of two characteristics: they are difficult to achieve, or they are radical. The last point is probably most important. Most of the capabilities one can now imagine utilize means to eliminate infectious disease as a factor in human affairs, or otherwise impact the human condition, in ways that many citizens might find disquieting (table 5).

In some cases, Period 2 technical capabilities cannot be attained by the guided research that characterizes Period 1, but rather will require setting a clear goal and then spending money on otherwise-undirected research for decades. Examples of such goals might include the ability to field, in 24 hours, specific combinations of epitopes and cytokines that can program the human acquired immune system to create immunity to a new pathogen in 24 hours. They might also include devising combination of protein and/or small molecular therapy to create, within 24 hours, a temporary increase in innate immunity during a period in which a population was under attack. These kinds of capabilities could well be achievable in a 20-year time frame, but their use would likely have severe side effects for some members of a population.

Other imaginable Period 2 defenses could be achieved by directed engineering and directed scientific R&D programs, but many citizens might find them dangerous or morally fraught. Examples include the creation of classes of live infectious gene therapy vectors that can be customized in a day to infect specific cell types or the majority of cells in the body, in order to deliver tailored protein vaccines, or small inhibitory RNAs

(siRNAs or RNAis) to block replication of the pathogen. Such live infectious gene therapy vectors could find "dual use" as weapons platforms. Another example would be to follow up on serious ongoing discussions, and begin to perform genetically engineering to extinguish microbial pathogens, and even create species- specific deleterious transposons to extinguish naturally occurring animal reservoir species (Morton, 2003). Yet another (and technically simpler) idea is to endow every human child, on conception *in vitro*, with a Human Artificial Chromosome (HuAC) that directs the synthesis of RNAis directed against genes specific to the top 25 human viruses, arranged so that it is flushed from the germ cells so that the children of resistant children can be endowed with an improved version (figure 8). Such HuACs could have been assembled (and tested in cell culture) using 2003 (or 2005) technology in 6-9 months, but the political debate that might affect their testing and deployment might span the full 20 years of Period 1.

Period 1, "the "Valley of the Shadow of Death", is of course unstable by definition. But because of the possible ingenuity of human attackers, there is no reason to assume that Period 2, when technical capabilities and trends favor strong defense, will be stable either. For that reason, even "Victory" by entry into Period 2 is likely to be only partial, as further trends and technical developments might sometimes shift the balance back to give the advantage to ingenious attackers, then as further work by the defenders shift the advantage back to favor defense. These possible shifts give Period 2, "Partial Victory", its other name, "Basin and Range"

6) Conclusion

The US faces the problem of articulating, creating and applying technology and policy to provide security in a situation made unsafe by an ongoing revolution in biological capability. This is a complex task. The US has, however, faced a task of similar complexity before, in the middle 20th century, as it sought security in a world that contained another superpower armed with nuclear bombs. In the first decades of the Cold War, the US generated technologies, policies and actions that collectively helped keep the peace, although the package required creation of entire new institutions (such as RAND) and took years (1945-1970) to perfect. The sooner the country can begin similar work in biology, the lower the chance that the US will suffer catastrophic loss of life after an attack.

However, by contrast with the situation for nuclear physics during the Cold War, the US needs to configure and execute its security strategy for biology in the middle of an ongoing revolution in the technical means to create the threat and to defend against it. This revolution is largely of US making. The country is benefiting greatly from it and must depend on its continuing progress to generate technical capabilities required for safety. Although this is a difficult set of starting constraints, there is some historical precedent for crafting security policies in such times. During the late 18th and early 19th century, the US successfully started a revolution and channeled its outcomes to acceptable ends, while crafting security policy that exploited the revolutionary forces that were then loose in the world.

Crafting and executing a sensible strategy will work to the advantage of the US. While good policy will increase human happiness and economic growth worldwide, many of its first fruits, in terms of better health, and the lion's share of the new economic activity, will come to the US. Moreover, articulating and embracing the proper policies will allow the US to exercise the strategic initiative in biology; and the advantages accruing to the US from strategic initiative in this sphere should be even greater than those that accrue to the US from its ability to exercise strategic initiative in computers and the Internet. To be most effective, the eventual US defense strategy should be subsumed into a larger strategy that, among other things, exploits biology to address issues of poverty and disease in the less affluent world. A thoughtful grand strategy for biology will help channel the revolution in biological capability to help bring about a safer, more democratic, more prosperous world in which Americans can lead good lives.

Acknowledgments and notes

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In general, technical progress between 2003-2005 has been substantial but steady, and the most noteworthy technical revisions in this 2005 document reflect developments in "proteomics" and molecule detection technologies that could provide promising capabilities during Period 1. By contrast, there has been very little progress in implementing defense measures. In particular, the major point of the 2003 paper, the

criticism of the "fixed defense" strategy implicit in the "Bioshield" legislation, still holds, and will continue until such time as it is replaced with a defense strategy that better reflects the realities of the 21st century world.

That said, there are two important differences between the analysis in 2003 and this apprehension of the strategic situation in 2005. The first is that, even though fixed defenses are Maginot lines, some effort on Maginot lines seems unavoidable. Just as, in a democratic France during the 1930s it would have been imprudent and politically impossible not to fortify the border with Nazi Germany, in the US in the 2000s, it is not politically possible not to stockpile defenses against pathogens such as unmodified smallpox and anthrax. The point is that policymakers now must consider when to halt construction of further fixed defenses and begin to build agile ones. I am grateful to Stephen Johnston and Ben Petro for making this point convincingly. The second is that, given the likely ingenuity of possible human attackers, success at bringing about strategic Period 2 ("Partial Victory") may not result in a lasting stable period. Should Period 2 begin, it is possible that the balance of technical trends may shift yet again to favor attack, and then perhaps shift yet again favor defense. Although I had realized that Period 2 would not necessarily be stable, I had not faced up to the necessity of articulating that as part of a proposed strategy. I thus am grateful to a number of people, including Drew Endy and Stephen Johnston, for making the point, and to David Relman for proposing the term "Basin and Range" to describe this likely landscape. If Period 2 does have an end, it likely lies in significant transformation of the human species by means including biological engineering. This is an important topic, but it lies beyond the scope of this article.

Finally, I dedicate this 2005 paper to Andrew Marshall, whose life's work has demonstrated consistently how useful good strategy can be.

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Tables and Figures

Table 1. Some key technical capabilities enabling the RBC that have developed significantly over the past two decades.

DNA sequencing
Oligonucleotide synthesis
Chemical synthesis of long stretches of double stranded DNA
Improved ability to make very large DNA constructs by recombination *in vitro* and by serial recombination *in vivo*
Improved ability to introduce DNA constructs into cells and organisms and control gene expression from them
Diversity-generation-selection techniques, including combinatorial affinity reagent approaches and "DNA shuffling"
Control of cellular phenotypes such as differentiation state, induced immortalization
Derivation of adult animals and plants from cells engineered *in vitro*

Table 2. Strategic periods 1 and 2. See also figure 4.

Period One: "The Valley of the Shadow of Death"
Technical trends shift ever more in favor of offense
Spans from present until start of Period Two (2025 at the earliest)
Patchwork of social and near-term technical measures initiated 2005-2006 begins to bring about rough equilibrium between trends favoring attack and trends favoring defense
Security during this period is less than US enjoyed in 1970-1995
Period Two: "Partial Victory" or "Basin and Range"
Technical work *(undirected scientific research, directed scientific research, and directed engineering)* initiated 2005-2009 bears fruit
Technical trends shift decisively to favor defense
Defense becomes good enough to offer deterrence
Race between defense and offense persists, trends may shift again to favor attack

Table 3. Stratification of possible attackers. Table guesses level of threat given continuation of current trends, including current efforts to build countermeasures assuming Period 1 type measures not undertaken. Threat level diminishes if realistic countermeasures are implemented.

Types of Attackers ***(2005)***	**Types of Possible Attackers** ***(2015-2025)***	**Level of Threat in** ***2005***	**Level of Threat in** ***2015***	**Level of Threat in** ***2025***
Nation States	Nation States	Low	Lower Still (relatively)	Can't Call
Sub and Trans-national Groups	Sub and Trans-national Groups	High	Very High	Very High
	Disaffected Individuals and Garage Hackers	Low	Medium	Very High

Table 4. Possible Period 1 technical capabilities. Table shows possible capabilities, including fixed defenses, general detection capabilities, and agile response capabilities, the types of attackers against which they might be effective, and a guess at the time needed to achieve them if the US started trying to develop them in 2005-2006.

Possible protection conferred by existing (2005) or newly initiated measures	Nation States	Sub and trans-national groups	Disaffected individuals and garage hackers	Time to OP/TAC capability if US initiated sensible actions soon
Deterrence and civil defense via stockpiles of drugs and vaccines against predictable threats or threats discoverable by intelligence	+/-	+/-	-	Could do some deterring of clueless terrorists and disaffected individuals now, but gets easier to engineer around so spent by 2010
Deterrence and civil defense via improved ability to detect and respond to an attack	+/-	+/-	-	Boxes below show time to attain different components
• Establishing baselines and broad-purposed detection systems in people	→			2009 for systems using 1990's tech
• Establishing baselines and broad-purposed detection systems for plants and animals	→			2009 for systems using 1990's tech
• Establishing baselines and broad-purposed detection systems in environment	→			2009 for systems using 1990's tech
• Agile ability to generate specific diagnostics	→			Exists for nucleic acids, 2008 for other markers
• Agile ability to generate vaccines	→			2006-2007 for DNA vaccines, 2010 for protein

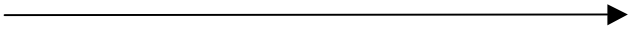
• Agile ability to generate small molecule drugs		2025
• Agile ability to generate human antibody and other prophylaxes		2009

Table 5. Period 1 social capabilities. Table shows non-technical protective capabilities that might be helpful during Period 1, attackers against which such measures might offer protection, and time it might take to achieve them if the US began seeking them in 2005-2006.

Possible protection conferred by existing (2005) or sensible future operational and tactical capabilities	Nation States	Sub and trans-national Groups	Disaffected individuals and garage hackers	Time to OP/TAC capability if we initiated sensible actions soon
Deterrence via international treaties and criminal law	+	-	+	Exists now. 2007, for improved regime
Deterrence via threat of military counterattack	+	-	-	Exists now
Disruption via counter-intelligence and counter-terrorism activities	+/-	+/-	-	Exists now? Must make way better
Surveillance of threatening activity using watchlists for equipment and reagents	-	+	+	2005-2006, May be of some utility

Surveillance, disruption and deterrence by stings, honeypots, and other spooky tactics	-	+	+	2005-2006, May be of some utility, in at least taking the pulse of the world

Table 6. Other imaginable protective capabilities. These are taken from Cold War period controls on nuclear materials and knowledge. Table illustrates that these may not be useful during Period 1 and Period 2.

Protection conferred by other imaginable future operational & tactical capabilities	Nation States	Sub and trans-national groups	Disaffected individuals and garage hackers	Reasons not a great idea
Control of biological material, strains, viruses, etc.	-	+/-	+/-	Almost irrelevant already. Irrelevant for all classes of attackers by 2010-2015
Control of microbiological equipment	+	-	-	Large production runs, weaponization, irrelevant for contagious diseases used by terrorist groups and by individuals
Control of key reagents	-	+/-	+/-	Would require worldwide enabling legislation, and worldwide enforcement
Synthetic DNA Internet surveillance, “Total Sequence Awareness"	-	+/-	+/-	Will be perceived as evil, and will be circumvented
Control of knowledge of weaponization	+/-	+/-	-	Nation States will learn anyway, concept is irrelevant for contagious diseases spread by some terrorists or Kaczynski-types

Control knowledge of construction techniques	-	-	-	Cat unstoppably out of bag, too much positive economic payback and power from ongoing revolution
Control knowledge about disease mechanisms	-	-	-	Unprecedented global censorship regime throws babies including future progress in defense out with the bathwater

Table 7. Possible technical capabilities characteristic of Period 2, "Partial Victory". These are examples only, as it impossible to be definitive as to what technical capabilities might be achievable in 20 years time.

Combination of antigen presentation schemes and cytokines allows rapid (~24 hour) programming of human acquired immunity against new pathogens.

Cocktail of cytokines and/or other small molecule drugs allows rapid (~24h) hyperactivation of human innate immunity.

Ability to rapidly deploy tailored transmissible genetic elements (transposons) to extinguish animal reservoir and vector species.

24 hour ability to make and release live broad host range self replicating gene therapy vectors that rapidly spread through population to counteract new pathogen.

Endowing humans at conception with Human Artificial Chromosome (HuACs) that makes siRNAs that confer immunity to top 20-50 human viruses.

Figure 1. Popular "how to clone" it manuals. Current Protocols in Molecular Biology is continually updated by subscription (1987-2005). It has about 10,000 subscribers worldwide. Molecular Cloning (first edition 1982) has sold almost 200,000 copies in various editions. The book at bottom is an authorized short version of CPMB in Japan. Pirated English editions of CPMB in China and Japan have been widely available for purchase for at least 15 years.

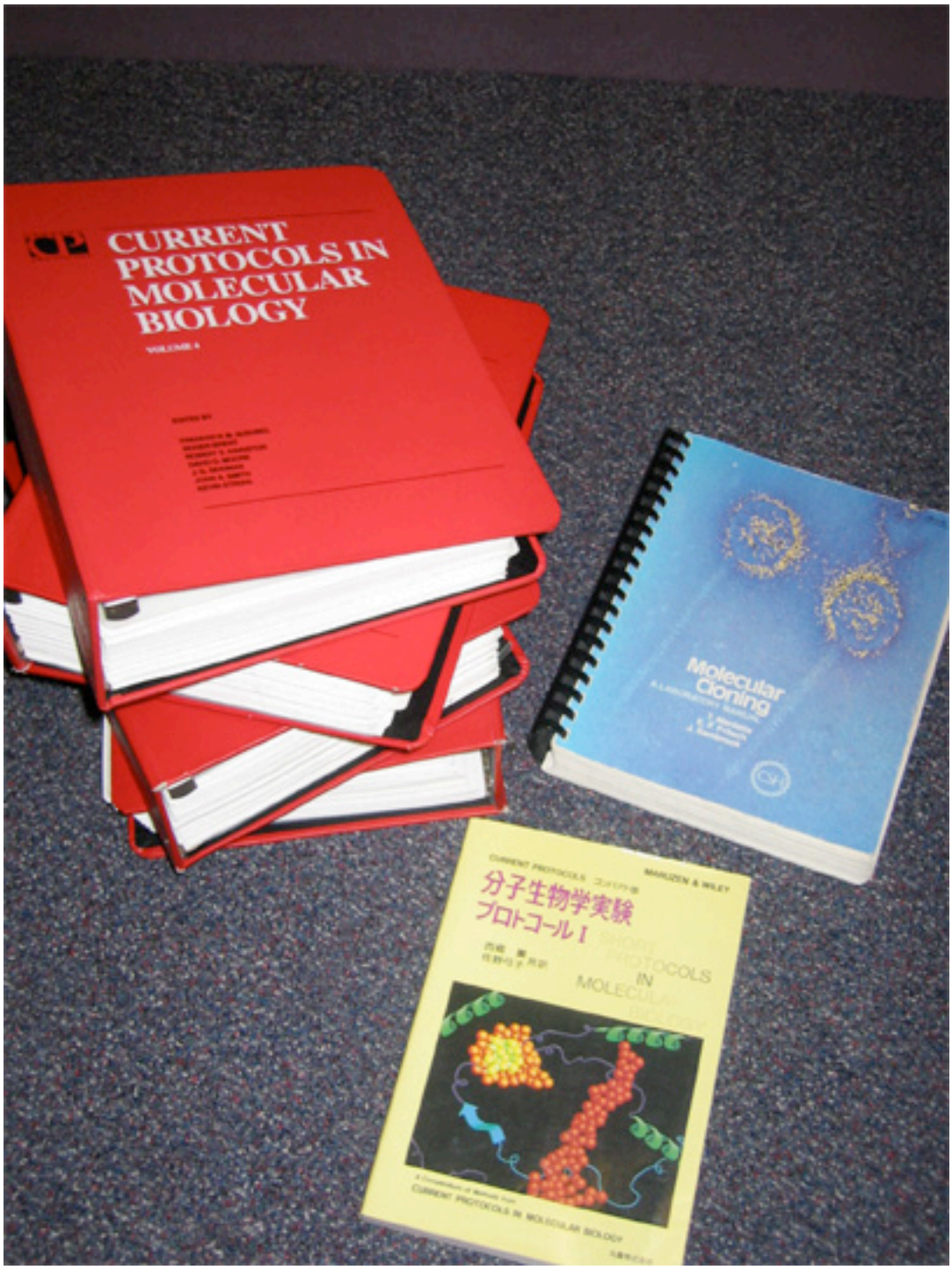


Figure 2a. **DNA synthesis in an everyday lab.** Work area for an ABI 394 DNA/RNA synthesizer. Post-it note shows scale; the entire machine takes up three feet of space on a lab bench. The synthetic DNA is made in the four columns in the upper left. The 394 can synthesize ~1000 bases of DNA per 24 hours. Tens of thousands of such machines are in daily use worldwide. New and used synthesizers are commonly sold on E-bay and other Internet market sites; in 2005, the market price of the used machine shown here would be about $12,000. Many labs do not synthesize their DNA but instead order it from one of many hundreds of small, transitory commercial suppliers in the US and in other countries. Photograph from MSI, Berkeley, California, 2003.

Figure 2b. Large scale DNA synthesis in a company dedicated to this task. The technician operates a commodity PC that controls a multiplex parallel DNA synthesizer built from off the shelf commercial components. Note the relatively modest footprint of even the large setup. Photograph courtesy Glen Evans, CEO, Egea Biosciences, La Jolla, California, 2003.

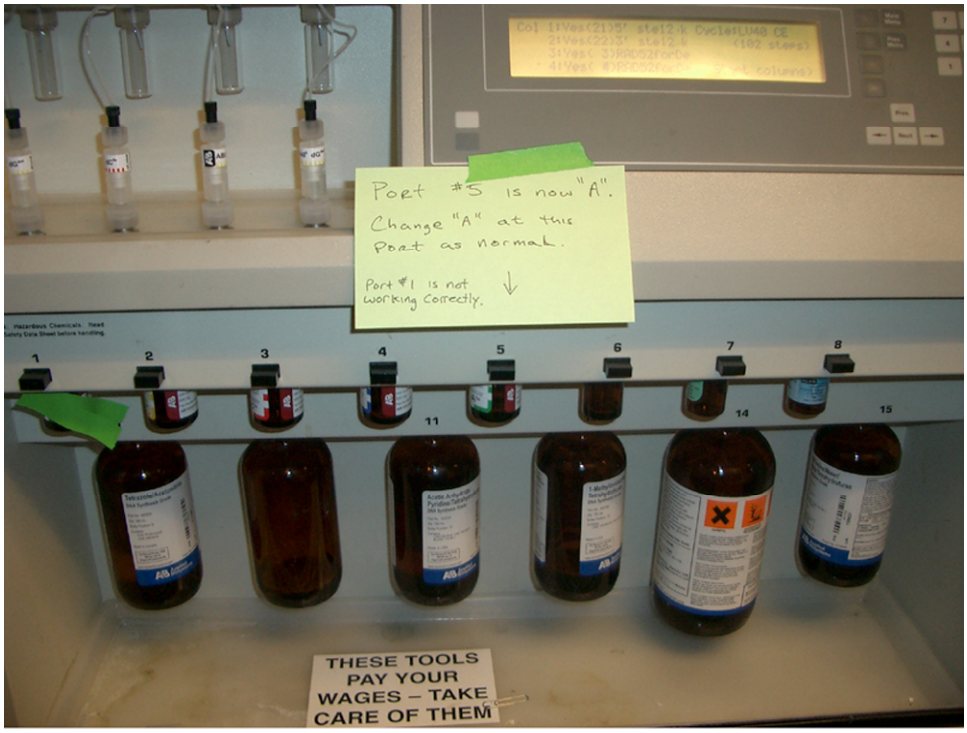

Port #5 is now "A".
Change "A" at this
Port as normal.
Port #1 is not
working correctly.
THESE TOOLS
PAY YOUR
WAGES – TAKE
CARE OF THEM

Figure 3. Increasing capability for DNA synthesis. Figure shows the "Carlson curve" for DNA synthesis and is redrawn from Carlson (2003). In this semi-log plot, the Y axis shows the number of DNA bases that a single person with appropriate equipment can synthesize in a single (24 hour) day. Y axis may overstate true numbers, in that DNA needs to be assembled into larger pieces and the sequence verified, but it makes the point that the trend is up and that capability is growing steadily, in fact, apparently exponentially. One can make similar curves for DNA sequencing (Carlson, 2003) and for the ability to assemble large DNA constructions such as complex plasmids and artificial chromosomes.

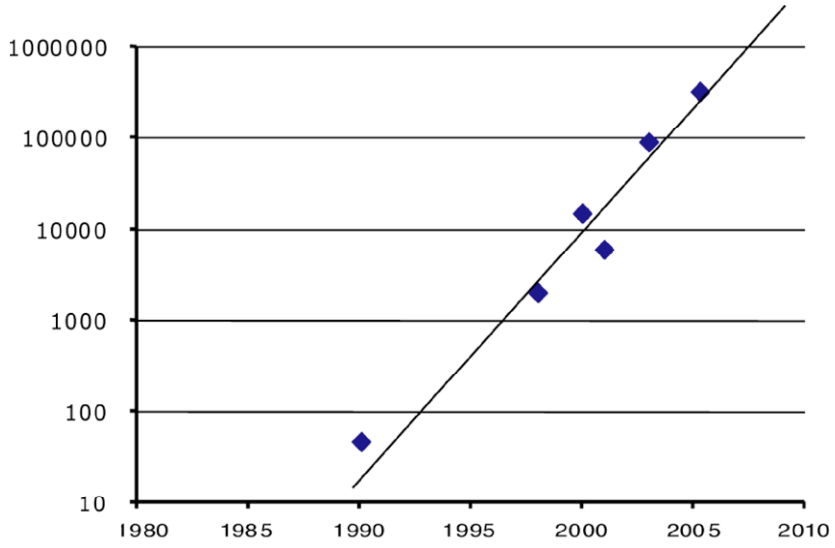


Figure 4. Risk of catastrophic biological attack on the US as a function of time. Here, I arbitrarily define "catastrophic" attack to mean >3M dead or so disabled as to require permanent care, and arbitrarily denote scale on the Y axis from "lower" to "higher". Figure shows three trend lines. A shows the "valley of the shadow of death", is the risk if current trends continue, even if "fixed defense" stockpiles of drugs and vaccines are built. B shows the risk if Period 1 general detection, agile response, and social capabilities become operational. C shows the trendline if strong Period 2 technical defenses can come on line. Dashed component of the C line indicates that technical trends could shift again to favor attack, and again to favor defense, which gives the period the name "basin and range".

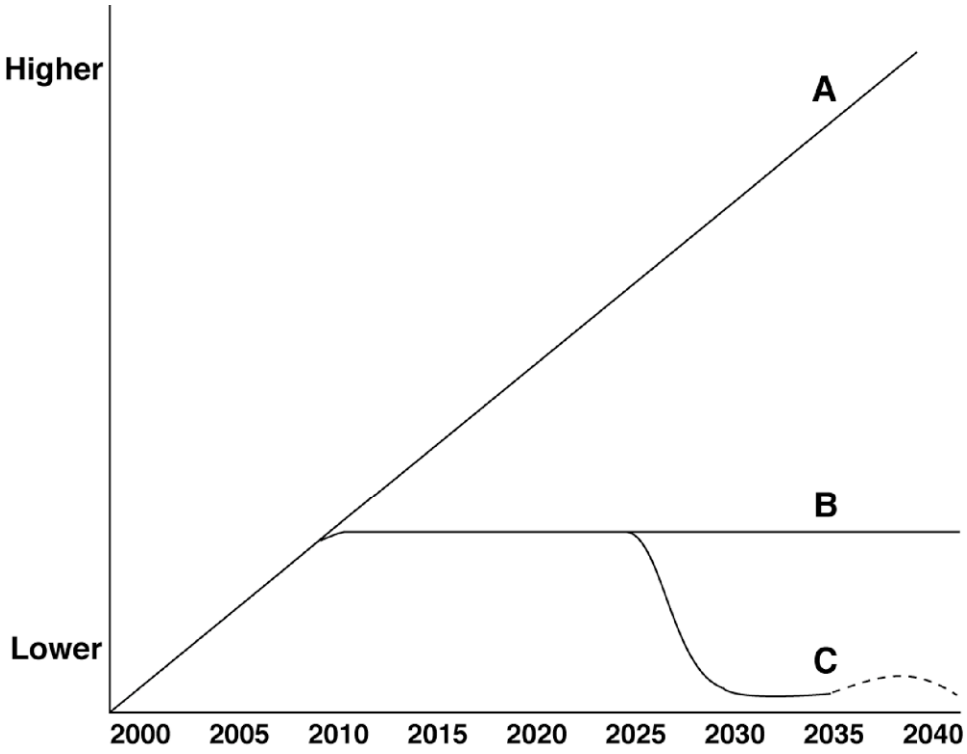


Figure 5. A system to provide situational awareness of the microbial genomic environment. This is a Period 1 technical capability for general detection. Construction of such a system would now be an engineering endeavor rather than a scientific one; the technology to build it continues to improve rapidly but all of its components have existed since the middle 1990s. New components can be inserted into the system and old ones replaced by newer ones as different monitoring methods become cost effective. Improvements in detection of proteins and other arbitrarily designated molecules should allow integration of the ability to detect and inventory non-nucleic acid molecules into the detection system by later this decade. A system that included these components would provide near real time information about the normal composition of the microbial environment and alert public health and defense authorities to deviations from it and the to appearance of new organisms. Diagram makes the point that the needed capability is not a set of deployed devices, but rather a system of systems much like the overlapping radar, satellite and other detection mechanisms that comprise the detection component of the North American air defense network. In the US, a few components of such a system, shown on the upper left, are in place: such as very limited monitoring of city air for a few known pathogen species. However, available public data suggests that most detection components, including the ability to gain general sequence information, and, in particular, the ability to assay RNA genomes, from the environment and from patient samples such as throat swabs, are not. Moreover, the US does not now possess other needed parts of this system, including proper analytical and software tools to visualize and exploit this data, and a national or international entity can integrate this data to generate a near-real-time assessment of the current microbial situation. Because an attack or emergent disease could begin anywhere in the world, detection components (sensing nodes) for a detection network would eventually need to be globally deployed.

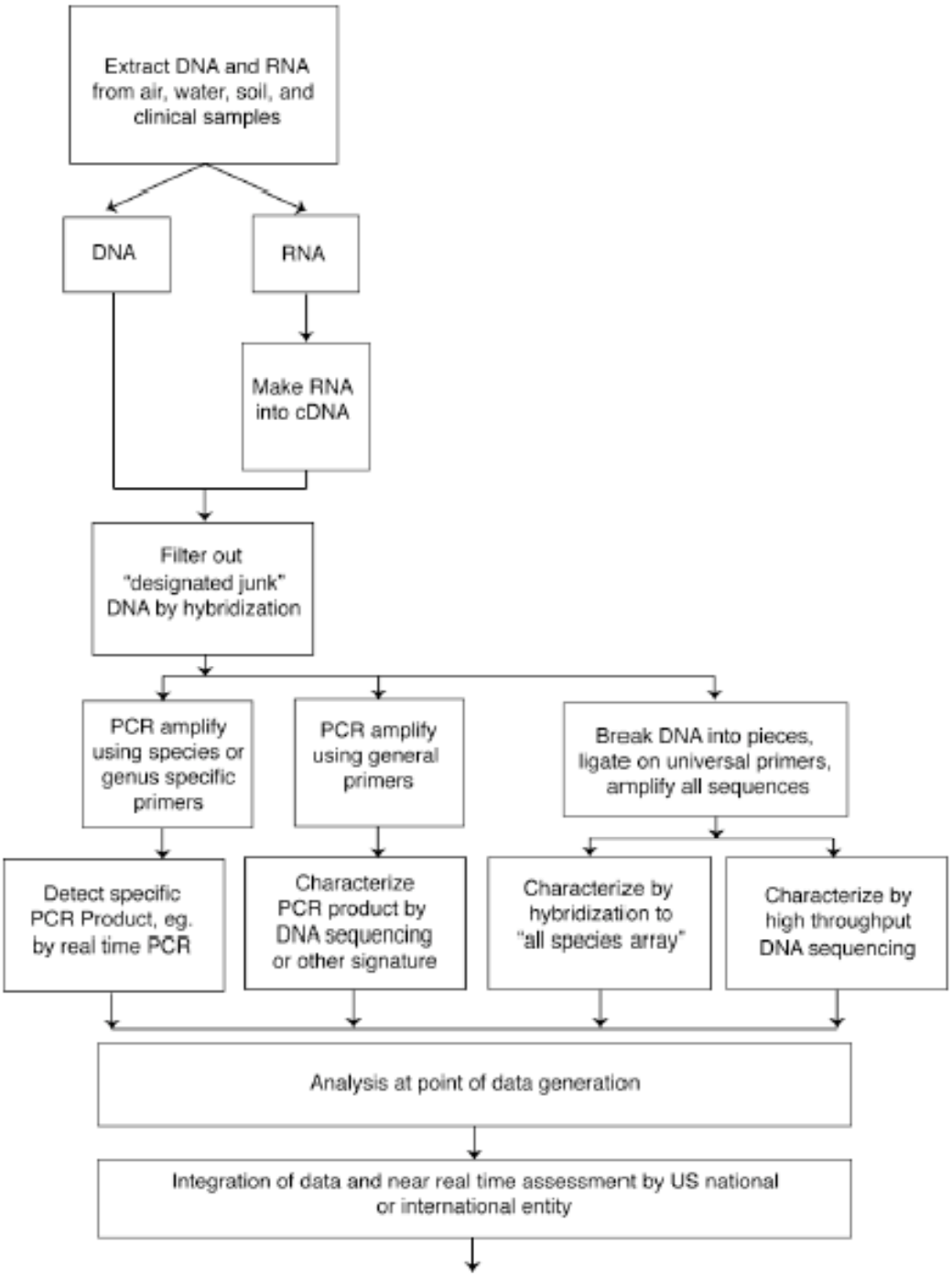

Extract DNA and RNA from air, water, soil, and clinical samples
DNA
RNA
Make RNA into cDNA
Filter out "designated junk" DNA by hybridization
PCR amplify using species or genus specific primers
PCR amplify using general primers
Break DNA into pieces, ligate on universal primers, amplify all sequences
Detect specific PCR Product, eg. by real time PCR
Characterize PCR product by DNA sequencing or other signature
Characterize by hybridization to "all species array"
Characterize by high throughput DNA sequencing
Analysis at point of data generation
Integration of data and near real time assessment by US national or international entity

Figure 6. Detection, diagnosis, and assessment of infections by surveying signatures of gene expression in white cells. Another Period 1 general detection capability. In this case the capability enables diagnosis and assessment of known diseases and new diseases in people. PBMCs (Peripheral blood mononucleocytes, here simply called white cells) circulate freely in the blood and so encounter most of the kinds of cells in the body. They respond to conditions they encounter, for example contact with inflamed tissue or infection, by changing the pattern of genes they express. Genes (in white cells as in all cells) are transcribed into messenger RNA (mRNA). In response to a new condition such as infection, some of the genes make less mRNA (down arrows), some make more (up arrows). The pattern of deviations from this baseline constitutes a signature of disease states. Some deviations from the normal state, shown in blue, may be common to all infections, while others, show in here in purple, may allow discrimination among diseases caused by different pathogens, and specific assessment of disease states. Information flowing from routine monitoring of sentinel individuals and from patients during outbreaks should flow to the same data integration and assessment entity shown in figure 5. The technology to collect these signatures dates from the 1990s. Leaving aside (for the moment) intellectual property and regulatory considerations, it is entirely reasonable to imagine that devices that enable such assessments could be manufactured for contract prices of $100 per unit in production runs of 1-10M units. Government action to create such large production runs could, as happened in the semiconductor industry, create a climate of continually increasing performance and reduction in cost, and jump-start an industry whose products will enable greatly improved point of care medical diagnosis and routine (for example, annual) monitoring for health maintenance.

Figure 6

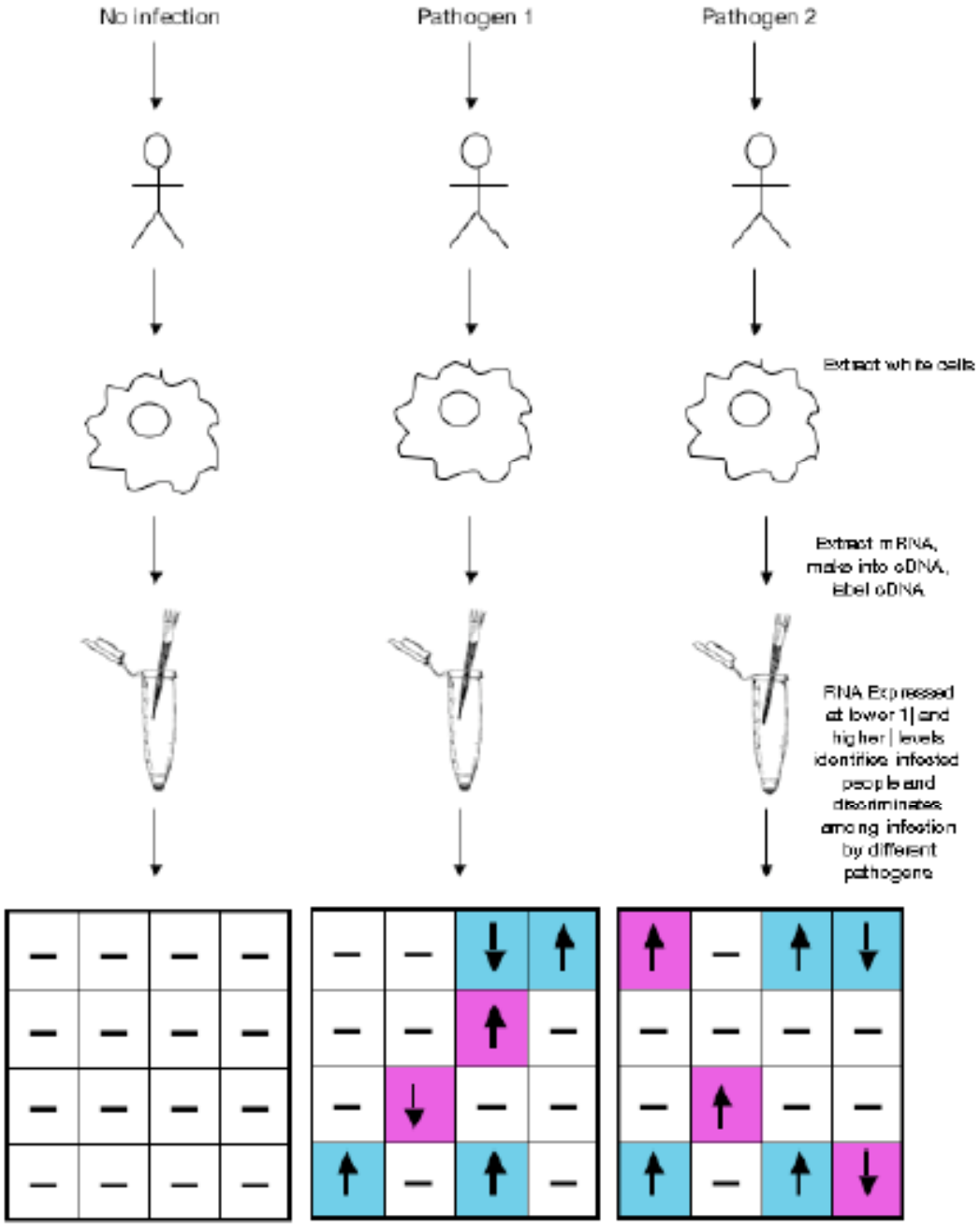

No infection
Pathogen 1
Pathogen 2
Extract white cells
Extract mRNA, make into cDNA, label cDNA
RNA Expressed at lower | and higher | levels identifies infected people and discriminates among infection by different pathogens

Figure 6

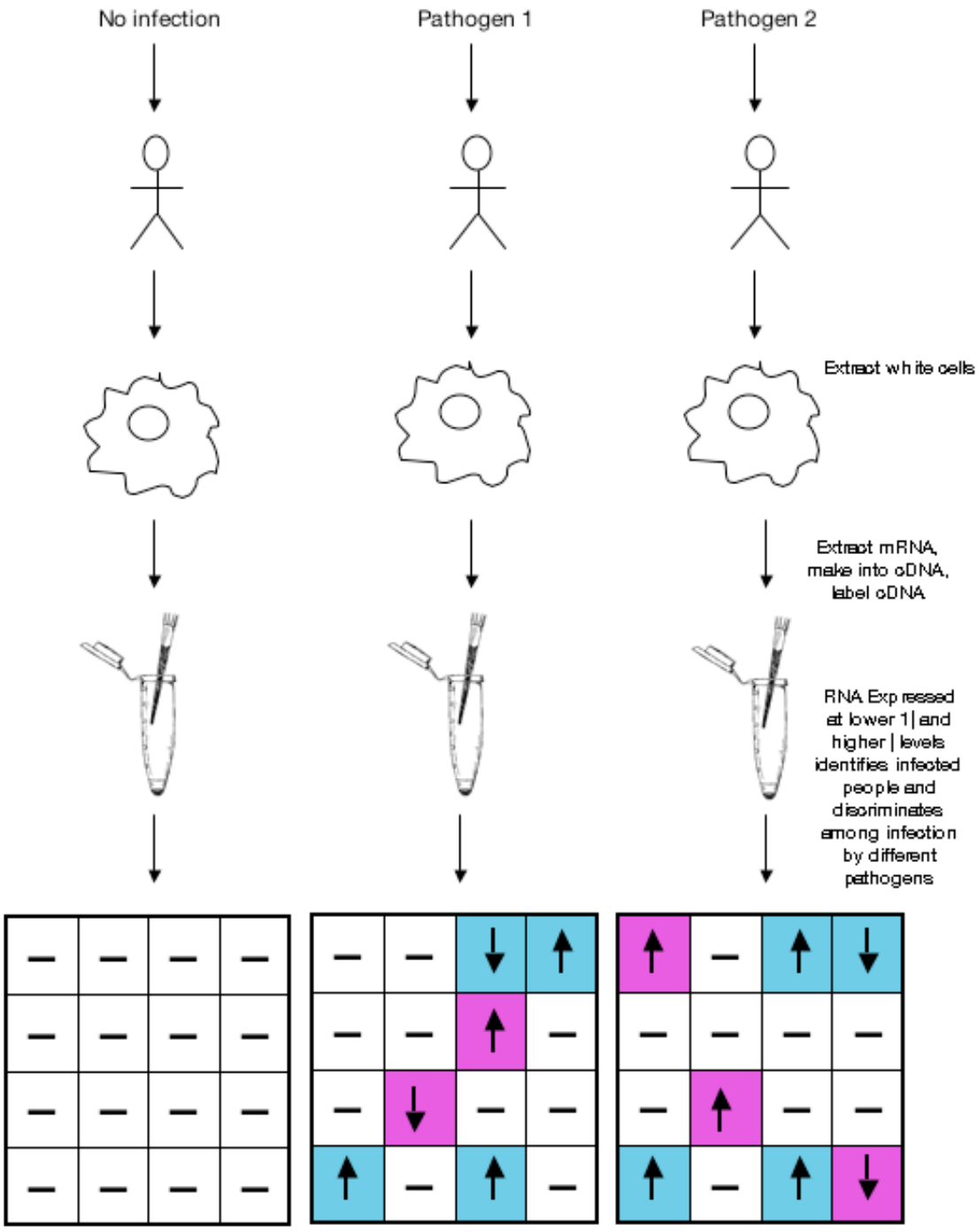

No infection
Pathogen 1
Pathogen 2
Extract white cells
Extract mRNA, make into cDNA, label cDNA
RNA Expressed at lower | and higher | levels identifies infected people and discriminates among infection by different pathogens

Figure 7. Industrial recombinant production of human antibodies in mammalian cells. An example Period 1 agile defense capability. Photograph shows plumbing and access through tops of two 12,500 liter reaction vessels ("bioreactors") in a production suite at a California biotechnology company; the bodies of the vessels extend downward by another 2 stories. Commercially, human antibodies are now used a therapeutics for human diseases such as cancer, but antibodies produced in such facilities could also be used for human disease prophylaxis, to confer temporary (six week), "passive" immunity to new pathogens. A kilogram of neutralizing antibody should be able to confer passive immunity to a million people. Current production levels for recombinant antibodies are well above 1mg/ml in two weeks, even using the "transient transfection" methods that would allow newly-cloned antibody genes to be put into industrial production most rapidly. A plant built around this production suite could produce more than 25 kg of antibody every two weeks, or more than 50 million doses of protective antibody from the first month's production run. There is at present considerable worldwide overcapacity in GMP-certified commercial plant that can produce antibodies (Thiel, 2004). Even when that overcapacity has disappeared, the capital costs of a purpose-built, dedicated reserve facility that could normally be used for civilian purposes but that could be diverted to defense production in time of need would be significantly less than that of a single F-22 aircraft.

Figure 8. An nontransmissable HuAC that confers resistance to 25 human viruses. This is an example of a technical capability that might be characteristic of Period 2 ("Partial Victory"), in which defense is so effective as to deter attack. Figure shows a Human Artificial Chromosome (HuAC) to be introduced into fertilized human egg on conception *in vitro*. Testis- and ovary-specific expression of a site specific recombination protein (Cre) deletes centromere (Cen) and origin of replication Ori), so will not be transmitted into sperm and eggs, allowing parents who carry this construction to introduce new HuACs that confer desired traits into their own children. Chromosome contains constitutive promoters that direct the synthesis of an set (here, 100) different small inhibitory RNAs (RNAis or siRNAs). These 100 RNAis block the expression of 4 genes encoded by each of 25 chosen human viruses. This design uses only 2000-2005 technology; artificial chromosomes have been used in other mammalian species in research and agriculture for more than a decade. In 2005, it would take less than 12 months for a small research group to make this construction and verify its ability to confer resistance to viruses in cell culture. It would then take some additional years to test it in mice and primates. This kind of approach exemplifies a Period 2 capability that requires engineering work and testing, but not basic research, and so in principle could be achieved quickly, but it shares with other Period 2 technical capabilities the characteristic that it seems radical, and, because its deployment seems to offer significant changes in the human condition, might in practice not be attainable in much less than 20 years.

Figure 8

Technical publication information

In the valley of the shadow of death
v3 to 2005 NAS committee

Draft
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