Biological Weapons of Mass Destruction: The Present and Future Threat

Anthony C. Littrell
United States Army Medical Research Institute of Infectious Diseases

CONTENT

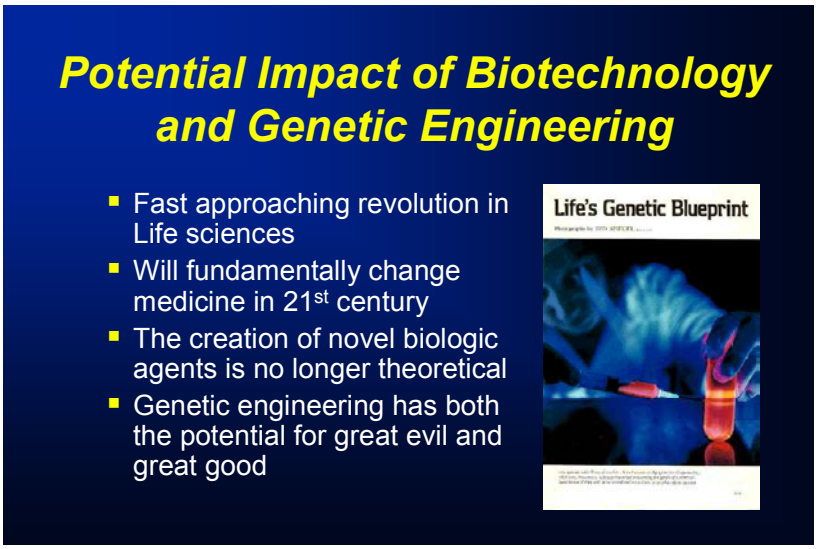
INTRODUCTION

This article discusses how the rapidly advancing field of Biotechnology is affecting the current threat of Bioterrorism and how this threat may evolve as we accelerate into the 21st century. We will also discuss how some of the current and developing technologies will change the way we respond to an episode of bioterrorism or biological attack. Topics for further exploration will include:

- The promise and risks associated with DNA recombinant technology.
- Black biology and how it could be used to attack our way of life.
- The promise of genomic analysis and how this promising new technology may be used to respond to a bioterrorist attack.
- Finally, I will conclude the article with a short discussion on the development of future preventive therapies and treatments for potential biological threats.

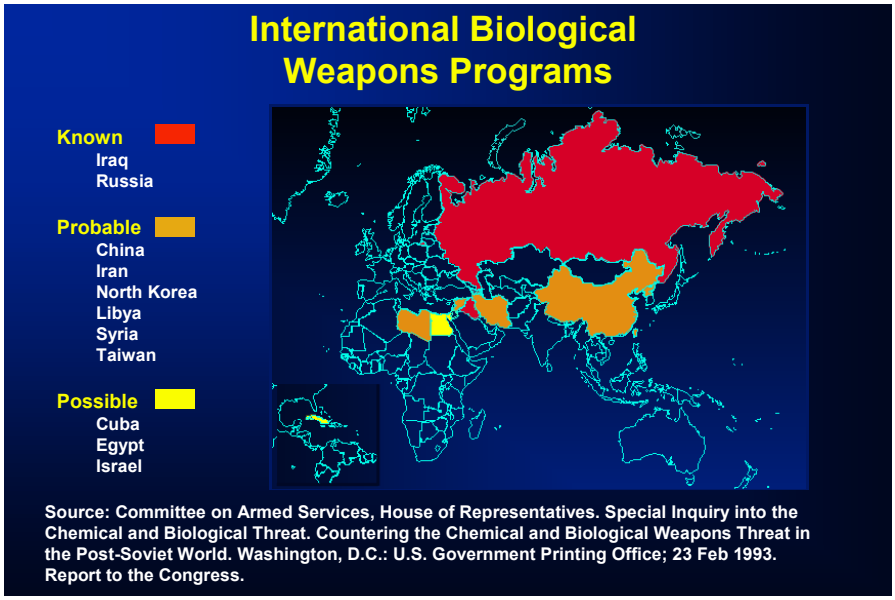
POTENTIAL IMPACT OF BIOTECHNOLOGY AND GENETIC ENGINEERING

The discovery that the basic nucleotide sequence data of virtually any biological entity could be purposefully altered, has profound implications for the future protection of civilization from the emergence of new or genetically engineered human pathogens. [1] Throughout the past several decades, scientists have been learning creative new techniques for altering DNA, which collectively now make up the rapidly advancing field of Biotechnology.[2,3] We currently stand on the threshold of a new era in which these advances in Biotechnology will begin to fundamentally change the practice of medicine in the 21st century. For example, the advent of gene therapy has begun in human subjects and is beginning to show promise in the treatment of metabolic diseases such as adenosine deaminase deficiency (ADA).[4] This is only the earliest ripple of a tidal wave of anticipated new forms of genetic therapy, which will involve the use of medically adapted genetic vectors.

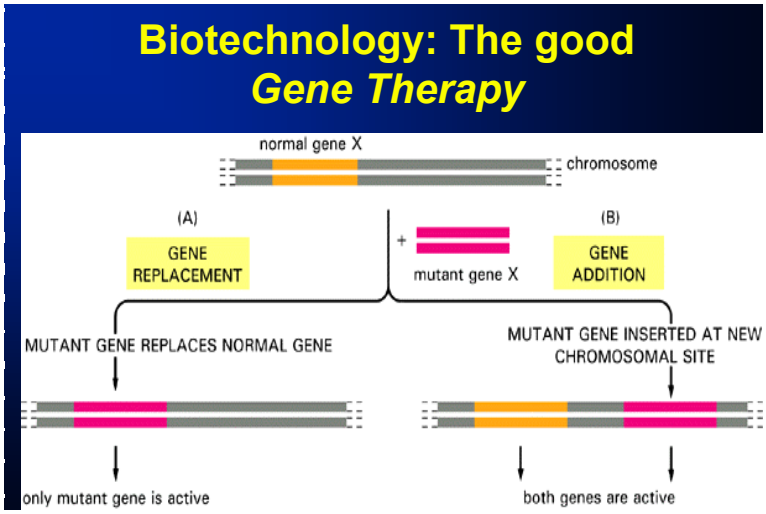


The rapid advance of the science of Biotechnology also has tremendous potential to alter the present and future threat of biological weapons of mass destruction [5,6,7] now as well as in the future. The explosion in the use of molecular biology to attempt to answer fundamental questions concerning microbial genetics, will lead to an increasing number of scientists with the basic understanding necessary to alter the underlying nucleotide sequence of a number of human pathogens. Already the complete or partial sequence data for a number of the most lethal human pathogens is known and widely available through the Internet. [8] This includes pathogens that have been responsible for some of mankind's most destructive epidemics including smallpox, human influenza, and the cause of the Black Death, pneumonic plague.

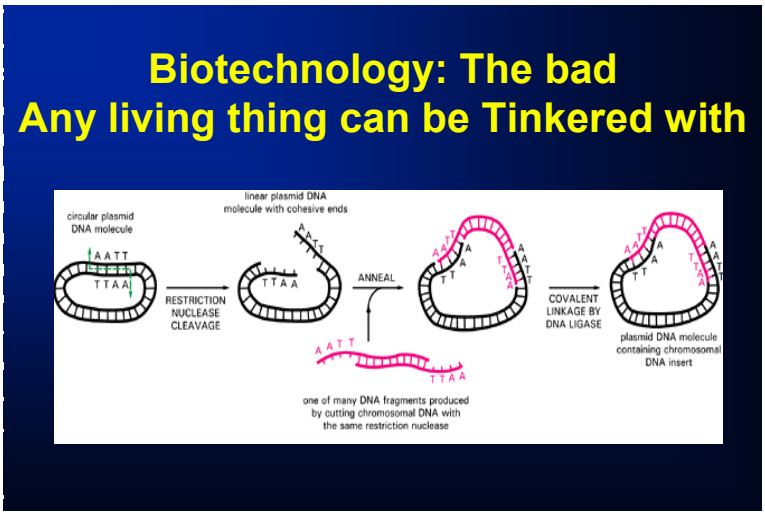
As we peer deeper into the genetic lock-box of human virulence characteristics of various viral and bacterial diseases, the pressure to experiment with these genes is likely to intensify and could result in either unintended release or a deliberate act of Bioterrorism. This could set off a biological arms race with far reaching and catastrophic consequences. The National Defense Authorization report of 1996 stated, "there is enormous potential—based on advances in modern molecular biology, fermentation and drug delivery technology—for making sophisticated weapons." [9] The potential for even a small group of sophisticated terrorists to wage a biological war against the United States is now at least technically feasible. Perhaps, even more disconcerting is the possibility that a genetically altered hybrid virus or bacterial pathogen could be unintentionally released into the environment. Both of these scenarios, while remote, present unique challenges to public policy-makers and those individuals and institutions charged with the responsibility for protecting the population of the United States from these kinds of potential threats.



Why should we take these threats so seriously at a time when government and public health resources are stretched to the limits of currently available funding? Because a number of technological trends have firmly taken hold and will collectively shape the future of our society. First, and perhaps most important is the increasing use of genetically engineered "vectors" for the delivery of medical treatments in the form of selectively engineered genetic information.[10] Altering somatically flawed DNA or replacing defective



genes with properly functioning genes offers the promise of new treatments to millions of patients now suffering from genetic diseases. To be effective, gene therapy takes advantage of specifically designed viral "vectors" such as adenovirus that delivers the new genes to targeted cells where they are integrated into the host's genome. Consider this statement, "Recombinant adenovirus is one of the most efficient viral vectors for gene transfer, both due to its high transduction efficiency, broad host range, ability to infect non-dividing cells, and potential for generating high titer virus." Its application is not just limited to gene therapy, but it can also be used as a basic molecular tool to introduce foreign genes into cells. [11]



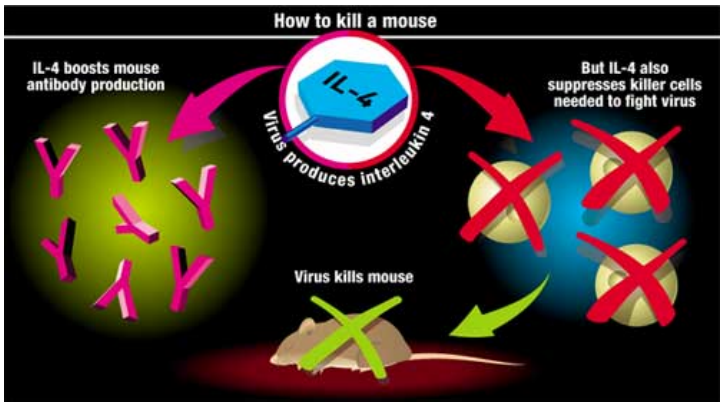
The pace of basic research on understanding the fundamental nature of microbial genetics and virology has accelerated tremendously over the past two decades. In addition, public access to basic nucleotide sequence data, through powerful new Internet based databanks, such as www.gdb.org and www.ncbi.nlm.nih.gov/BLAST, makes this information available to virtually anyone with a computer and Internet access. [12] While the vast majority of this information is of tremendous public benefit, some of this information has the potential to cause great harm as well. Table 1 below, lists a few of the many human bacterial pathogens that now have their entire genomes available for scientific study. [13]

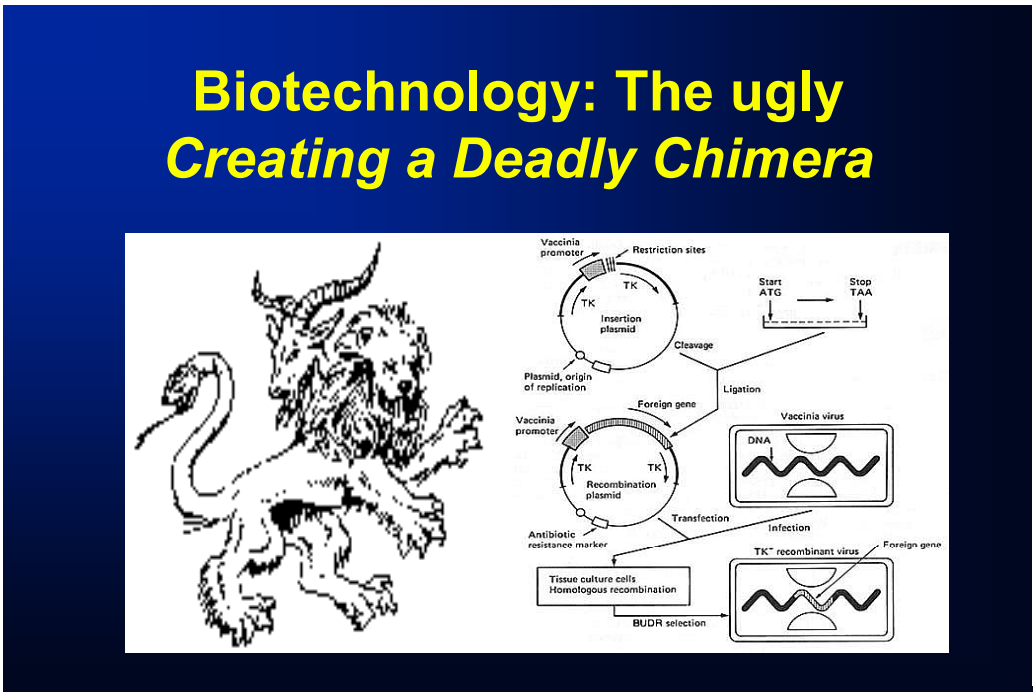
Table 1. Whole-genome sequencing of bacterial pathogens[a]

Bacterium	Status (ref.)		
Actinobacillus actinomycetemcomitans	In progress	*Bacillus anthracis*	In progress
Bartonella henselae	In progress	*Bordetella bronchiseptica*	In progress
B. parapertussis	In progress	*B. pertussis*	In progress
Borrelia burgdorferi	Finished	*Campylobacter jejuni*	Finished
Chlamydia pneumoniae	Finished	*C. trachomatis*	Finished
Clostridium difficile	In progress	*Enterococcus faecalis*	In progress
Escherichia coli K12	Finished	*E. coli* O157:H7	In progress
Haemophilus influenzae	Finished	*Helicobacter pylori*	Finished
Listeria monocytogenes	In progress	*Mycobacterium avium*	In progress
M. leprae	In progress	*M. tuberculosis*	Finished
Mycoplasma genitalium	Finished	*M. mycoides*	In progress
M. pneumoniae	Finished	*Neisseria gonorrhoeae*	In progress
N. meningitides	In progress	*Porphyromonas gingivalis*	In progress
Pseudomonas aeruginosa	In progress	*P. putida*	In progress
Rickettsia prowazekii	Finished	*Salmonella* serotype Typhi	In progress
S. Typhimurium	In progress	*Shigella flexneri*	In progress
Staphylococcus aureus	In progress	*Streptococcus mutans*	In progress
S. pneumoniae	In progress	*S. pyogenes*	In progress
Treponema denticola	In progress	*T. pallidum*	Finished
Ureaplasma urealyticum	Finished	*Vibrio cholerae*	In progress
Yersinia pestis	In progress		

[a]Table derived from a recent article on genomics and bacterial pathogenesis

In addition to this enormous explosion in knowledge about human pathogens, is a parallel understanding of the complexities of human immune response to foreign proteins and toxins. Such knowledge has led to a deeper understanding of how we develop basic immunity to a number of different human diseases. With this increase in scientific knowledge, comes the power to manipulate the immune system at its most fundamental level of cellular immunity. By altering the signaling pathway of these immune cells, researchers have manipulated the basic immune response in multiple animal models. Several years ago, a team of Australian researchers showed that mouse cellular antibody responses to ectromelia could be manipulated by the insertion of IL-4 gene into the pox-virus. [14]





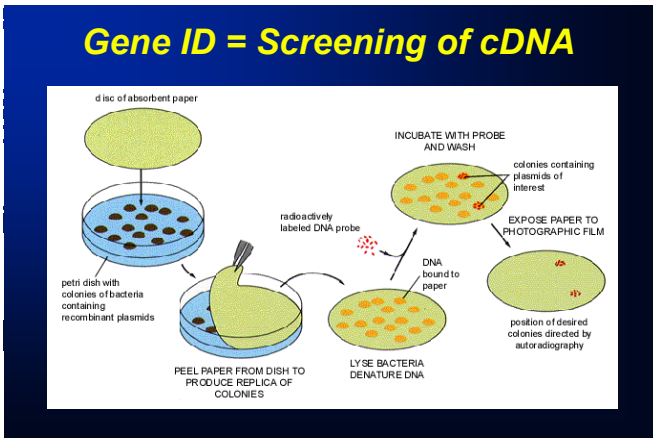
POTENTIAL TYPES OF NOVEL BIOLOGICAL AGENTS

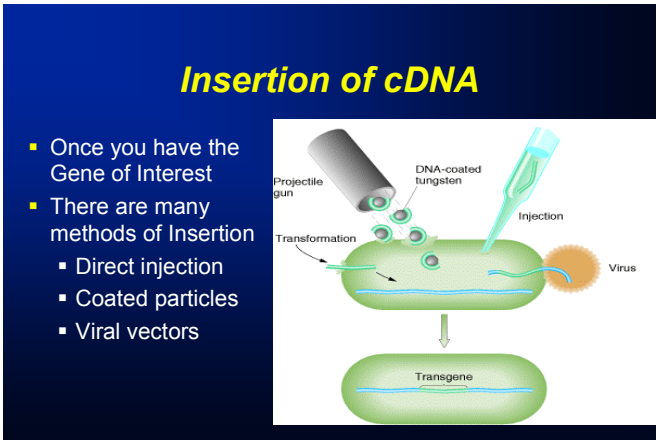
Results from basic research such as this, has fueled concern that a bioterrorist could use such knowledge to build biological weapons that might override the body's basic immune response or overcome the protection afforded through immunization.

Since the release of Anthrax bacteria into the postal system last Fall, much of the focus on Bioterrorism preparedness has been on the traditional threats posed by classical biological agents and what we still do not know about these threats. As we prepare for future threats, we must not ignore the potential quantum leap that biotechnology offers our potential enemies in developing new biological warfare threats. In fact, there is already mounting evidence that novel biological agents may have already been produced by some of our former enemies.[15] Examples of such novel agents and the kind of potential effects they might have on human subjects have already been widely published in several intelligence documents, as well as popular literature.[16] Examples of novel biologic threats that could be produced through genetic engineering technology include:

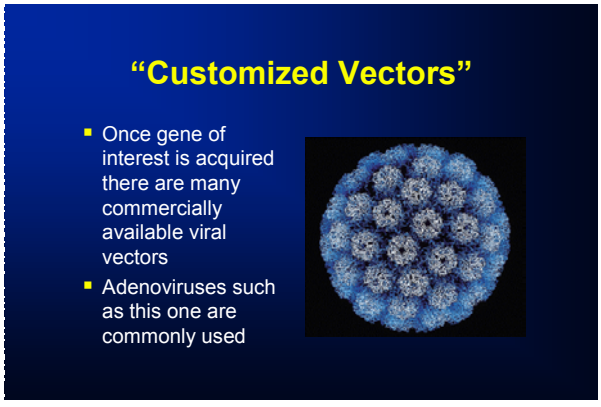
- Innocuous microorganisms genetically altered to produce a toxin, poisonous substance, or endogenous bioregulator.
- Microorganisms resistant to antibiotics, standard vaccines, and therapeutics.
- Microorganisms with enhanced aerosol and environmental stability.
- Immunologically altered microorganisms able to defeat standard identification, or diagnostic methods.
- Combinations of any of the above with improved delivery systems.

Several investigators have already described examples of potential hybrid microorganisms that fit the criteria listed above. Many of these organisms are routinely used in university laboratories around the country. In addition, genetic vectors that are used to routinely transfer genes into human cells fall into the category of man-made or novel biological agents. [17] Viral vectors, such as adenovirus, vaccinia, or other associated viruses, as well as naked or plasmid DNA, have been engineered for the sole expressed purpose of delivering foreign genes into new cells. These highly specialized genetic vectors are used in gene therapy experiments and are genetically modified through the deletion of several important viral genes. This creates space for foreign genes and renders the virus incapable of replication once used in the host genome.



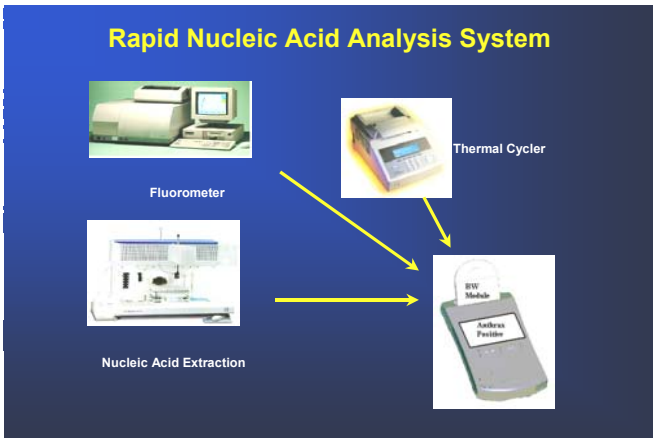


For the moment, Adenovirus and Adeno-associated vectors, seem to be the favorite viral vectors for experiments involving the introduction of foreign genes into human cell types. These vectors have high transduction efficiency, ability to invade non-dividing cells, and are used to infect a wide variety of cell-types. Most successful gene therapy experiments, have involved the use of this viral vector as the source for the introduction of new genetic-based therapies. [18] While the use of such specifically engineered viral vectors hold great promise as potential delivery agents for human gene therapy, they could also be used to cause great harm if improperly used to conduct biological warfare. [19]



These viral vectors hold tremendous promise for the developments of new treatments, while at the same time, pose a significant threat if they are engineered to cause harm rather than cure disease. This conundrum concerning risk verses benefit to society has been at the crossroads of every debate about new technological development. We have already passed through this

phase in the chemical and nuclear industries. With the sequencing and public release of the human genome, we stand on the threshold of a revolution in the diagnosis and treatment of many human diseases. [20] It is likely, in the not too distant future, that physicians will employ powerful new DNA-based analytical tools and diagnostic technologies capable of nearly instantaneous responses. For example, current PCR-based assays can amplify and report on specific nucleic acid sequence information in as little as 30 minutes. This powerful analytic tool, when coupled with rapid computer-based nucleic acid search capabilities, can deliver DNA specific reporting capability into the hands of a single operator. This kind of diagnostic information has the potential to transform medical care in the 21st century, and should be pursued with the vigor and enthusiasm it deserves.



DIAGNOSTIC DILEMMAS

One of the current diagnostic dilemmas in responding to a potential biological attack is that many of these diseases have a similar clinical presentation. Making the diagnosis of a particular agent can vary, from hours to days, and this delay in diagnosis leads to the loss of valuable response time. This delay in diagnosis can be overcome by employing new gene-based technologies, such as micro array diagnosis or gene chip technologies. Micro array or gene chip technology evaluates the simultaneous expression of multiple genes at a given point in time. This technology brings the genome to life, by giving the researcher the power to look at expression of multiple genes within a single cell or tissue sample. [21] Armed with this powerful new technology, scientists gain a more complex understanding of molecular genetic interaction. Soon, gene chip technologies will approach the power of integrated circuits, allowing for immediate processing of biological information, and this technology and its improvements will usher in the Bioinformatic age.

All of these biotechnologies are in the very early stages of practical development and are likely to have profound effects on medical technology and future therapies for disease.

For instance, the molecular basis for many human cancers is just now being discerned through complex genetic experiments involving animal cell models and tissue culture technology. This knowledge will likely lead to future preventive therapies aimed at early detection and treatment of cancer cells, before they have the power to spread throughout the body and destroy healthy tissue. Such molecular-based therapies will fundamentally change the nature of many medical encounters, shifting it further in the direction of primary and secondary prevention, and away from tertiary treatment of disease.

Already some of the information discovered through the various genome projects underway, have led to important new discoveries concerning the molecular interactions of many biological agents. For instance, we know many of the genes responsible for virulence in bacterial diseases, such as anthrax or plague, are mediated by small circular DNA inclusions known as plasmids. [22] Such knowledge may fuel new treatments aimed at selectively inhibiting or inactivating these genes before they are able to cause wide spread damage to the body. Virologists have already developed techniques for genetic insertion that often leads to gene inactivation or selective so-called gene knockout experiments. [23]

ANTHONY LITTRELL

Major Anthony Littrell received his medical degree from Uniformed Services University of Health Sciences in 1995 and went on to complete a residency in Preventive Medicine at Walter Reed and Johns Hopkins School of Medicine in 1998. Since completing post-graduate training he has worked on a number of public health programs in several tropical countries around the world. After completing a tour of duty in the Special Forces, he was recently transferred to U.S. Army Medical Research Institute for Infectious diseases (USAMRIID) where he works in the medical operations division. He is currently involved in advanced projects related to the prevention and detection of Bioterrorism.

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