Review

How biotechnology will change healthcare?

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Abstract

Biotechnology is about to change health care and its delivery in profound ways. The new genomic tools emerging from the biotechnology have revolutionized medicine and transformed our understanding of health and the provision of healthcare. Its implications pervade all areas of medicine, from disease prediction and prevention to the diagnosis and treatment of all forms of diseases. In the past 5-10 years genomics, proteomics and high-throughput microarray technologies gave understanding of the molecular basis of cells and tissues in health and diseases such as tumor classification and prognostication. Personalized medicine is the concept that patients should be treated with therapies and medicines based specifically on each patient's unique genetic makeup, for optimal results. Applied biotechnologies arising from genomics will be used for effective prediction of diseases and risks associated with drugs. However, the introduction of biotechnology based tests into routine health care requires both a demonstration of cost-effectiveness, and availability of appropriate accessible testing systems. A major movement in healthcare is pharmacogenomics. Pharmacogenomics takes advantage of the fact that individuals have unique genomes which is likely to react differently to a particular drug and dose amount. The discovery of single nucleotide polymorphisms (SNPs) was one of the major breakthroughs in genetic testing. Approximately 10 million SNPs have been identified in the human genome. In US alone, an estimated $30 to $45 billion is spent annually on diagnostic laboratory services, and the gene-based testing component is growing at an annual rate of 25 percent. Scientists are studying gene therapies for a number of inherited human diseases involving defective genes, by replacing them with new, functional genes. Stem cell therapy aim is to replace the damaged cells with healthy, disease-free cells-hence the term regenerative medicine for this approach. This review is an attempt to understand how biotechnology should transform the traditional medications that are effective for every member of the population to personalize medicine and therapy.

Keywords: Healthcare, genomics, medicine, gene therapy, stem cell therapy.

INTRODUCTION

Biotechnology is the application of scientific and engineering principles to the processing of materials by biological agents to provide products and services. While biotechnology applications date back to 6000 BC, developments since the 1970s in genomics, genetics, cell and tissue engineering have identified a range of possible novel applications and given the field new impetus. Recent advances in molecular biology and genetic engineering have led to enormous progress in the ability to understand the biomolecular roots of human disease (Pavlou and Reichert, 2004). Its facilitation

through nanotechnology, materials and information technology has fuelled research and development of new technologies with broad applications in health care, agriculture, environment and industrial production (Anton et al., 2001).

These approaches have not only produced or improved biological products and processes, but also invented more than 200 new therapies and vaccines (Cubukçuoğlu et al., 2008). Since the Human Genome Program was launched in the 1990s, the pace at which science is unlocking the molecular underpinnings of complex disease has accelerated remarkably. All the 'omics' (genomics, proteomics, metabolomics), and an ever-expanding toolkit (DNA and protein chips, microarrays or microfluidics), are rapidly redefining the

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taxonomy of disease (Batchelder and Miller, 2006).

In the next 10 to 20 years, health care is expected to shift towards molecular and preventive medicine and the use of recombinant DNA (rDNA) and monoclonal technologies. Genetic testing, gene therapy and personalized medicine may become common practice. New surgical tools and techniques such as antioplasty, laser surgery and hybrid imaging techniques promise to be largely non-invasive. They will not only improve survivability, but could reduce patient costs related to lengthy hospital stays. Advances in cell and tissue regeneration promise to develop organic and artificial tissues for repair and replacement functions (Anton et al., 2001).

According to United Nations (UN) projections, the world's population will grow from 6.1 billion in 2000 to 8 billion in 2025 and 9.4 billion in 2050. Exacerbating the matter will be the inability of health-care providers to cover the medical costs for the growing patient populations, many of whom will require several treatments for a variety of age-related conditions such as cancer, cardiovascular disease, and neurodegenerative diseases. Health-economic studies indicate that most of an individual's health-care spend is used in the last years of life, and seniors consume about five times the number of drugs of their working-age counterparts. The sheer magnitude is evidenced by the US $2 trillion spent in 2000 in the seven main pharmaceutical markets (United States, France, Germany, Italy, Spain, United Kingdom, and Japan). A key hope is that biotechnology will deliver technological advances that create cost-effective strategies for both treating and preventing disease (Nagle et al., 2003).

Global economics is driving international competition among biotechnology companies to develop new products and applications. The growing recognition biotechnology as an economic and social growth factor has prompted governments in many countries to provide financial support to their local biotechnology companies to encourage research, development and commercialization of ideas and products (Australian Bureau of Statistics, 2002).

This article is an effort to discuss the implications of biotechnology in improving health care in areas like therapeutics, preventive medicine and emphasis will be made on key areas where gene technology can contribute to advance human health and personalized medicine.

Biotechnology: past, present and future

The "new biotechnology" started in the early 1970s with direct manipulations of the cell's genetic machinery through recombinant DNA techniques. Its application on an industrial scale since 1976 has fundamentally expanded the utility of biological systems. Scientists and engineers can now confer new characteristics to microbes, plants and animals by changing the genetic make-ups. Just like inanimate matters, some biological molecules can now be biologically manufactured or biofactured. The new biotechnology, combined with the existing industrial, government, and university infrastructure in biotechnology and the pervasive influence of biological substances in everyday life, has set the stage for unprecedented growth in products, markets, and expectations. To date, the principal impact of the new biotechnology has been in the pharmaceuticals arena, but the scope has been expanding (Lim, 2009).

In the 1980s, biotech-related diagnostic devices mainly consisted of reagents such as monoclonal antibodies (mAbs) that were used in serological tests. In 1990s, the advent of molecular probes allowed biotech companies to provide more sensitive and accurate tests (Wong, 2008). As a result of the sequencing of the human genome in 2000, the diagnostic product landscape has changed dramatically.

Today we are in the midst of another technology revolution in the diagnostic sector. With the discovery of disease associated genes and biomarkers, physicians can now determine either an individual's predisposition to or their current status in a particular disease. Example: screening for the presence of oncogenes such as BRCA 1 to determine a woman's predisposition to breast cancer. Proteins and oligonucleotides represent a new wave of biomarkers currently being developed as diagnostic agents. They serve as indicators of gene expression either during a disease process or when drugs are administered to a patient. Transcription factors and epigenetic modifiers have recently been associated with numerous pathological conditions as markers for drug toxicity and resistance. These types of tests will bring the health status of a patient into sharper focus while guiding physicians in their use of targeted, genetic-based therapies (Bohunicky and Mousa, 2011).

The recent influenza vaccine shortages have provided a timely reminder of the tenuous nature of the world's vaccine supply and the potential for manufacturing issues to severely disrupt vital access to important vaccines. The application of new technologies to the discovery, assessment, development and production of vaccines has the potential to prevent such occurrences and enable the introduction of new vaccines. Gene-based vaccines, virus-like particles, plant-derived vaccines and novel adjuvants and delivery systems represent promising approaches to creating safer, more potent vaccines. As a consequence, more people will have faster access to more effective vaccines against a broader spectrum of infectious diseases. However, the increased cost of producing new vaccines and regulatory uncertainty remain challenges for vaccine manufacturers (Ulmer et al., 2006).

Biotechnology Growth And Its Market Value

Health biotechnology has rapidly become vital in helping healthcare systems meet the needs of the poor in developing countries. This key industry also generates revenue and creates employment opportunities in these countries. To successfully develop biotechnology industries in developing nations, it is critical to understand and improve the system of health innovation, as well as the role of each innovative sector and the linkages between the sectors. (Abuduxike and Aljunid, 2012).

Countries' science and technology capacities can be strengthened only if there are nonlinear linkages and strong interrelations among players throughout the innovation process; these relationships generate and transfer knowledge related to commercialization of the innovative health products. The private sector is one of the main actors in healthcare innovation, contributing significantly to the development of health biotechnology via knowledge, expertise, resources and relationships to translate basic research and development into new commercial products and innovative processes (Abuduxike and Aljunid, 2012). The role of the private sector has been increasingly recognized and emphasized by governments, agencies and international organizations. Many partnerships between the public and private sector have been established to leverage the potential of the private sector to produce more affordable healthcare products. Several developing countries that have been actively involved in health biotechnology are becoming the main players in this industry. (Abuduxike and Aljunid, 2012).

Many substances produced naturally in a wide range of living organisms have been identified to be of benefit in the treatment of human disease. Current health biotechnologies recreate DNA-recombinant cellular processes in laboratory settings to produce 'natural' therapeutics: these are potentially a step forward from traditional pharmacology which has developed synthetic analogues or sought to extract products from donor material. However, with increasing financial pressures, decision makers require evidence that the benefits of biotechnologies justify their costs. The challenges experienced when evaluating the cost-effectiveness of biotechnologies are explored with reference to three examples: HA-1A human monoclonal antibody, erythropoietin and DNase (Mason and Drummond, 1997).

Biopharmaceuticals are medical drugs produced using biotechnology. They are proteins (including antibodies), nucleic acids (DNA, RNA or antisense oligonucleotides) used for therapeutic or diagnostic purposes, and are produced by means other than direct extraction from a native biological source. The total sales of biologics in the United States reached $44 billion in 2007, a 10% increase over 2006 sales. This growth rate is still nearly three times the US pharmaceuticals sales growth, which

lagged at 3–4% in 2007 (Aggarwal, 2007). Growth factors are the highest selling category of biologics with sale of $14.1 billion in 2006 and EPO being the largest selling factor, but mAbs, mostly indicated for cancer and inflammatory disorders, hormones (such as insulin analogs, glucagon-like peptide-1 (GLP-1) analogs and human growth hormone), and cytokines (interferon and interleukins), as well as three kinds of blood factors (factor VIII, factor VIIa and factor IX) increasingly contribute to the market.

In 2011, the US biotech sector grew modestly, with total sales reaching $53.8 billion, or a 4.9% increase over 2010 sales. Driven by rising uptake of monoclonal antibodies (mAbs) and insulin products, this increase was slightly better than the overall pharmaceutical sector, which experienced growth of 3.0% in 2011 (IMS Health Top-Line Market Data). The outlook for 2012–2013 seems to be improving, as several promising products, which are driving the current growth, reach the market. However, in the long term, the sector faces increasing difficulties with reimbursement and the potential launch of biosimilars, which could impose downward pressure on unit sales and pricing in this sector (Aggarwal, 2012)

Biotechnology In Preventive Medicine

Vaccines

According to the World Health Organization, each year more than 17 million people die from infectious diseases, preponderantly in the developing world. Human ingenuity has permitted humankind to protect itself against many infectious diseases through vaccination, a process that has been successful for more than a century. There is probably no area of biomedicine that has a greater potential for affecting human health than studies of the immune system, a critical component in the body's defense against disease assault (Bains and Evans, 2001; Clark, 2006). The development of vaccines has been one of the most important contributions to medicine and public health. Although the conventional "old" vaccines, which consist of disease-causing organisms in a killed or attenuated form, have been instrumental in reducing the incidence of many infectious diseases and plagues, they have not eliminated the danger from both existing and newly emerging diseases (Clark, 2006).

Unlike conventional protein or polysaccharide based vaccines, DNA vaccines comprise plasmids encoding the vaccine antigen along with a strong eukaryotic promoter used to drive protein expression (Rajcani et al., 2005). Such nucleic acid based vaccines can be delivered intramuscularly, subcutaneously or mucosally with the aim that they will gain access to the cell cytoplasm and thereby

induce antigen expression in vivo that, like the protein vaccine they mimic, will then elicit a desired immune response. DNA vaccines have been successfully applied to animal models to variously prevent or treat infectious diseases, cancer, autoimmunity and allergy (Ulmer et al., 1996). On the positive side, the straight forward plasmid structure of DNA vaccines gives them inherent advantages over traditional protein or carbohydrate based vaccines. The one-step cloning of target coding sequence into plasmid vectors offers more convenient development and production when compared to culture and inactivation of whole infectious pathogens or expression and purification of recombinant proteins. Furthermore, by inducing expression of proteins in vivo, antigenic structure is more likely to resemble the native protein structure and include any essential post-translational modifications. From a safety perspective, amplification of the nucleic acids encoding a potential antigen avoids the need to directly handle dangerous pathogens (Li et al., 2012).

The convenient manipulation of plasmid DNA *in vitro* allows easy introduction of beneficial mutations into the antigen coding sequence. In vitro mutation also enables modification of antigen coding sequences to counter rapidly drifting virus strains. Plasmid DNA is stable at room temperature allowing for convenient storage and shipping. In addition to these physical properties, DNA vaccines enable expressed antigens to be presented by both MHC class I and class II complexes, thereby stimulating Th1 and Th2 CD4 and CD8 T cells in addition to B cells (Liu, 2011). To date, veterinary DNA vaccines have been approved for use in fish (infectious haematopoietic necrosis virus), dogs (melanoma), swine (growth hormone releasing hormone) and horses (West Nile virus) (Kutzler and Weiner, 2008). However, success in veterinary approvals has not translated into successful human DNA vaccine applications, with low immunogenicity remaining the Achilles heel of human DNA vaccines. In recent years, many clinical trials have been undertaken on DNA vaccines covering the full range of prophylactic through to therapeutic vaccines against infections (Li et al., 2012). However, despite more than 100 such clinical trials, more work is still clearly required on design and delivery to lift the immunogenicity of DNA vaccines to the levels required for human regulatory approval and commercial exploitation.

Recent years saw an interest in developing therapeutic vaccines, for diseases such as AIDS, tuberculosis, and peptic ulcer, cancer, diabetes, and autoimmune diseases. Additionally, therapeutic vaccines are being developed against Alzheimer's disease, mad cow disease, and possibly Huntington's disease (Arnon and Ben-Yedidia, 2003; Sela and Hilleman, 2004; Campbell et al., 2012). Of note, the US sales of recombinant vaccines in 2007 almost tripled from $0.5 billion to $1.5 billion, which was primarily driven by a fivefold increase in sales of human Papilloma virus (HPV) vaccine.

Diagnostics

Infectious diseases continue to devastate the developing world. Diagnostics are crucial for identifying the presence and cause of disease at both the individual and the population level. In developing countries there is a lack of diagnostic tests that can be performed at low-infrastructure sites. Without these tests healthcare workers are unable to differentiate between diseases with similar visible symptoms (i.e. fevers) and to be able to apply the correct treatment, monitor the effects of intervention (whether preventative or therapeutic) and to assess levels of drug resistance or recurrence of existing diseases (Batchelder and Miller, 2006). Most diagnostics capture approximately 80% of the infectious disease market, with the remainder made up of the 900 or more assays related to genetic diseases, predictive testing, cancer and paternity testing (Batchelder and Miller, 2006).

Current available diagnostic equipment is mostly inadequate for serving health needs in most developing countries. Commercial companies have mostly shown a lack of willingness to commit to the development of accurate and affordable molecular-based diagnostic tests for infectious diseases in the developing world. Most existing diagnostic systems have been formulated for industrial countries and are generally inappropriately complex in operating and manpower skills and costs, to be utilized in developing countries. There is great need for massive funding to speed up the development and delivery of diagnostic solutions to the disease problems of the developing world.

However, biotech-derived competencies have already begun to affect certain markets, such as oncology, for which genetic tests have been designed to identify those at risk for breast and ovarian cancers (*BRCA1* and *BRCA2* mutations), colon and uterine cancers (*MLH1* and *MSH2* mutations) and melanoma skin cancer (p16/ *CDKN2A* mutations) (Nagle et al., 2003). Approximately $11 billion portion of the diagnostics market that is US based is growing by 4% annually, with the $2.5-billion US molecular-diagnostic segment (DNA and RNA tests) expanding 15% annually.

Biotechnology In Personalized Healthcare

With more than 100,000 avoidable deaths per year in the USA alone, adverse drug reactions (Schmidt, 1998) represent a leading cause of hospitalization and death, as well as a significant economic burden on the

healthcare system. Thus, predicting which patients are genetically predisposed to react adversely to specific drugs, or to not react at all, has both life saving and cost reducing potential. It is often stressed that many currently-used medicines have a relative efficiency. For instance, anti-depressants are not effective among 20% to 50% of the patients, beta-blockers fail in 15% to 35% of the persons treated, and one out of five or even three persons suffering from migraine cannot find a proper medicine to alleviate his/her pain (Mamou, 2004). It is therefore expected that a personalized medical care with drugs taking account of the genetic make-up of every individual will improve the situation. These practices use preventive, diagnostic, and therapeutic interventions that are based on genetic tests and family history information (Downing, 2009).

The goal of personalized health care is to improve health outcomes and the health care delivery system as well as the quality of life of patients everywhere. According to the United States department of health and human services personalized health care (i) predicts our individual susceptibility to disease, based on genetic and other factors; (ii) provides more useful and person-specific tools for preventing disease, based on that knowledge of individual susceptibility; (iii) detects the onset of disease at the earliest moments, based on newly discovered chemical markers that arise from changes at the molecular level; (iv) preempts the progression of disease, as a result of early detection; and (v) targets medicines and dosages more precisely and safely to each patient, on the basis of genetic and other personal factors in individual response to drugs.

Potential Future Therapeutics

Gene Therapy

The knowledge that certain diseases can be attributed to defects in DNA has led naturally to the development of therapies that deliver functional genes into patients to compensate for altered or abolished functions (Friedmann and Roblin, 1972). This therapeutic gene transfer process is called gene therapy. Two great breakthroughs in gene therapy were achieved at the beginning of the 21st century. In 2000, a French group led by Alain Fischer reported the impressive improvement of the immune function of two children with X-linked severe combined immunodeficiency (SCID) after receiving a reinfusion of bone marrow cells modified by a murine retroviral vector (Cavazzana-Calvo et al., 2000). In 2002, Claudio Bordignon's group reported another trial on ADA-SCID using a similar bone marrow transplantation method, but included additional non-myeloablative conditioning steps to enrich for genetically corrected cells (Aiuti et al., 2002). In the follow-up report in 2009, this study demonstrated that out of 10 patients receiving ADA gene therapy, eight had excellent immune reconstitution without taking polyethylene glycol-modified bovine adenosine deaminase (PEG-ADA) drugs (Aiuti et al., 2009). Another encouraging breakthrough came in 2008 and 2009 when three independent phase I/II trials using rAAV serotype 2 to treat 30 patients with Leber congenital amaurosis (LCA) type 2 improved visual functions in the majority of treated eyes (Colella and Auricchio, 2012). A recently published report states the use of rAAV to transfer human coagulation factor IX (FIX) into six patients with severe hemophilia. A single dose of intravenous rAAV resulted in enhanced FIX expression and improved clotting in all patients (Nathwani et al., 2011).

At present, cancer and cardiovascular disease both leading causes of death and two of the biggest potential markets in the western world are the main targets for future gene therapies. Examples are Introgen's Advexin and Onyx Pharmaceutical's ONYX-015 for head and neck cancer therapy; and Vical's Allovectin-7 (HLA-B7 gene therapy) for melanoma. Other active areas of development for gene therapies include infectious diseases (such as HIV/AIDS, hepatitis and human papillomavirus) and central nervous system disorders (Nagle et al., 2003).

Stem Cell Therapy

Stem cells, which possess the ability to self-renew and differentiate into tissue-specific cells with specialized functions, have the potential to revolutionize regenerative medicine (Moore and Lemischka, 2006). They have been identified in almost all organs of the human body and play important roles in development, homeostasis, and disease (Hipp and Atala, 2008; Glotzbach et al., 2011). Several major classes of stem cells have been described, including embryonic stem cells (derived from pre-implantation embryos), tissue-resident stem cells (obtained from adult tissues), and induced pluripotent stem cells (iPSCs) (generated via genetic reprogramming). Given the role of stem cells in development, they have been touted as a "fountain of youth," representing the immense potential of regenerative medicine to eradicate human suffering (te Riele, 2009).

Medical researchers believe that stem cell therapy has the potential to dramatically change the treatment of human disease. A number of adult stem cell therapies already exist, particularly bone marrow transplants that are used to treat leukemia (Gahrton and Bjorkstrand, 2000).

In the future, medical researchers anticipate being able to use technologies derived from stem cell research to treat a wider variety of diseases including cancer, Parkinson's disease, spinal cord injuries, Amyotrophic lateral sclerosis, multiple sclerosis, and muscle damage,

amongst a number of other impairments and conditions (Lindvall, 2003; Goldman and Windrem, 2006; Razvi, 2012). Two clinical problems that have benefitted from stem cell therapy include hematologic cancers and severe burn injury. Transplantation of hematopoietic stem cells from the bone marrow has been extensively used to restore ablated blood cell populations after chemotherapy and may have a role in treating certain autoimmune diseases (Li and Sykes, 2012). Additionally, epithelial stem cells harvested from skin biopsies can be commercially expanded to create autologous skin equivalents used for coverage of extensive burn wounds (Atiyeh and Costagliola, 2007). These therapies highlight the potential of stem cell-based approaches to combat human suffering. Broadly speaking, regenerative medicine aims to exploit this intrinsic potential of stem cells to restore or establish normal biologic function in complex multicellular systems (Mason and Dunnill, 2008). However, there still exists a great deal of social and scientific uncertainty surrounding stem cell research, which could possibly be overcome through public debate and future research, and further education of the public.

Single Nucleotide Polymorphism

Single nucleotide polymorphisms, are the most common type of human genetic variation and have been associated to disease development and phenotype forecasting. A SNP is a site on the DNA in which a single base-pair varies from person to person. If a SNP is found within a small, unique segment of DNA, it serves both as a physical landmark and as a genetic marker whose transmission can be followed from parent to child. SNPs have gained popularity in recent years and are touted as the genetic markers of choice for the study of complex genetic traits (Risch and Merikangas, 1996; Collins et al., 1997). The analysis of human genetic variability can lead to the comprehension of medical issues and to the development of personalized therapeutic protocols. The recent technologies for DNA sequencing and bioinformatics analysis are now giving the opportunity to develop new diagnostic and prevention approaches also through health promotion protocols. The genetic data management is at the same time underlining technical limitations and old ethical issues (Giampaoli et al., 2012).

Besides the common diseases in humans (such as cardiovascular diseases, psychiatric disorders, autoimmune diseases and cancer), response to medication (in terms of both beneficial response and adverse reaction) is also a complex trait governed by a large number of genes. For example, a genetic variability in N-acetyl transferase (NAT-2) is associated with a high incidence of peripheral neuropathy when taking isoniazid, an antituberculosis drug (Nebert, 1997), and patients with a variation in the core promoter of the gene ALOX5 have diminished clinical response to treatment with a drug that targets the 5-lipoxygenase pathway (Drazen et al., 1999). The drug companies in The SNP Consortium (TSC) hope to use a genetic approach in the general population to identify those likely to benefit from new medications being developed and those likely to suffer adverse side-effects. Armed with this knowledge, it is hoped that even medications that cause some people significant side-effects can be developed for a subset of patients who will derive therapeutic benefits from them. This approach of targeting drugs to each unique genetic profile is the promise of the new field of pharmacogenomics (Housman and Ledley, 1998; Wade, 1999).

Future Directions And Impact Of Biotechnology On Healthcare

The biotech industry has produced several technologies to support faster, cheaper and more targeted drug discovery and development. Ultimately, the goal of these technologies is to reduce discovery time and increase the number of new chemical entities entering the development stage. The benefit of biotechnology cannot be underestimated; with the world's population continuing to grow and the oldest old doubling in size in many westernized countries, health-care providers have to maximize treatment benefits and to limit disabilities, while at the same time minimizing costs will be a key driver in the success of biotech-derived diagnostics and therapeutics. Early identification of disease-causing factors and, more importantly, early intervention strategies will ultimately change the face of health care by shifting its focus from empirical treatment of the symptoms to evidence-based treatment and prevention on the basis of an individual's molecular make-up (Nagle et al., 2003).

Besides the medical potential, biotechnology will also be an extremely important economic factor. Due to improved diagnostics, healthcare costs will decrease by providing more appropriate treatments. There will be fewer hospitalizations that currently occur because of adverse reactions to drugs, continuing acute illness because of lack of efficacy and inaccurate dosing. Adverse events currently cause more than 2 million hospitalizations and 100,000 deaths annually in the US alone, with a cost of $100 billion to the healthcare system (Batchelder and Miller, 2006). Another factor in healthcare cost reduction is that a two-tiered system will emerge, in which concerned individuals will focus on their own wellness and prevention, and will personally assume the costs of buying pre-symptomatic diagnostics tests and making the lifestyle changes that these diagnostics suggest. Their out-of-pocket payment for prevention will reduce their morbidity and therefore reduce the costs to taxpayers and employers of serving them.

Gene-based medicine can help individuals identify their particular susceptibilities to disease while they are

well and take effective preventive steps. In the future, it will help detect the onset of disease much earlier, enabling treatment to prevent disease progression, and can help bring about medical products that are tailored more precisely to the needs of each individual.

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