POLICY FORUM: GENOMICS

Genomics and the World's Economy

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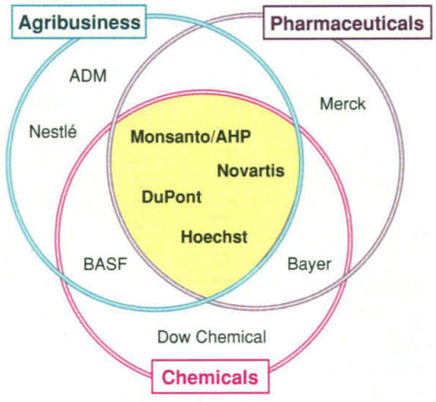
Genomics now allows us to study, design, and build biologically important molecules. As new discoveries in this arena are applied, companies and industries are being restructured in a way that will change the world's economy. Thus, this new science of genomics is forcing some of the world's largest companies to reinvent themselves as borders between pharmaceutical, biotech, agricultural, food, chemical, cosmetics, environmental, energy, and computer industries blur and erode. Genomics is so intertwined with other technologies and products of the molecular revolution that it is hard to trace its influence in a single company or industrial structure. An idea of what is happening and what is to come can be gained, however, by examining the restructuring and realliance of existing companies and the creation of a new economic sector, the life sciences (*1*).

The flow of genomics information is so massive that it threatens to overwhelm existing R&D budgets, labs, and knowledge bases. It is driving megamergers, as companies seek to lock in patents and licensing agreements. The U.S. Patent and Trademark Office (PTO) received 4000 patent requests for nucleic acid sequences in 1991 and 500,000 in 1996 (*2*). Genomics has substantial government support, massive corporate investment, powerful enabling technologies, and short-term cash-generating potential.

Significant portions of the world's economy are already changing as biotech, chemical, pharmaceutical, and agribusiness companies invest in molecular technologies. The largest pharmaceutical merger to date, of Ciba-Geigy and Sandoz, created a conglomerate, Novartis, with enough money and breadth of R&D to compete not just in health care but also in nutrition and agribusiness. It is valued at over $100 billion. The near-union of Glaxo with SmithKline would have created the world's third largest company, with control over approximately 7.5% of the global pharmaceutical market. The new company's research budget would have, in 1 year, exceeded the total estimated cost of sequencing the human genome, and its market capitalization would have been larger than the yearly gross national product of 143 of the world's nations. These two examples are not exceptions but a preview of many larger and more complex mergers to come.

Pharmaceutical companies are establishing a multitude of partnerships. From 1993 to 1996, these alliances increased almost sixfold and, in 1997, provided eight times more capital to U.S. biotech companies than did initial public offerings. The value of these partnerships doubled between the first and the fourth quarters of 1997 (*3*). Some pharmaceutical companies also sought to build up in-house expertise. Novartis created a genomics institute, betting $250 million on integrated in-house research (*4*). Glaxo-Wellcome budgeted $47 million to create a genomics directorate and doubled its research staff (*5*). SmithKline invested aggressively by signing a $125 million deal, unprecedented in size in the genomics industry, to acquire genetic sequences from Human Genome Sciences. SmithKline also increased the number of bioinformaticians on its staff from 2 to 70 and based over 25% of its drug discovery programs on genomics (*6*).



The life sciences industry. These companies are examples of each sector.

The genomics-driven metamorphosis of chemical companies is even greater than that which is occurring in pharmaceuticals. Monsanto, a traditional chemical company, reinvented itself as a life science company. Starting in 1985, it began spinning off many of its core businesses. Since 1997, Monsanto has invested $6.6 billion in biotech and genomics. This strategy assumes that molecular research in plants and animals will be applicable in the short term to agribusiness and will allow the company to integrate and expand its pharmaceutical subsidiary, Searle. Wall Street loved this vision. Monsanto's stock quintupled from 1995 to mid-1998. Now Monsanto is continuing its strategy by merging with a major pharmaceutical company, American Home Products.

Monsanto's success put tremendous pressure on other chemical companies' management. DuPont tried, and failed, to remain primarily a chemical and energy company while expanding life sciences. In April 1998, DuPont announced its reorganization into three business units, led by life sciences. Within a week, its stock increased 12%. This was not enough. Despite previous denials, DuPont announced in May 1998 that it would be divesting the energy company Conoco and investing the proceeds in building itself up as a life science company. It bought out Merck's share of a joint pharmaceutical venture for $2.6 billion to "capitalize on the considerable synergies at the research level in genomics, biology, chemistry and biotechnology" (*7*). Other chemical companies are also restructuring. Dow Chemical spent $900 million to buy Eli Lilly's 40% share of a joint venture to modify crops and foods. Starting this summer, Dow announced that it intends to become a life science company. Hoechst sold its basic chemicals divisions and invested in pharmaceuticals and biotechnology through Hoechst Marion Roussel and an agribusiness venture with Schering—AgrEvo. It also bought Plant Genetic Systems for $600 million.

As health strategies shift from treatment to personalized prevention, agriculture, food, and nutrition are also merging with biotech and pharmaceuticals. Genzyme Transgenics is "pharming" genetically engineered goats. One herd may produce enough antithrombin III to replace a $115 million factory. Producing medicine from transgenic animals costs less than one-tenth of cell culture methods (*8*). Novartis is trying to modify corn to fight osteoporosis. In May 1998, Monsanto bought DeKalb Genetics and Delta & Pine Land for $4.2 billion and created a joint venture with Cargill, one of the world's largest private companies, to process and package genetically engineered foods. Other major food processors are also creating joint ventures to process and distribute genetically engineered crops. This is creating a new industrial sector, agriceuticals (*9*).

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The field of comparative genomics is discovering an abundance of shared genes among life forms. NemaPharm, which studies the genetic makeup of the nematode *Caenorhabditis elegans*, is providing clues for human gene research (*10*). Mitotix is working with DuPont on the premise that studying cell division in yeast can lead to therapeutics for human cancer (*11*). Other companies are developing software to identify human gene equivalents across other species (*12*).

Genomics is not the biotech of the 1980s, which promised much and delivered little. Biotech companies tended to act alone, trying to integrate from the research bench through the drug counter. They remained relatively small, and their technology did not drive massive divestments and mergers among the world's largest corporations. The objective of a life science company is no longer to generate breakthroughs in a single area such as medicine, chemicals, or food, but to become a dominant player in all of these.

Today the breadth of complementary technologies is far greater. Molecules can be studied, designed, and produced more efficiently because of advances in robotics, nanotechnology, high-throughput screening, photolithography, spectroscopy, combinatorial chemistry, transgenics, and bioinformatics. Rather than being limited to the study of a few genes at a time, these technologies have enabled the development of products such as gene chips, which can analyze hundreds of thousands of compounds simultaneously.

Future mergers will increasingly take place outside a company's traditional industry. It would not be surprising to see major pharmaceutical companies ally with Dow, DuPont, Nestlé, or Archer Daniels Midland. Soon medical prescriptions may be personalized to our genotype, along with specific neutraceutical foods. Some vaccines will be delivered through foods such as raw potatoes or bananas (*13*). Companies that produce cosmetics and products such as soap may merge with pharmaceuticals to create biologically active cosmeceuticals. Cosmetic companies are already recruiting molecular biologists (*14*). It is conceivable that Procter and Gamble, L'Oreal, and others may build alliances with genomics firms. One of their first targets might be to apply the research carried out on cell aging mechanisms (*15*). These new products may be delivered through your health management organization, a merger of supermarket and pharmacy, or perhaps even through a series of national health club chains.

Three other industries are also starting to converge at the molecular level: energy, mining, and environment. Energy companies are beginning to look at different forms of energy production. We see a glimpse of this in the potential of engineering *Methanobacterium* (*16*). Eventually, energy companies may engineer energy sources from plants rather than resorting to fossil fuels. Some already do this, using subsidies to produce ethanol for instance, but genomics may make it economically logical. *Deinococcus radiodurans* may be a key to cleaning up heavy metal and radiation contamination (*17*).

Countries other than the United States are also pushing very hard. Despite its severe economic crisis, Japan is trying to double its genomics research in 1998 (*18*). Korea has been promising to invest billions through its Biotech 2000 program (*19*). Germany, France, Switzerland, and Scandinavia are generating companies at an unprecedented rate (*20*). The United Kingdom's investment in structural biology is second only to that of the United States (*21*).

However, the future is not completely rosy. There are three key risks associated with the new life science industry. Current market valuations of life science companies are very high. To meet short-term expectations of huge earnings, some conglomerates will have to quickly create a series of blockbuster life science products. But if these megacompanies go through the "boom-bust" cycle that characterized the smaller biotechnology companies, it could result in substantial changes on the international stock market.

The second risk is that pressure to quickly introduce genetically engineered products may lead to their dispersal without the rigorous tests required for pharmaceuticals. The U.S. Food and Drug Administration (FDA) and other agencies will face difficult questions about what and how to regulate as foods and cosmetics start performing quasi-medicinal functions (*22*). For instance, despite FDA opposition, Pharmanex imports red yeast rice to produce cholesterol-reducing capsules that contain the same active ingredient as Merck's prescription drug Mevacor (*23*).

The third problem is that discoveries and company restructurings are moving far ahead of general public comprehension. Accidents and lack of communication with the general public may slow the molecular revolution. Gaps in knowledge can easily become credibility gaps if a crisis occurs or if the message is mismanaged or untruthful. The recent "mad cow"crisis is one example of the enormous costs associated with lack of trust and communication. European beef markets collapsed, and there were motions to impeach the whole European Commission. The eventual cost of cleaning up the disaster will approach $20 billion. A large part of these costs was incurred by a bureaucracy trying to control research and minimize public concerns (*24*). Genetic engineering already faces great skepticism. Despite losing competitiveness and potentially tens of thousands of jobs, European farmers planted no commercial acreage with genetically modified seeds through 1996. Some U.S. companies faced protests and export restrictions.

Research requires extensive cross-border discussion, cooperation, and conflict resolution, not only on technical affairs such as patent protection but in more complex areas such as welfare, morality, and ethics. Academic centers and life science companies should lead a far broader debate that can enlighten the experts and the general public. Academic, government, and industry leaders should think about how to deal transparently and effectively with the inevitable mistakes a nascent industry makes. Life science companies should create an international forum where they can discuss some of the more controversial techniques and establish standards for what is allowable and how fast it can be introduced. There are enough benefits at stake from the molecular revolution to warrant extreme care, rigorous standards, and a clear vision (*25*).

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