# Is Japan a Boon or a Burden To U.S. Industry's Leadership?

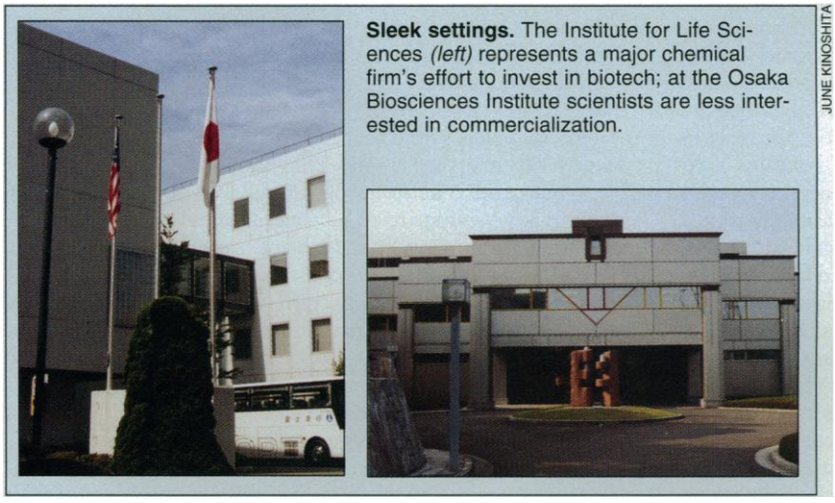
Back in the early 1980s, today's thriving $10 billion biotech power Amgen was just another startup struggling to survive in the Southern California sun. Across the Pacific, Japan's Kirin Brewery faced the opposite conundrum: It had become so successful that the Japanese government had topped off its beer sales: Kirin was barred from increasing its 50% market share. How could diminutive Amgen and the beer-making behemoth help each other?

Driven to dream of new profit centers, Kirin's corporate executives had quietly decided to launch a drug division. They authorized a half-dozen researchers to tinker, and the toy of choice was a hormone that had been isolated from urine early this century. What attracted researchers to this hormone was its known ability to stimulate red blood cell production. They were intrigued by the prospect of treating anemia in patients undergoing dialysis—patients whose failed kidneys couldn't make the hormone on their own. The potential market was small, but as one original Kirin researcher recalls, "We thought it would be a learning experience." It proved a great deal more than that—thanks to tiny Amgen.

The hormone that captivated Kirin was erythropoietin, or EPO, and in October 1983, Fu-Kuen Lin, an Amgen molecular biologist, cloned it. But Amgen hardly had the resources to develop the potential lifesaver, and because it doggedly refused to hand over the U.S. market to any would-be suitor, no U.S. company could be enticed into a marriage. But for Kirin, which had its sights on the Japanese market, Amgen was a bride after its own heart. Within a few months, Kirin representatives approached Amgen's CEO, George Rathmann, with a proposal to develop EPO jointly.

The rest is history: By 1991, sales of EPO and a second jointly developed drug (granulocyte colony stimulating factor, which boosts white blood cell production) had propelled Amgen's revenues even past those of biotech role model Genentech. Last year, the two drugs raked in more than $1 billion for Amgen. In less than a decade, the Japanese-American alliance that spawned these sales had transformed Amgen into a biotech industry leader and Kirin into a major pharmaceutical player in Japan. Isn't everyone happy?

No. Though many U.S. biotech entrepreneurs cheered the Kirin-Amgen alliance, some academics and industry analysts looked on with mounting unease. Through the 1980s, hundreds of U.S. biotech startups and even universities had tied the knot with cash-rich Japanese corporations. These alliances, the experts fear, are enabling Japan to siphon off U.S. technology, much as it had already done with electronics and computers. Even the National Research Council (NRC) is worried. A recent NRC report penned by a blue-ribbon panel of industry and academia experts warns that if the trend continues, "The U.S. biotechnology industry will lose its strong leadership position in several industry segments at the end of the decade" (*Science*, 22 May 1992, p. 1133).



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**Sleek settings.** The Institute for Life Sciences *(left)* represents a major chemical firm's effort to invest in biotech; at the Osaka Biosciences Institute scientists are less interested in commercialization.

Other knowledgeable observers think such fears are inflated. Take Michael R. Reich, an authority on the Japanese pharmaceutical industry at the Harvard School of Public Health. Although many innovative drugs have emerged from Japanese firms, he says, none has yet arisen from biotech. "The NRC report says the Japanese are coming, but they haven't." Indeed, although some 60 biotech drugs are currently in clinical trials in Japan, they either are licensed from U.S. firms or mimic drugs being developed in the United States. Even more ironically, although Japanese scientists have made seminal contributions to many biotech drugs, it has been U.S. companies rather than Japanese that have profited most from them.

So should the United States worry or not? Is biotech about to become the next debacle for U.S. high-tech industries, or is the U.S. leadership secure for the foreseeable future?

To assess the strengths and weaknesses of Japan's budding biotech industry, *Science* spent several weeks visiting labs at Japan's top universities, government research institutes, and companies, and interviewing dozens of bench scientists, lab directors, corporate research managers, and industry analysts on both sides of the Pacific. We appraised Japan's basic research base, technology transfer mechanisms, and government efforts to nurture biotech, especially pharmaceuticals, which are the focus of 60% of Japan's R&D spending for biotech. Our goal was to determine whether access to U.S. biotech has enabled Japanese firms to leap across the technology gap, and whether it is credible to believe, as the NRC panel seemed to, that these giant firms will, like huge but agile sumo wrestlers, sweep the U.S. industry off its feet.

Our survey found that Japan has many of the ingredients for success: world-class scientists and labs, stable environments for long-term R&D, and government policies that encourage cross fertilization between basic research and industry. Yet in findings that would seem to support observers like Harvard's Reich, serious obstacles stand in the way of Japan's efforts. Basic research remains underfunded, industry is unable to recruit top scientists, and Japanese institutions are not adept at responding swiftly to fast-moving fields like biotech. Perhaps most critically, Japan lacks the entrepreneurial culture that may be needed to win the high-risk, high-stakes game of biotech.

And that culture will be particularly critical for biotechnology, since the drug industry—unlike cars and electronics—is not protected in Japan. As a result, while an American car is a rare sight in Tokyo—limited to the occasional Corvette or Cadillac ostentatiously shoehorning its way into a narrow alley—pharmaceuticals are another story. In drugstores, Japanese brands jostle with Bayer and Johnson & Johnson. A jetlagged traveler seeking relief from insomnia will be prescribed Halcion. Fifty percent of Japan's medications are licensed from overseas. "The Mercks of the world are not sleeping giants," warns Philip Hall, a drug industry analyst for Baring Securities in Tokyo. "There's no guarantee that any Japanese company will emerge as a full global player."

Further clouding the picture on the Japanese side is the fact that Japanese soil has proved notably stoney for startups—partly,

it seems, because scientist are blasé about commercializing their discoveries. Shigekazu Nagata of the Osaka Biosciences Institute, for instance, would rather pursue his ongoing quest for the fas antigen receptor, which he thinks mediates programmed cell death, than fret about missing out on profits from his cloning work with genes such as the one for granulocyte colony stimulating factor. "Companies always want to know if something can become a drug," he says as he tossed some stray hair out of his eyes. "But our institute doesn't care."

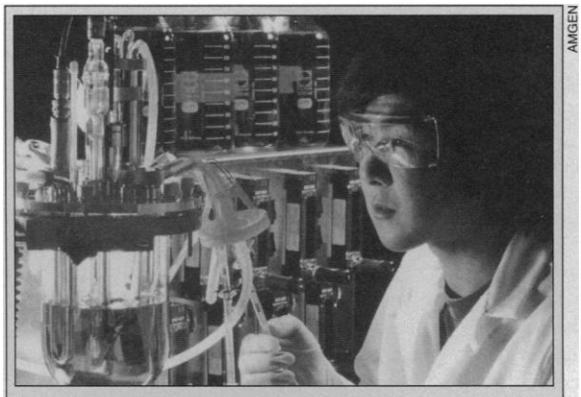
Why this lack of interest? "We don't have the frontier spirit," laments Masao Kamijo, president of TechnoVenture, one of only two venture capital firms in Japan. "People look down on success. If a top Ph.D. from Tokyo University started a company, everyone would think he was crazy." Of the 140 or so Japanese startups in TechnoVenture's portfolio, he notes, not one is in biotech.

Instead, biotech in Japan is dominated by large, diversified companies. The lion's share of research goes on in the asteroid belt of corporate labs and institutes encircling greater metropolitan Tokyo. Clusters of labs also orbit Osaka. In semirural suburbs all around these major cities, edifices of sparkling glass and steel have sprung up amid rice paddies and new tract houses. Spacious, brimming with the latest equipment, these labs hum with activity as scientists busily clone, sequence, synthesize, and express.

Many of these labs are the fruit of the 1980s, a decade in which Japanese companies binged on biotech. Some of the corporate sponsors are the predictable pharmaceutical firms, but even companies like Japan Tobacco are getting into the act—with difficulty. The tobacco company has struggled to extract new drugs from its work on platelet activating factor and transgenic-mouse monoclonal antibodies. "The base technology doesn't transfer easily into new applications," sighs Tatsuji Chuman, JT's general manager of technological planning. "We're having a very hard time."

Having learned that there is no shortcut to biotech nirvana, some companies have pulled back. But others are reexamining their approach. One is the Institute for Life Sciences, a pioneering biology lab founded in 1971 by Mitsubishi Kasei, a major chemical firm. Located in Machida, a bedroom community 40 minutes by train west of central Tokyo, the institute nurtures a university-like atmosphere enhanced by state-of-the-art equipment, plenty of technical support, and well-scrubbed labs with picture windows looking out on pine groves—a far cry from the dingy, mildewed, and understaffed facilities typical of academic settings in Japan.

Conditions at the institute seem ideal, but "frankly speaking, we haven't reached the top scientific level," says its present director, Kazutomo Imahori, flashing a grin. "Our organization was too much like a university. Individual scientists were too independent. I tell them, scientific freedom can only be maintained by assuming scientific responsibility." When Imahori took over 5 years ago, he set new agendas that forced scientists to collaborate on such broad questions as the basic mechanisms of Alzheimer's disease, which have potentially large payoffs, scientifically and commercially.



AMGEN

**Blood ties.** A researcher at Amgen studies ways to improve production of EPO, a factor for growing red blood cells that the firm produces in collaboration with Kirin.

Only in the past few years have a few other companies, including Hitachi and Upjohn, joined Mitsubishi Kasei by building lavish biology centers of their own. Meanwhile, to coax industry to invest more in long-range biotech research, the Ministry of International Trade and Industry (MITI) has set up key technology centers like the Protein Engineering Research Institute (PERI), where industry researchers can rub elbows with university professors. Housed in a new smoke-gray building sleekly contoured like a Sony boombox, some 60 PERI researchers, from protein purifiers to mathematical modelers, join their talents to improve on nature's protein designs.

In spite of the fact that many of the large companies dominating Japanese biotech are having difficulties getting their efforts off the ground, the fact that corporations rather than tiny startups are in the driver's seat will ultimately play to Japan's advantage, believes Robert Yuan, a member of the NRC panel. Yuan is director of BioTechnology International, a program at the University of Maryland that assesses biotechnology research and industries worldwide. "Japanese biotech firms are operating companies," he explains. "Unlike U.S. startups, they're not dependent on raising capital. They're looking for market niches and give priority to production. It's not that their technology is better. But their priorities are better."

In the 1980s, Yuan says, U.S. firms regarded their Japanese partners as cash cows, rather than as founts of technology. That was a mistake, in his estimation. "These people will say that Japanese technology is no better, but at the end of the day, why are Japanese products better and cheaper?" He cites the example of a fermentation method that U.S. companies had rejected as unprofitable. "Some Asians bought it, and in a year and a half, they made it very profitable. Americans look for dramatic technologies. But Asians are very good at incremental improvements."

Yuan predicts that fermentation-based companies such as Ajinomoto (of monosodium glutamate fame) and Kyowa Hakko will emerge as major players. These firms started out making fermented food staples such as soy sauce and miso (soybean paste) and have become expert in fermentation technology. By screening their vast archives of microorganisms, they have discovered and developed many potent antibiotics and chemotherapy drugs. But Susan Clymer questions how relevant fermentation will remain. "When you see that manufacturing is not a large part of the cost in pharmaceuticals, and you see the most advanced forms of biotech moving towards small molecules," she muses, "you have to wonder where that fermentation capability is going to lead."

Tuan Ha Ngok, who negotiated the Genetics Institute's licensing deal with Japan's Yamanouchi Pharmaceuticals, contrasts drugs and software—another area in which the U.S. leads—to automobiles and semiconductors, where superior manufacturing clearly was the key to Japan's success. "But in software and pharmaceuticals, manufacturing is not the key," he says. "Innovation is." And Ngok thinks biotech innovation begins not in big companies, but outside, in universities. "If you look at Japanese academia," he remarks, "it will take years for them to change."

That will not be for lack of trying. For years, people like University of Tokyo molecular biologist Kenichi Arai have been trying to force government and industry to face up to their neglect of basic research. "Maybe," says Arai hopefully, "biotech will provide the motivation to change."

Like a growing number of prominent (and tenured) academics, Arai has made something of a second career out of lambasting the government's miserly support of university research. The Ministry of Education, Science, and Culture (Monbusho) doles out about $45,000 a year to cover operating costs for each kouza—a unit consisting of one full professor, two assistant professors, and a few technicians—along with competitive research grants of between roughly $10,000 and $70,000. The government admits that these amounts would have to be tripled to

bring funding up to U.S. levels. Professors cannot apply for grants from other ministries, such as MITI or the Ministry of Health and Welfare (Koseisho), because Monbusho forbids it.

If Japanese scientists are angered by this lack of support, in the interests of fairness it must be noted that Japanese scientists have not rushed to support Japanese industry, either. When Mitsubishi Kasei's Institute for Life Sciences opened its doors, for example, it had to struggle to recruit researchers, even though it offered superior facilities and complete scientific freedom. Today, the institute, though successful at attracting bright young researchers, doesn't expect to keep them permanently. Instead, it has become a stepping stone on their way to a university professorship, which suits director Imahori fine, he says, because it "keeps the place fresh."

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**East meets West.** "Thinking of Sowing New Seeds" says a poster at Japan Tobacco, which has invested heavily in biotech.

Still, although coaxing a future Nobel laureate on board is something Japanese firms only fantasize about, they find access to top scientists in other ways. MITI's key technology centers bring together academic and industry scientists on leave from permanent jobs, a system that skirts the problem of wooing people away from lifetime posts—or getting rid of them later on.

In another initiative to encourage technology transfer, stodgy Monbusho, which once opposed any university-industry linkages, now sponsors hundreds of collaborations between academic researchers and their industry colleagues. This merging of talents and resources has spawned development of such drugs as Takeda's endothelien inhibitor and a second antihypertensive drug, atrial natriuretic factor, which was synthesized by a university professor and is now in large-scale clinical trials at Suntory, a beer and whiskey maker that, like Kirin, has a vigorous drug division.

Links between top academics and industry have become so pervasive, in fact, that Keiko Oishi-Nakamura, Genentech's manager of research collaborations in Japan, can scarcely find a professor to work with the California biotech legend. "They're all committed to a Japanese company," she says, wrinkling her nose.

In the past, Japanese industry ignored its compatriots' seminal work relating to such substances as interferons, interleukin-2, and granulocyte colony stimulating factor—which U.S. companies exploited first. By nurturing close ties with scientists, they intend not to let opportunity slip by again. When scientists at the Osaka Biosciences Institute discovered two sleep-regulating hormones known as D2 and E2, companies from around the world beat a path to the 5-year-old laboratory's postmodern portals, but a Japanese firm won out over the multinationals. "We don't intend to discriminate," says lab director Osamu Hayaishi, "but it's easier to communicate and gain access when the partner is also Japanese."

Do sentiments like that mean Japanese companies and U.S. biotech firms are going to turn away from each other, reversing the trend of the 1980s that the NRC and others warned about? Some, on both shores of the Pacific, think that would mean a loss for both partners. Says Takamoto Suzuki, manager of research planning and licensing for Kirin's pharmaceuticals division, "In Japan, it's hard to keep the staff young. They need these injections of youthful energy from U.S. ventures." Rathmann agrees that entrepreneurial spirit is something U.S. biotech firms have in abundance. In contrast to the conservative Japanese firms, he says, "at Amgen, everyone owns stock. You own it, you love it, you have tremendous drive—it goes way beyond a normal job. You just can't duplicate that in a large organization."

Given those reciprocal needs, it seems unlikely the partnership between Japanese corporate giants and small, innovative U.S. biotech firms will come to an end any time soon. That, naturally, raises the question of who benefits from this partnership, the question that the NRC thundered about in its report. In an interview, Suzuki paused to ponder that unasked question, considering his words carefully before answering: "As for the Japanese running away with the profits—look where Amgen is now."

**–June Kinoshita**

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GERMAN SCIENCE

# Kohl Replaces Science Minister

For the past 11 years, German Science Minister Heinz Riesenhuber has been a fixture in the ever changing line-up of Europe's senior science policy makers. But no more. As part of a wider cabinet reshuffle, German Chancellor Helmut Kohl last week replaced Riesenhuber with one of the country's rising young politicians—Matthias Wissmann, a 43-year-old lawyer who's spent the past few years as the parliamentary economic spokesman for Germany's two main conservative parties.

The change is causing some unease in the scientific community. While Riesenhuber came into politics from a career as an industrial chemist, Wissmann has no scientific background and has made few public statements on research policy. And he enters the research ministry at a time when German science has its back to the wall, facing budgetary squeezes, the quandary of how to integrate researchers from the former East Germany, and deep-seated public opposition to genetic engineering and animal research. "I'm concerned about the timing of the change," admits Thomas Trautner, a vice president of the Max Planck Society and codirector of its Institute for Molecular Genetics in Berlin.

Nevertheless, Riesenhuber's departure had been rumored for many months. The conventional wisdom is that he's being replaced simply to bring new blood into the cabinet at a time when Kohl's coalition government has slumped to an all-time low in the popularity ratings, and to counter complaints that Wissmann's home state of Baden-Württemberg has been poorly represented in the German federal government. Certainly, there's no indication that Riesenhuber himself had decided it was time to go. "[He] had not become disenchanted with his position," asserts Max Syrbe, president of the Fraunhofer Society, an independent but largely publicly funded agency that runs almost 50 applied research institutes.

Leading German researchers contacted by *Science* last week said that Riesenhuber will be remembered for investing heavily in basic research during the 1980s—supporting such projects as the construction of the HERA electron-proton collider at the DESY high-energy physics lab in Hamburg. But he wins lower marks for failing in 1990 to prevent the German parliament from passing the infamous "gene technology law," which has burdened biology labs with regulatory red tape (*Science*, 31 January 1992, p. 524). And some researchers are disappointed that Riesenhuber did not defend the science budget more vigorously in the face of the unexpectedly high costs of German unification. "People fear that basic science is in danger," says Marburg University cell biologist Horst Kern.

Now researchers are counting on Wissmann to make their case. Some argue that the fact that he has come fresh from a prominent position in the German parliament may be an advantage. "I would hope that he retains the support of his former colleagues," says astronomer Klaus Pinkau, scientific director of the Max Planck Institute for Plasma Physics in Munich.

**–Peter Aldhous**