Government-led research is the most clear-cut. All the programs have clear missions, and everyone knows what role to play. But even then, things do not work that smoothly. In this category of joint research, a wide range of government administrators and policy-determining bureaucrats is involved in all projects, and their influence must always be kept in mind (3).

Industry-led and university-led joint research may at first glance appear to be two sides of the same coin. However, their cores do not coincide. Industry-led research functions from the point of view of industry's need to recruit good students as employees and to get access to original ideas before rivals do, while keeping them secret as long as possible. University-led research aims to increase the quality and quantity of research activity on campus and have it generally freely accessible.

In the early 1960s industry called for university-industry research, but this call was drowned out by the student movement that disrupted campuses in the late 1960s and early 1970s. Faculty feared if they worked with industry, radical students would destroy their labs. By the mid-1980s there were no more such threats, research costs had risen sharply, and facilities had deteriorated because of tight government budgets. In this context, a group of academics, especially those in experimental research, believed worthwhile work in universities would come to a halt without new funding sources. For the first time there had been a confluence of industry and university needs. Although their reasons differed, the aims were the same.

It is difficult to predict where Japanese universities are headed. Two things should be noted—both familiar to researchers elsewhere. One is the serious problem of the deterioration of science and engineering department facilities since the government's tight budget policy was adopted in 1982. The other is the future of the relationship between science and society.

What is to be done about the anti-industry allergy and the concern about freedom of research? In principle most university people now agree on the need for cooperation with private companies, but there is still disagreement on specifics. There are academics who believe current funding problems are not really that dire. Some simply are not interested in cooperative research. So the status quo prevails. How much—and how easily—university-linked joint research will be done remains an open question. As solutions are worked out, one hopes researchers, companies, and government policy-makers on both sides of the Pacific can benefit from comparing notes and sharing thoughts on what is a common issue.

REFERENCES AND NOTES

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2. Kagaku Gijutsu-cho (Science and Technology Agency), Ed. *Kagaku gijutsu hakusho 1981* (Science and Technology White Paper, Tokyo, 1981), p. 115. White papers are published annually by a number of government units as reports on the previous year and look-ahead policy statements. The Japan Institute of International Affairs publishes English abstracts of them, with a lag time of about a year, as *White Papers of Japan* (Tokyo).
3. There is a growing literature in English on various aspects of Japanese government-led as well as industry-industry joint research. [See, for instance, J. Levy and R. Samuels, *Institutions and Innovation: Research Collaboration in Japan* (MIT–Japan Science and Technology Program, Cambridge, MA)]. There have also been studies of Japanese firms linking with U.S. firms and research institutions [see, for example, Office of Japan Affairs, National Research Council, *U.S.–Japan Technology Linkages in Biotechnology: Challenges for the 1990s* (National Academy Press, Washington, DC, 1992)].

4. This article is extracted from a larger study. I wish to express sincere appreciation to the many people who generously supplied information, much of it normally unavailable. I would especially like to thank N. Saito, H. Suzuki, and K. Nagata of Waseda University; K. Marumo of Japan Techno-Economic Society; C. Watanabe of the New Energy and Industrial Technology Development Organization; and Y. Fujii and S. Kobayashi of Bunkyo University. I have also benefited from discussions with R. Samuels of Massachusetts Institute of Technology and H. Patrick of Columbia University.

Underfunding of Basic Science in Japan

Akito Arima

Japan's higher education system is made up of 98 national, 41 prefectural, and about 400 private universities. Approximately 30 of these schools are strong in scientific research as well as education, but they are suffering from lack of adequate funds for both basic research and education.

Over the past 20 years, the research activities of Japanese universities have rapidly expanded, especially in applied science. Japan competes strongly with other leading Western countries. For example, comparing the number of publications in the field of electronics and pharmaceuticals, Japan ranks second to the United States, followed by the United Kingdom and West Germany. In 1986 Japan ranked third in the number of physics papers published worldwide, exceeded only by the United States and the former Soviet Union.

One might assume that Japan's leading industrial research centers contribute the majority of published scientific works; however, this is not the case. According to publishing figures, a total of 92,363 physics papers were published in Japan between 1976 and 1986. Of these, 47% came from ten of the leading national universities including the University of Tokyo, Kyoto University, and Osaka University. Four leading private institutions, Keio, Waseda, Nihon, and Tokyo University of Science, contributed about 3%, while Hitachi, NTT, Toshiba, and other private industry contributed about 10%. The remaining 40% came mainly from national laboratories and smaller public and private universities. These statistics clearly indicate the importance of the national universities in advancing scientific research in Japan.

While research flourished in the universities during the 1970s and 1980s, the

The eroding infrastructure of Japanese universities.

Japanese government took economic measures that began to seriously affect the established national universities.

In an effort to stimulate the economy, the Japanese government sold national bonds both domestically and abroad that created funds for schools, roads, and other public works. As a result, the Ministry of Education, Science and Culture built many new national universities and laboratories

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in part with the help of these funds. In 1980 when the bonds matured and interest was due, higher education suffered a blow. University construction budgets were slashed by half and general funds for basic research and education were not increased during the last decade.

For example, Kyoto University and the University of Tokyo were the hardest hit among the national universities. Buildings deteriorated, and research laboratories became outdated, lacking in the latest scientific equipment. At the same time, graduate school enrollment was increasing, especially the number of foreign students, adding an even greater burden to the cramped facilities.

Only in the past 2 years has the severity of the problem been recognized and addressed by the central government, politicians, and leaders of the corporate and financial community as an urgent problem. The Ministry of Education, Science and Culture intends to double its entire budget for higher education and research over the next several years. One plan being considered is to revitalize the research-centered universities by increasing their budgets for basic research.

In 1992 funds for the Grant-in-Aid for General Scientific Research, a program similar to the National Science Foundation in the United States, were increased by 10%. The grant will increase from 52 billion yen in 1989 to 75 billion yen in 1993.

In addition to the national universities' annual construction budget of 80 billion yen, another 20 billion yen per year was approved exclusively for the repair and reconstruction of already existing leading national universities. These budget approvals will contribute immensely to solving many of the problems faced by higher education.

However, that is only part of the solution. Japan has been very successful at providing the average citizen with an outstanding education from elementary school to undergraduate school. But it is time that Japanese society at large begin to recognize the value of a graduate and postgraduate education; only then will our graduate schools improve and scientific research continue to thrive.

To provide incentives and financial support, universities must create more scholarships for graduate students. Currently, most students must take low-interest loans from the government in order to pay for their graduate education.

In the applied science and high-tech industries, doctorate degrees (Ph.D.'s) are not required for employment nor are employees with such degrees rewarded with better salaries or higher job placement. Instead they enter the work force at the same level as someone with an undergraduate or masters degree. Why go to graduate school when you can get the same job and the same salary without a higher degree?

In conclusion, Japan must increase its financial support for basic research and education and for technology education. There is an urgent need to upgrade the quality of graduate schools so that Japan can continue to make significant contributions to the welfare of the world.

Seppuku and Autoimmunity

Tasuku Honjo

An organism must react to and destroy the many foreign antigens it is exposed to in its lifetime. To accomplish this, the immune system of vertebrates is equipped with a powerful genetic mechanism (DNA rearrangement) to amplify its repertoire of antigen receptors. This mechanism is a double-edged sword, however, as it inevitably creates immune cells that react against antigens present in the organism itself and these cells can potentially cause autoimmune diseases.

These self-reactive lymphocytes are usually removed by clonal deletion or inactivation upon interaction of these antigen receptors with antigens in the body (*1*), which triggers programmed cell death (*2*). The principle that the self-sacrifice of a few can save the whole life reminds me of *seppuku* or cutting of the belly, a practice common to the Japanese soldier (samurai) until 130 years ago, when his death was required to save the lives of his retainers or his family pride.

Unfortunately, selection of lymphocytes bearing antigen receptors specific to a particular antigen has been difficult to study in normal animals, because only a few in a million lymphocytes can recognize a given antigen. Recently, transgenic mice expressing autoreactive immunoglobulins (Igs) have been generated so that one can follow the selection of self-reactive B lymphocytes, which in these mice represent the majority of the B cells (*3, 4*). These studies have clearly shown that autoreactive B cells are either clonally deleted or inactivated (anergized), depending on the type and amount of autoantigen. We have generated transgenic mice expressing an antibody to murine red blood cells (RBCs) (*4*). These mice were derived from strain NZB, which is prone to develop autoimmune diseases (*4*). The number of spleen B lymphocytes, almost all of which express antibody to the RBCs, is reduced to 1 to 10% of the number seen in the spleens of control mice. B cells that escape deletion are anergized. Nonetheless, in spite of this loss of B cells, about 50% of the mice show symptoms of autoimmune anemia, indicative of remaining immune activity against RBCs. Two questions arise: (i) where are these remaining autoantibodies produced? and (ii) why do only 50% of the animals, all of which have the same genetic background, become sick?

The answer to the first question resides in the belly (*5*). All of the transgenic mice contain the same number of B cells expressing the cell surface marker CD5 in the peritoneal cavity as do normal mice, indicating that $CD5^+$ B cells can escape clonal deletion. However, only in the anemic mice are $CD5^+$ B cells producing the autoantibody. Our speculation is that $CD5^+$ B cells in the peritoneal cavity are not deleted because the self-antigen (RBC) is not available in this sequestered compartment of the mouse body. The simplest experiment to test this idea is to inject RBCs into the peritoneal cavity of the transgenic mice. When this is done, exposure to the self-antigen induces apoptotic death of $CD5^+$ B cells in the peritoneal cavity, resulting in a drastic reduction in the $CD5^+$ B cell number. Repeated injection of RBCs into the peritoneal cavity of severely anemic transgenic mice can completely cure their symptoms; anemia disappears and autoantibody production ceases.

Environmental factors may be involved in the variation in symptoms among transgenic individual animals. The most obvious candidate is infection. When we give lipopolysaccharide (LPS) to nonsymptomatic transgenic animals in order to mimic natural infection, all of them become autoimmune and develop severe anemia. Only oral administration of LPS has this effect on peritoneal B cells; intramuscular or intraperitoneal administration does not. We are curious to know how LPS in the gut lumen can stimulate the peritoneal B cells. The gut contains probably the most ancestral, yet still important, part of the immune system and contains $CD5^+$ B cells and $\gamma\delta$ T cells. LPS in the gut lumen appears to activate lymphocytes in the lamina propria of the gut epithelium, cells that can also escape clonal deletion. On the other hand, B cells in Peyer's patches as well as in mesenteric

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