53. Lung disease patients with negative DTHR-T had: caseating granuloma (1), silicosis (3), tuberculosis with pleural effusion (1), intravascular angiogenic tumor (1), chronic bronchiectasis (5), chronic organizing interstitial pneumonitis (4), recurrent cyst (1), coccidioidomycosis (1), sarcoidosis (2), chronic obstructive pulmonary disease (8), chronic asthma emphysema, and pneumonitis (5), pneumonia (3).
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56. Patients with the following cancers reacted negatively (one of each): B-cell lymphoma; extrapulmonary carcinoid; astrocytoma; glioma; glioma-astrocytoma; liposarcoma; leiomyosarcoma; sarcomatous chordoma; localized, encapsulated papillary-, mixed papillary-, and medullary low-grade thyroid carcinoma. In addition, four patients with acute or chronic myelocytic leukemia and two with Hodgkin's disease in remission reacted negatively.
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National R & D Policy: An Industrial Perspective

Roland W. Schmitt

Industrial policy has become one of the hot issues on our national agenda, with various advocates telling us how to beat the Japanese and solve the problems of unemployment, inflation, and industrial stagnation. The 1984 presidential candidates are picking up these ideas and testing them.

Industrial policy has many components—fiscal, monetary, and regulatory, for example. It touches on many areas, from international trade to retraining the work force. I can bring my expertise to only one corner of this many-sided subject: research and development policy. To me, industrial policy means what the government must do to shape our national industrial posture, and a clear understanding of what government should not do.

There has been no lack of proposals. Bills put before Congress in recent years have called for such changes as the establishment of a National Technology Foundation, or a Cabinet-level Department of Trade and Industry; the selection of a National Commission on Technological Innovation and Industrial Modernization to tell us "what the economic, educational, and industrial priorities of the United States ought to be"; a Presidential Program for the Advancement of Science and Technology; and a Commission on High Technology and Employment Potential. Another proposal would establish a government program to conduct research and development on improved manufacturing techniques; others would exempt joint research and development efforts from the antitrust laws.

All these proposals to aid U.S. R & D show a healthy and encouraging concern about the state of American industrial technology, but they may at the same time distract politicians and policy-makers from the most important need and the most important step that government can take to strengthen U.S. innovation. That task is to ensure and strengthen the health of our university system—in both the performance of basic research and the training of research manpower. The distraction is especially great if Washington pays too much attention to the growing number of calls for the government to take over the job of selecting and supporting R & D programs aimed at commercial results.

The Federal Role

In the commercial R & D area there are some things that government must and can do, and other things it cannot and should not do. Government has a crucial role to play in creating favorable conditions for commercial innovation, but not in actually producing those innovations. There are several reasons for this.

First, successful innovation requires a close and intimate coupling between the developers of a technology and the businesses that will bring products based on that technology to market and are themselves in touch with that market. This is essential in a diversified company, and even more essential in a complex and diversified economy. The R & D people must comprehend the strategies of the business as well as know what the market constraints are and what the competition is up to. The business people, in turn, must understand the capabilities and limitations of the technology. They must possess the technical strength to complete the development and believe strongly enough in the technology's potential to make the big investment needed to bring it to market.

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perspective, the Department of Energy's program expense for just one unproved, highly speculative energy technique, magnetically contained fusion, was $295 million in 1982 alone. We face the same problem in several other crucial areas of university research. This is particularly true of engineering research—fundamental research in such areas as software engineering, automation, machining systems, materials engineering, and computer-aided engineering techniques.

The crucial distinction again is between support of the underlying research (the job that the government should be doing) and support of efforts aimed directly at generating products (the job the government should stay away from). Some of the bills before Congress do not clearly make this distinction. Consider, for example, the calls for government support of R & D in manufacturing technology. If a program for conducting the underlying research at universities is to be established, I will support it wholeheartedly. But when programs to produce more efficient manufacturing technologies are proposed, I worry that someone has ignored the difference between broadly relevant research and the job of selecting specific technology targets for new products and processes. And when anyone proposes conducting research utilization activities to encourage widespread adoption of these technologies, then I have serious reservations.

In the technology of controls, for example, fundamental theoretical advances are needed to catch up with the speed and power of microelectronics. Such work should be strongly supported at universities. But the job of putting research to work in, say, robots or machine tool controls for commercial markets should be addressed by private companies.

Some may be concerned that with so much emphasis on support of academic research in fast-moving areas, such as microelectronics and computer science, the needs of core industries, such as automobiles and steel, will be neglected. That is not so. The increases in efficiency needed by these industries will be provided much more by some of these fast-moving areas than by advances in the core technologies. These industries, too, are dependent on strong university research in the fast-moving areas. Moreover, these industries suffer from a lack of investment in already available technology. Giving them new technology without the corresponding investment to use that technology is hardly likely to improve their plight.

Immigration Policy

Another policy issue that strikes at the heart of our universities, yet is rarely discussed in the context of R & D policy, is immigration policy. In 1982 as many foreign students received engineering Ph.D.'s in our universities as did American students. Some regard these foreign students as a problem, and there even have been proposals to reduce their numbers. But the real problem is that not enough Americans are entering doctoral programs. The solution is to encourage more of our students, through adequately supported graduate fellowships, to go on to graduate studies. What is clearly not a solution is to force foreign students to leave. They are an important resource for our country. They account for a disproportionately large portion of our skilled manpower in the fast-moving areas of science and technology. They are not taking jobs away from Americans. They are filling a void and advancing U.S. science and technology. Historically the United States has benefited immeasurably from opening our doors to immigrant scientists and engineers. I need only mention such greats as Steinmetz, Alexanderson, and Giaever at General Electric; Tesla, Zworykin, and Ipatieff at other companies; and Fermi, Debye, Mark, and many others at American universities. Yet current laws create obstacles for foreign scientists who seek employment here. If we are truly concerned about enhancing U.S. industry's capability to do R & D, we should ease the regulatory barriers to hiring foreign-born students, especially those trained in this country. Proposed amendments to the Simpson-Mazzoli immigration bill now before Congress would do exactly that. Unfortunately, for reasons that have nothing at all to do with science and technology, that bill is now stalled in the House. The critical role that foreign scientists play in the United States must be addressed directly, rather than as an afterthought to a bill intended to deal with the problem of illegal, and largely unskilled, aliens.

Technology Leaks

A related national issue also directly affects the health of our universities: the problem of leakage of technology to the Soviet Union. In an attempt to stop that leakage, the Department of Defense and the Department of Commerce proposed regulations that would prevent foreign nationals from taking part in advanced microelectronics research in universities and industry. This is intended as just a first step. In the long run, the two departments are proposing to impose the same restrictions on virtually all fast-moving areas of advanced technology considered to be militarily critical.

There is no question that we must do a better job of preventing the Soviets from acquiring our technology, but such regulations are overkill. The Defense and Commerce Departments propose to change the export control regulations in ways that would seriously disrupt the nature of scientific discourse in U.S. universities and industrial R & D laboratories. No doubt some technology does leak to the Soviets in the course of our open scientific discourse. But by the Administration's own account, this is a very small part of the problem. It is counterproductive to impose such major restrictions on U.S. science and technology for such a small part of the problem. Again, foreign scientists play a critical role in most of our important areas of science and technology. Deny them access to these areas of research and we will do far more to damage our technological capabilities than any of the proposals being made in the name of industrial policy will do to help.

Conclusion

National R & D policy today poses both risks and opportunities. The excitement and attention that proposals for industrial R & D policy have generated threaten to distract us from the federal government's most important tasks. We need to go back to the basics. We need to remind ourselves of what it is that the government can and cannot do, and what it is that industry can and cannot do.

In summary, I want to suggest four specific guidelines for federal R & D policy: (i) concentrate direct support on academically based research, not on government-targeted industrial R & D; (ii) concentrate on sunrise science and technology, not on sunrise industries and products; (iii) concentrate on strengthening the climate for privately based innovation, not on government-selected innovation; (iv) concentrate on development for the government's own needs, not on development for market needs. I believe that these simple guidelines—many of which we have followed with success in the past, some of which we have violated with pain—will go a long way toward greatly strengthening and rejuvenating the dynamic innovative powers of our American system of research and development.

Second, innovation works best if this close coupling is in place during the entire innovation process. It should exist when the R & D project is identified and should continue through planning and development. It must survive the inevitable adjustments during development, caused by shifting market constraints and technical surprises. It must withstand the decision points—when to go ahead or when to quit.

Finally, in a free-enterprise system, governments not only do not create the markets for products but are notoriously slow in reacting to shifts in the marketplace. They lack the crucial entrepreneurial spirit to perceive or acknowledge opportunities early in their development.

During the years of heavy government involvement in energy R & D, we used to hear over and over again the expressions "technology transfer," and "commercialization." Those terms embodied the notion that once a technology was developed by a government contractor or a national laboratory, the technology could then somehow be transferred to the marketplace and commercialized.

That did not happen for a simple reason. Technology transfer is not a separate process occurring downstream from R & D. The user and the performer of targeted R & D need to have established a close relation before there is anything to transfer.

In energy R & D, there were some who fell into the trap of thinking that if they got a concept defined, the technology to work, and someone to produce a favorable economic analysis, then commercialization would follow. They forgot to find out whether the customers would buy the product. The result was a misdirection of effort and money into technologies that never had a chance of commercial success.

Even in agriculture, where the United States has a great history of innovation, underlying research on corn genetics was performed at university research stations and largely supported by government. But private seed companies converted that research into hybrid corn products.

A close relation between the user and the performer of R & D cannot, in general, form when government selects commercial R & D targets. Instead, the government ends up being a third party—one that knows a great deal less about the technology than the developer and a great deal less about the market than the user.

As an example, there are proposals that the government fund R & D in manufacturing technology, in such application areas as programmable automation, robotics, advanced sensors, and computer-aided design and manufacturing. Part of this funding is to support R & D work to be done by industry.

These are key technologies for the future but, because they are so important, a large and growing number of companies are already addressing them. General Electric is investing millions of dollars in each of them. And, in each one, we are faced with a large number of tough competitors—foreign firms and U.S. firms, established firms and new ventures, joint ventures and industry-university cooperative programs. In just one corner of computer-aided design, for example, the field of solid modeling, we are competing against at least a dozen capable firms—established giants, smaller rivals, and newer ventures.

It is simply not plausible for an administrator in Washington—even with the help of a blue-ribbon advisory panel—to pick the winning solid-modeling product better than the dozen firms slugging it out in the marketplace. And even if government could pick the winner, that is only the first step. The suppliers of the funds, the performers of the R & D, and the businessmen who deal with the customers have to tie themselves together in a long-term relation. A government funding agency cannot create that kind of relationship.

There is, however, one important exception. It occurs when the government is the customer for innovation—as in defense R & D. Government should concentrate its development efforts on these needs of its own. If history is any guide, it will thereby also generate products and technology that can be tapped for commercial uses.

The government has clear needs in the area of supercomputers for weapons research, cryptanalysis, weather forecasting, economic modeling, the design of improved airfoils and projectiles, and many other uses. By meeting its needs in supercomputers, the government will also be sponsoring the development of a product that has many valuable civilian uses, such as improved oil exploration, better understanding of crack formation and propagation in alloys, new techniques in computer-aided engineering, and the design of new materials based on theoretical principles. The supercomputer is a prime example of a technology in which the government should take the lead.

In very large scale integrated circuits (VLSI) the government will also be a major customer and thus has a major role in sponsoring development work. One emerging opportunity is in the area of inference chips—VLSI implementations of intelligent electronic systems that work in real time, based on custom chips rather than computers. These inference chips could be used in military systems, for example, to help the pilot of an F-18 with an engine hit by shrapnel make the best use of the 3.6 seconds he has in which to decide whether he can limp home or should bail out.

Inference chips will also have great value in many commercial uses, such as in creating three-dimensional computer-aided design images in real time and in helping smart robots plan their paths. Again, by meeting its own development needs, the government may advance technology that can be used in commercial innovations. When the government is not the customer, government selection of developments is unlikely to promote such innovation and economic growth.

Summary. An analysis of how the government can and cannot use research and development policy to improve the nation's industrial posture suggests four guidelines for federal R & D policy: (i) concentrate direct support on academically based research, not on government-targeted industrial R & D; (ii) concentrate on sunrise science and technology, not on sunrise industries and products; (iii) concentrate on strengthening the climate for privately based innovation, not on government-selected innovation; (iv) concentrate on development for the government's own needs, not on development for market needs.

Competition from Japan

At this point, I would expect some people to be thinking about the Japanese. Did their government bureaucracy not pick the commercial technical winners and put money behind them? No, it did not. At the heart of that question is a misunderstanding about the Japanese government's Ministry of International Trade and Industry (MITI). The popular picture depicts MITI as selecting target industries, picking out the technological developments they need, establishing a consortium of Japanese firms, and supporting the commercial R & D needed

Boom Time for British Biotechnology?

Venture capital is now flowing into small companies and the government is encouraging the commercialization of university research it funds

London. After a relatively slow start in the late 1970's, Britian's biotechnology industry is beginning to pick up speed. Government officials, academics and industrialists all claim that a recent report from the U.S. Office of Technology Assessment (OTA) was excessively pessimistic in its claim that Britain lacks the "dynamism" to produce serious competitors to American companies. They also contest the OTA's conclusion that Britain ranks second behind West Germany among European nations.

"I think that conclusion is completely wrong, particularly if you take the combination of the science and its applications into account" says Gerard Fairtlough, chief executive of Britain's principal biotechnology company, Celltech, which is currently riding a crest of investor enthusiasm.

British industry has benefited from various forms of direct government support for biotechnology. Many smaller companies, for example, have made good use of consultancy grants and other special funds offered as part of a $24-million biotechnology package launched by the Department of Trade and Industry in November 1982. Other industrial initiatives in fields such as fermentation technology have been successfully catalyzed by the Biotechnology Directorate of the Science and Engineering Research Council (SERC).

According to Robin Nicholson, chief scientific adviser in Prime Minister Margaret Thatcher's Cabinet Office, broader political changes must also share the credit. "The policy of the government since 1979 has been to free restrictions and to remove barriers to enterprise," says Nicholson. "The relatively healthy state of biotechnology in the U.K. seems partly to reflect the success of those policies."

He picks out, for example, efforts to encourage Britain's venture capital market—now considered the second largest in the world after the United States—through developments such as the Business Expansion Scheme, which allows individuals to write off against tax an investment of up to $60,000 in a small company, provided the money is left in for up to 5 years.

"The Business Expansion Scheme was the first real fiscal change in small company funding for 50 years" says Peter A. Laing of Biotechnology Investments Limited (BIL), a venture capital fund set up by merchant bank N. M. Rothschild in 1981 and chaired by a previous top government science adviser, Lord Rothschild. BIL is said to be the largest biotechnology-oriented venture capital fund in the world. Partly due to this recent flow of venture capital, Britain now has more small biotechnology companies than any of its European competitors.

The government's willingness to let the commercial and industrial communities act as the senior partner in its efforts to boost biotechnology research and development has played a large part in both

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Celltech chief says OTA misjudged Britain.

the establishment and subsequent operation of Celltech. The company was set up in 1980 primarily at the initiative of the National Enterprise Board, a government body recently amalgamated into the British Technology Group. Although initially providing 44 percent of Celltech's start-up capital, with the four remaining stakes of 14 percent each divided between a group of financial and industrial institutions, the government always intended to hand over its share to private enterprise. It moved in this direction last year when Rothschilds' venture capital company—previously criticized for not investing its funds in any British biotechnology company—bought out a proportion of the government's stock and gained with it a seat on the board of the company.

Like similar companies in the United States, Celltech has actively sought collaboration with larger companies with broader industrial interests or special marketing skills. A joint venture was launched last year with Britain's largest pharmacy chain, Boots, for example, to develop the application of monoclonal antibodies to new diagnostic products. And a technology licensing agreement has been signed with the Japanese company Sankyo to develop tissue plasminogen activator and calcitonin.

Fairtlough says that Celltech, with a current research staff of about 120 scientists and technicians, does not at present share the ambitions of companies such as Genentech to grow into a major corporation. However, with a number of clearly defined product lines, each in a potentially large market, "We could be talking about a turnover of hundreds of millions of dollars in a few years."

Celltech is already earning profits from a reagent for the purification of interferon and has recently created a Culture Products Division which, based on techniques developed with direct government funding, already claims to be the world leader in the in vitro bulk production of monoclonal antibodies.

One reason for Celltech's early success is a unique—and in some quarters highly controversial—agreement with Britain's Medical Research Council (MRC), under which the company was initially given first option on the rights to all results produced in the fields of genetic engineering and monoclonal antibodies in the council's laboratories. These include the prestigious Laboratory of Molecular Biology in Cambridge.

This arrangement was approved by the Conservative government over the opposition of officials in the Treasury, who felt it wrong that one company should be granted exclusive access to what was considered public property. One factor in the decision, it is widely rumored, was the failure in the late 1970's to take out a patent on the technique for producing monoclonal antibodies, which was first developed in the MRC's Cambridge laboratory. Giving Celltech exclusive rights to MRC's work might avoid such lapses in the future.

When Celltech started to register its

first commercial successes, criticism of its deal with the MRC shifted from the political to the industrial community. Both large and small companies complained at being locked out of access to MRC's research. "The academic excellence in places like the MRC should be treated as a national resource and the government should be providing even-handed access to it," says Chris Keightley, managing director of one of the newest and most active small biotechnology companies on the British scene, IO (Bio) Ltd. in Cambridge.

The main product of Keightley's company, set up in 1981 by Acorn Computers and recently recipient of a $1.2-million investment from Rothschild's BIL, is a technique for improving the sensitivity of enzyme-based diagnostic tests. It is based on the research of a scientist whose work was not supported by the MRC, Colin Self of Cambridge University's biochemistry department.

Given the growing pressure to encourage similar initiatives, the MRC has recently renegotiated its licensing arrangements with Celltech. The company will retain first option to developments in fields in which it has already started to develop products. In other fields, however, it will now have to become a competitive bidder, for the MRC is setting up an industrial liaison office to distribute licenses more widely among companies interested in turning its research into commercial products.

The new arrangements have met with general approval in both the industrial and academic worlds. Sydney Brenner, director of the MRC's laboratory in Cambridge, says that at the beginning "there is no doubt that in terms of goodwill, the MRC connection was a major asset to Celltech."

Since then, however, the laboratory has been receiving an increasing number of direct approaches from industry. "In the past, we have had to tell them to go away, since the first options on research in the defined fields had to be offered to Celltech. Now we no longer have to do so."

Brenner and other British scientists point out that there are several differences between the United Kingdom and the United States in the factors affecting the growth of links between the academic biomedical research community and the private sector.

One is a greater reluctance on the part of British academics to get involved in the process of transferring research results from the laboratory, a tradition which is admittedly changing as cuts in government support for the universities as well as general, increase the pressure for university scientists—and universities in general—to look elsewhere for financial support.

A second factor until now has been the tax structure, which has made it more difficult to offer stock options to employees in small companies with initially low turnovers (or profits). The budget proposed in mid-March brings British policy in this area more in line with that in the United States, however.

On the other side of the coin has been a greater willingness to combine public

Pressure for Patent Reform

Cambridge, England. British scientists contend that differences in patent laws between Europe and the United States give U.S. companies a potential advantage in the commercialization of biotechnology. Under European patent laws, a scientific discovery cannot be patented once it has been published in the open literature or even referred to in public debate. In contrast, up to 1 year is allowed after publication for a patent application to be filed in the United States.

"I believe that the greatest inhibitory influence on a closer working relationship between academic and industrial scientists, and the greatest management problem for people like me, comes from this business of prior disclosure," says Sydney Brenner, director of the U.K. Medical Research Council's Laboratory of Molecular Biology in Cambridge, England.

There has long been an awareness of this discrepancy, particularly among patent officers on both sides of the Atlantic, but until now no serious pressure for change. Large corporations, in particular, often welcome being able to scan the scientific literature for new (and unpatented) ideas while employing patent attorneys to keep a close watch on the proposed publications of their own scientists. They tend to argue that they find little wrong with the current system. Robin Nicholson, chief scientific adviser to the British Cabinet, claims that "no one brought the issue to our attention" when his office was preparing a recently published set of recommendations for changes in the British patent law, and expresses some doubt over whether change is really necessary.

Among smaller companies, however, the situation is seen differently. "In this field, the 1-year grace period after publication gives the Americans a considerable competitive advantage" says Gerard Fairtlough, chief executive of Celltech. "I feel that Europe should have the same system."

Although admitting that biotechnology patents can frequently be successfully challenged by sufficiently motivated competitors, such companies also argue that patent rights are seen as crucial assets by potential investors.

Brenner also argues that it would ease the management problem in basic research laboratories such as his—as well as taking some of the pressure off individual scientists—by removing the immediate conflict between the professional demands for fast publication and the commercial demands of patent application. "Patents could be the currency of the interaction between research scientists and industry" says Brenner. "At the moment they are just a burden."

Change will not come easily. Friedrich-Karl Beier, director of the Max-Planck-Institute for Foreign and International Patent Law in Munich, and long a campaigner in favor of a 6-month grace period in Europe to bring it more in line with the United States, points out that this would now require an internationally agreed change in the European Patent Convention. "To do this, it will mean finding sufficient support within the whole European community," says Beier. However, he has already convinced the International Association for the Protection of Intellectual Property to endorse the idea, and suggests that there may be a general move in this direction "within the next 2 or 3 years."

Some British government officials point out that a grace period would help avoid situations—such as that which occurred with monoclonal antibodies in the mid-1970's—where the commercial potential of a discovery is only realized after it has been published, and when it can no longer, under the present system, be patented in the United Kingdom.—**D.D.**

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Venture capital is now flowing into small companies and the government is encouraging the commercialization of university research it funds

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"I think that conclusion is completely wrong, particularly if you take the combination of the science and its applications into account" says Gerard Fairtlough, chief executive of Britain's principal biotechnology company, Celltech, which is currently riding a crest of investor enthusiasm.

British industry has benefited from various forms of direct government support for biotechnology. Many smaller companies, for example, have made good use of consultancy grants and other special funds offered as part of a $24-million biotechnology package launched by the Department of Trade and Industry in November 1982. Other industrial initiatives in fields such as fermentation technology have been successfully catalyzed by the Biotechnology Directorate of the Science and Engineering Research Council (SERC).

According to Robin Nicholson, chief scientific adviser in Prime Minister Margaret Thatcher's Cabinet Office, broader political changes must also share the credit. "The policy of the government since 1979 has been to free restrictions and to remove barriers to enterprise," says Nicholson. "The relatively healthy state of biotechnology in the U.K. seems partly to reflect the success of those policies."

He picks out, for example, efforts to encourage Britain's venture capital market—now considered the second largest in the world after the United States—through developments such as the Business Expansion Scheme, which allows individuals to write off against tax an investment of up to $60,000 in a small company, provided the money is left in for up to 5 years.

"The Business Expansion Scheme was the first real fiscal change in small company funding for 50 years" says Peter A. Laing of Biotechnology Investments Limited (BIL), a venture capital fund set up by merchant bank N. M. Rothschild in 1981 and chaired by a previous top government science adviser, Lord Rothschild. BIL is said to be the largest biotechnology-oriented venture capital fund in the world. Partly due to this recent flow of venture capital, Britain now has more small biotechnology companies than any of its European competitors.

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first commercial successes, criticism of its deal with the MRC shifted from the political to the industrial community. Both large and small companies complained at being locked out of access to MRC's research. "The academic excellence in places like the MRC should be treated as a national resource and the government should be providing even-handed access to it," says Chris Keightley, managing director of one of the newest and most active small biotechnology companies on the British scene, IO (Bio) Ltd. in Cambridge.

The main product of Keightley's company, set up in 1981 by Acorn Computers and recently recipient of a $1.2-million investment from Rothschild's BIL, is a technique for improving the sensitivity of enzyme-based diagnostic tests. It is based on the research of a scientist whose work was not supported by the MRC, Colin Self of Cambridge University's biochemistry department.

Given the growing pressure to encourage similar initiatives, the MRC has recently renegotiated its licensing arrangements with Celltech. The company will retain first option to developments in fields in which it has already started to develop products. In other fields, however, it will now have to become a competitive bidder, for the MRC is setting up an industrial liaison office to distribute licenses more widely among companies interested in turning its research into commercial products.

The new arrangements have met with general approval in both the industrial and academic worlds. Sydney Brenner, director of the MRC's laboratory in Cambridge, says that at the beginning "there is no doubt that in terms of goodwill, the MRC connection was a major asset to Celltech."

Since then, however, the laboratory has been receiving an increasing number of direct approaches from industry. "In the past, we have had to tell them to go away, since the first options on research in the defined fields had to be offered to Celltech. Now we no longer have to do so."

Brenner and other British scientists point out that there are several differences between the United Kingdom and the United States in the factors affecting the growth of links between the academic biomedical research community and the private sector.

One is a greater reluctance on the part of British academics to get involved in the process of transferring research results from the laboratory, a tradition which is admittedly changing as cuts in government support for the universities as well as general, increase the pressure for university scientists—and universities in general—to look elsewhere for financial support.

A second factor until now has been the tax structure, which has made it more difficult to offer stock options to employees in small companies with initially low turnovers (or profits). The budget proposed in mid-March brings British policy in this area more in line with that in the United States, however.

On the other side of the coin has been a greater willingness to combine public

Pressure for Patent Reform

Cambridge, England. British scientists contend that differences in patent laws between Europe and the United States give U.S. companies a potential advantage in the commercialization of biotechnology. Under European patent laws, a scientific discovery cannot be patented once it has been published in the open literature or even referred to in public debate. In contrast, up to 1 year is allowed after publication for a patent application to be filed in the United States.

"I believe that the greatest inhibitory influence on a closer working relationship between academic and industrial scientists, and the greatest management problem for people like me, comes from this business of prior disclosure," says Sydney Brenner, director of the U.K. Medical Research Council's Laboratory of Molecular Biology in Cambridge, England.

There has long been an awareness of this discrepancy, particularly among patent officers on both sides of the Atlantic, but until now no serious pressure for change. Large corporations, in particular, often welcome being able to scan the scientific literature for new (and unpatented) ideas while employing patent attorneys to keep a close watch on the proposed publications of their own scientists. They tend to argue that they find little wrong with the current system. Robin Nicholson, chief scientific adviser to the British Cabinet, claims that "no one brought the issue to our attention" when his office was preparing a recently published set of recommendations for changes in the British patent law, and expresses some doubt over whether change is really necessary.

Among smaller companies, however, the situation is seen differently. "In this field, the 1-year grace period after publication gives the Americans a considerable competitive advantage" says Gerard Fairtlough, chief executive of Celltech. "I feel that Europe should have the same system."

Although admitting that biotechnology patents can frequently be successfully challenged by sufficiently motivated competitors, such companies also argue that patent rights are seen as crucial assets by potential investors.

Brenner also argues that it would ease the management problem in basic research laboratories such as his—as well as taking some of the pressure off individual scientists—by removing the immediate conflict between the professional demands for fast publication and the commercial demands of patent application. "Patents could be the currency of the interaction between research scientists and industry" says Brenner. "At the moment they are just a burden."

Change will not come easily. Friedrich-Karl Beier, director of the Max-Planck-Institute for Foreign and International Patent Law in Munich, and long a campaigner in favor of a 6-month grace period in Europe to bring it more in line with the United States, points out that this would now require an internationally agreed change in the European Patent Convention. "To do this, it will mean finding sufficient support within the whole European community," says Beier. However, he has already convinced the International Association for the Protection of Intellectual Property to endorse the idea, and suggests that there may be a general move in this direction "within the next 2 or 3 years."

Some British government officials point out that a grace period would help avoid situations—such as that which occurred with monoclonal antibodies in the mid-1970's—where the commercial potential of a discovery is only realized after it has been published, and when it can no longer, under the present system, be patented in the United Kingdom.—**D.D.**

and private ventures, and the lack of any moral imperative frequently felt in the United States to maintain, at least in principle, a sharp dividing line between the two. Furthermore, as with the Celltech/MRC deal, negotiations have often been conducted discreetly out of the public eye.

Either way, there has been little of the public controversy over the restructuring of traditional relationships between the research community and the rest of society that has accompanied similar moves in the United States.

The situation has not been without its critics. Edward Yoxen, lecturer in the University of Manchester's department of liberal studies in science, points out in a recent study *The Gene Business* that many significant policy changes, such as the dispensation on access to MRC research awarded to Celltech, have taken place with little open discussion, even though the basic discoveries on which the new technologies are based were financed largely from public funds. "There has been virtually no public debate on this type of issue," says Yoxen.

"The academic excellence in places like the MRC should be treated as a national resource and the government should be providing evenhanded access to it," says Chris Keightley.

Few concerns were expressed, for example, over the government's recent decision to drop the "public interest" members from its main regulatory watchdog, the Genetic Manipulation Advisory Group, when this body was recently reformulated as the Advisory Committee on Genetic Manipulation, and its day-to-day responsibilities for registering and monitoring experiments passed to the Health and Safety Executive.

The lack of such debate, however, has certainly not hampered the gradual dismantling of barriers to open cooperation between the academic and the commercial communities, a process openly encouraged by the government. The SERC's Biotechnology Directorate, for example, has recently established what is described as a "protein engineering club," in which major companies such as Glaxo and Unilever will help sponsor research in various academic institutions into ways of producing proteins to order in large quantities.

Similarly, several university institutions are using government money, both from the research councils and the Department of Trade and Industry, to help set up commercial operations. The University of Leicester, for example, has recently obtained backing from five major corporations to establish a center for research into yeast genetics. And the Imperial College of Science and Technology in London has established a company known as Imperial Biotechnology to exploit its research facilities in fermentation techniques.

Keen that the nation should reap a profit from its past and present scientific investments, the government is increasingly engaging in as much industrial planning as it feels it can get away with behind its free-enterprise, non-investment image. Responding to demands from companies such as Imperial Chemical Industries, as well as officials within the SERC, for some form of "national biotechnology program" to cover the spectrum of possible initiatives from tax incentives to information networks, the Department of Trade and Industry has recently set up a special advisory committee made up primarily of senior industrialists to look at areas where an extra push might be useful.

Taken in isolation, none of these moves is itself seen as a guarantee of success. But behind them lie two additional factors that help account for the current bullishness of Britain's biotechnologists. One, as Nicholson of the Cabinet Office puts it, is that "there is more optimism in the business sector than there was 6 or 9 months ago; we certainly started pulling out of the recession faster than either Germany or France."

The other is the gradual emergence of a new spirit of entrepreneurialism among British academics. "In the past, most academics had no idea about how to start up in business; but all that is now changing," says Keightley of IQ(Bio), a Cambridge biochemist who was about to emigrate to the United States when Acorn offered him the opportunity of helping start up the new company.

Similarly, Celltech points out proudly that it has managed to persuade one of the top teams of MRC scientists, headed by immunologist William Hunter of Edinburgh University, to join the company's new venture with Boots. "We have a fabulous opportunity here in Britain," says Keightley. "We are now learning how to capitalize on it."—David Dickson

Meselson Meets a Shower of Yellow Rain from Bees

Matthew Meselson, the Harvard biochemist waging a one-man challenge to the U.S. State Department's version of Yellow Rain warfare, went into the jungles of Thailand last month to test his thesis. He returned at the end of March with a new evidence, declaring the trip a greater success than he had anticipated.

Along with two bee experts who joined him in looking for natural forms of Yellow Rain, Meselson was caught in a 5-minute shower of bee droppings, which he thinks may be the real source of Yellow Rain samples being analyzed by U.S. military labs. Meselson and Thomas Seeley, a biologist at Yale University, last year developed a theory that Yellow Rain spots regarded as chemical weapon deposits were actually the feces of the wild Southeast Asian honey bee, *Apis dorsata* (*Science*, 24 June 1983, p. 1356). The theory was based on the knowledge that honey bees periodically make "cleansing flights" away from the hive, that their droppings contain pollen, and that most of the government's samples of Yellow Rain collected from the environment contain pollen.

Meselson noticed that the government's data on Yellow Rain were gathered in Southeast Asia between February and May. Using funds recently awarded him by the John D. and Catherine T. MacArthur Foundation, he went to Thailand in the middle of this ripe evidentiary season hoping to find proof that Southeast Asian honey bees do produce yellow, pollen-laden rain.

Meselson and Seeley reported at a press conference at Harvard on 28 March that they have proof that *A. dorsata* performs "massive defecation flights which can cover a swath thousands of square meters in area with 100 or more spots of yellowish feces per square meter." They found and studied ten swaths in Thailand and were caught in a bee feces shower that left "about a dozen spots . . . on each member of our three-man team." Meselson says this occurred near a tree in which they had spotted *A. dorsata* nests, but the bees were so far above the ground that he could not see or hear them.

Will Deficits Put a Damper on R & D?

Ninth AAAS Colloquium on R & D worries about looming budgetary gaps, asks if some new initiatives are too much of a good thing

In its annual look at the new federal budget, the AAAS Colloquium on R & D this year found the prospect of outsize federal deficits to be a threat to a currently prosperous R & D regime. And there were also misgivings that initiatives in the new R & D budget would cause trouble in coming years.

As has become the colloquium custom, the President's science adviser was the de facto keynote speaker, providing an interpretation of the R & D budget to which later speakers frequently referred, although not necessarily deferred. Incumbent science adviser George A. Keyworth, II provided a bullish review of the Administration's R & D policy and its implementation, but, at the outset, took issue with what he described as the "generally gloomy view of federal R & D" found in the introductory chapter of the annual budget analysis issued by AAAS to coincide with the colloquium.*

The authors early state their ambivalence with the comment that "It is a strong budget for R & D, but analysis of the totals raises questions. The big increase is almost entirely on the military side. Total non-defense R & D budget authority increases only about as much as inflation." The main concern is not directed at the makeup of the new budget. Rather, "Questions on R & D spending plans in the FY 1985 budget are overshadowed, however, by the need for drastic actions to reduce the deficit. Beneath the political posturing on both sides there is a realization that something has to be done."

The analysis predicts a continuing pattern of deficits in 1985 and after. "Thus the FY 1985 budget is not a budget in the traditional sense of the President's plan for dealing with the problems of the nation. It is instead a statement of the problem with the answers left up in the air—to be found in bipartisan negotiations with Congress, unilateral Congressional actions, or a new Presidential initiative some time after the election."

Another strain of ambivalence was expressed by National Academy of Engineering President Robert M. White who seemed to be asking, in essence, whether the R & D budget amounted to too much of a good thing. Like other speakers, White was complimentary about the Administration's actions in fashioning a budget that reflects strong confidence in R & D, noting that the real growth in total federal R & D funds under its aegis has been the largest since the 1960's. But he questioned whether the Administration's commitment to technology might amount to an overcommitment.

Noting examples like plans for a manned space station, a space-based missile defense, "a multitude and diversity of defensive and offensive strategic and tactical systems," and an ambitious strategic computing program, he said these contributed to what he termed a "technological flood tide."

Citing the "bow-wave effects" of such initiatives over time on the economy, on the availability of manpower and materials, and on the industrial competitiveness of U.S. industry, he urged that the issues be examined with caution. "My concern is that, as a community of scientists, engineers and technologists, we will be perceived as careening from worrying about insufficient investments in science, engineering and technology to meet national needs to a concern that we may be embarked on a course with unanticipated ends."

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Keyworth concentrated on an explication of the Reagan Administration's R & D policy, but along the way he did offer some general answers to the critics. He noted, for example, that they tend to lump funding increases and decreases together "with the result that we can't appreciate the impacts of either." And he observed, "That view seems to imply that changes are inherently bad."

He also took exception to the way comparisons between defense R & D and civilian R & D are made. Keyworth noted that many of those who insist on casting R & D policy "in that simple-minded mold of guns and butter" arrive "at the absolutely false conclusion—or maybe they start there—that the federal government's only R & D priority is for defense."

Keyworth said that the Administration had assuredly given a high priority to strengthening defense, but the point the critics miss is that it "also strongly stated a similar priority for university basic research." The core of Keyworth's case was contained in his remark that "Most of the increases in defense R & D come from development costs associated with the modernization of the nation's strategic forces—an action to restore strength that was eroded during the previous decade. On the other hand, the flat curve in civilian R & D reflects two countervailing trends—a steady drop in development and a steady rise in basic research. The essential point is that the Administration is targeting strong funding growth in both defense and basic research."

Keyworth dealt with the deficit issue obliquely. In his text, he said, "we all recognize that one of the most serious detriments to good science is what we might call roller coaster funding. The best protection against that phenomenon is for the science community to demonstrate, year after year, that R & D funds are being used wisely and effectively." And in his conclusion he developed the theme of shared responsibility. He acknowledged that the Administration had to articulate goals clearly and said "we have to stick to those goals in practice. I see this consistency as a major element of science policy, an element that I hope the Administration, the Congress, the science community and the public will be able to maintain in coming years."

In summarizing comments at the end of the colloquium, AAAS Executive Officer William D. Carey phrased his major point as the answer to the question, "What should science watchers watch?" Carey observed that in present circumstances they should not be preoccupied with minor trends in the R & D budget itself, but rather should consider such things as economic policy, export policy, and policies for defense. Carey noted that Reagan Administration treatment of basic research and higher education has been favorable. He suggested, however, that "consistency is not to be counted on," since future decisions will be determined by policies senior to science policy.—JOHN WALSH

*AAAS Report IX: Research and Development, FY 1985. AAAS. 284 pages.

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and private ventures, and the lack of any moral imperative frequently felt in the United States to maintain, at least in principle, a sharp dividing line between the two. Furthermore, as with the Celltech/MRC deal, negotiations have often been conducted discreetly out of the public eye.

Either way, there has been little of the public controversy over the restructuring of traditional relationships between the research community and the rest of society that has accompanied similar moves in the United States.

The situation has not been without its critics. Edward Yoxen, lecturer in the University of Manchester's department of liberal studies in science, points out in a recent study *The Gene Business* that many significant policy changes, such as the dispensation on access to MRC research awarded to Celltech, have taken place with little open discussion, even

"The academic excellence in places like the MRC should be treated as a national resource and the government should be providing evenhanded access to it," says Chris Keightley.

though the basic discoveries on which the new technologies are based were financed largely from public funds. "There has been virtually no public debate on this type of issue," says Yoxen.

Few concerns were expressed, for example, over the government's recent decision to drop the "public interest" members from its main regulatory watchdog, the Genetic Manipulation Advisory Group, when this body was recently reformulated as the Advisory Committee on Genetic Manipulation, and its day-to-day responsibilities for registering and monitoring experiments passed to the Health and Safety Executive.

The lack of such debate, however, has certainly not hampered the gradual dismantling of barriers to open cooperation between the academic and the commercial communities, a process openly encouraged by the government. The SERC's Biotechnology Directorate, for example, has recently established what is described as a "protein engineering club," in which major companies such as Glaxo and Unilever will help sponsor research in various academic institutions into ways of producing proteins to order in large quantities.

Similarly, several university institutions are using government money, both from the research councils and the Department of Trade and Industry, to help set up commercial operations. The University of Leicester, for example, has recently obtained backing from five major corporations to establish a center for research into yeast genetics. And the Imperial College of Science and Technology in London has established a company known as Imperial Biotechnology to exploit its research facilities in fermentation techniques.

Keen that the nation should reap a profit from its past and present scientific investments, the government is increasingly engaging in as much industrial planning as it feels it can get away with behind its free-enterprise, non-investment image. Responding to demands from companies such as Imperial Chemical Industries, as well as officials within the SERC, for some form of "national biotechnology program" to cover the spectrum of possible initiatives from tax incentives to information networks, the Department of Trade and Industry has recently set up a special advisory committee made up primarily of senior industrialists to look at areas where an extra push might be useful.

Taken in isolation, none of these moves is itself seen as a guarantee of success. But behind them lie two additional factors that help account for the current bullishness of Britain's biotechnologists. One, as Nicholson of the Cabinet Office puts it, is that "there is more optimism in the business sector than there was 6 or 9 months ago; we certainly started pulling out of the recession faster than either Germany or France."

The other is the gradual emergence of a new spirit of entrepreneurialism among British academics. "In the past, most academics had no idea about how to start up in business; but all that is now changing," says Keightley of IQ(Bio), a Cambridge biochemist who was about to emigrate to the United States when Acorn offered him the opportunity of helping start up the new company.

Similarly, Celltech points out proudly that it has managed to persuade one of the top teams of MRC scientists, headed by immunologist William Hunter of Edinburgh University, to join the company's new venture with Boots. "We have a fabulous opportunity here in Britain," says Keightley. "We are now learning how to capitalize on it."—**DAVID DICKSON**

Meselson Meets a Shower of Yellow Rain from Bees

Matthew Meselson, the Harvard biochemist waging a one-man challenge to the U.S. State Department's version of Yellow Rain warfare, went into the jungles of Thailand last month to test his thesis. He returned at the end of March with a new evidence, declaring the trip a greater success than he had anticipated.

Along with two bee experts who joined him in looking for natural forms of Yellow Rain, Meselson was caught in a 5-minute shower of bee droppings, which he thinks may be the real source of Yellow Rain samples being analyzed by U.S. military labs. Meselson and Thomas Seeley, a biologist at Yale University, last year developed a theory that Yellow Rain spots regarded as chemical weapon deposits were actually the feces of the wild Southeast Asian honey bee, *Apis dorsata* (*Science*, 24 June 1983, p. 1356). The theory was based on the knowledge that honey bees periodically make "cleansing flights" away from the hive, that their droppings contain pollen, and that most of the government's samples of Yellow Rain collected from the environment contain pollen.

Meselson noticed that the government's data on Yellow Rain were gathered in Southeast Asia between February and May. Using funds recently awarded him by the John D. and Catherine T. MacArthur Foundation, he went to Thailand in the middle of this ripe evidentiary season hoping to find proof that Southeast Asian honey bees do produce yellow, pollen-laden rain.

Meselson and Seeley reported at a press conference at Harvard on 28 March that they have proof that *A. dorsata* performs "massive defecation flights which can cover a swath thousands of square meters in area with 100 or more spots of yellowish feces per square meter." They found and studied ten swaths in Thailand and were caught in a bee feces shower that left "about a dozen spots . . . on each member of our three-man team." Meselson says this occurred near a tree in which they had spotted *A. dorsata* nests, but the bees were so far above the ground that he could not see or hear them.

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for the development of new products.

That picture represents a misunderstanding. Although MITI does indeed sponsor R & D programs, such as the highly publicized ones on integrated circuits and the fifth-generation computer, the R & D tends to be basic and engineering research. In the United States, such R & D efforts are centered in our universities.

The commercial R & D successes of Japan, as opposed to efforts to develop the underlying technologies, have been driven not by MITI but by Japanese industry, even in integrated circuits. The participants in the MITI-sponsored cooperative integrated circuits program went back to their own laboratories to develop the actual commercial 64K random access memory chips that have been so successful in the marketplace. Oki Electric, the fastest growing Japanese producer of 64K chips and the first Japanese company to test a 256K chip, did not even participate in the MITI program.

The Japanese government, which has played an important role in promoting its industries' fortunes through such means as protectionist trade policies, has not been a significant force in commercial technology selection and development. The successes of Japan in businesses based on advanced technology are mainly the result of smart, persistent industrial R & D management. Private corporations in Japan make long-term R & D commitments to relatively narrow areas. They pick a target, such as video recorders, assemble large teams to pursue that target, and stick with it for as long as is necessary to bring a winning product to market. They do not try to cover the R & D waterfront, and they do not back out if the payoff is not immediate. They also practice a technique that I call "innovation by experiment," whereby they put a product out on the market, even in imperfect and sometimes expensive form, and learn from the customers how to improve it. And finally, they are aggressive in acquiring, improving, and implementing technology that they did not develop.

These strategies do not explain all of Japan's success in commercial technology, but they do indicate that the real source of that success is Japanese industry. Also, they underscore the lesson that we should learn from Japan: that the selection of the product technology and its development is best left to the people intimately familiar with the technologies and the markets. Technology selection and development should not be managed from afar.

Creating Conditions for Innovation

What role should the U.S. government play with respect to R & D? That role is not to manage technology-based commercial innovation but to create the conditions for such innovation. The government should provide an encouraging and supportive environment and infrastructure within which industries select and develop commercial technology.

There are many features of such an environment that deserve attention: a favorable tax climate exemplified by R & D tax credits, by extension of those credits to software, and by fast depreciation of R & D equipment; modified antitrust laws that encourage cooperative R & D and limit damages for civil violations; export control laws and regulations that do not disrupt the interchange of scientific and technical information that is so vital to the progress of technology; and immigration laws that permit outstanding foreign scientists to remain in the United States to do R & D.

Support for University Research

The most important role for government in creating the conditions for commercial innovation is to support universities in their efforts to generate research and provide manpower. The most crucial issue we face is a lack of skilled manpower, a shortage of faculty in universities for training that manpower, and a deteriorating research capability in our great universities because of the shortages of both faculty and modern equipment for instruction and for research.

American industry today simply cannot get enough of the people it needs in such fields as microelectronics, artificial intelligence, communications, and computer science. The universities are not turning out enough R & D people in these areas, or enough research faculty. There is little that private companies can do about this. We contribute to the support of universities, but industry will never be able to meet more than a small fraction of university R & D funding needs. Even after a decade of steadily increasing industry support for universities, industry provides only about 5 percent of total university R & D funding. Congress is considering additional incentives for industry support of universities, but the fact remains that the primary responsibility for ensuring a strong, healthy academic research system and thereby for providing an adequate supply of research and skilled people must rest with the federal government.

There is wide agreement that the federal government should support the universities, and, in fact, federal basic research obligations to universities and colleges, measured in constant dollars, have grown by more than 25 percent over the past 3 years. But this is only a start in filling the needs. Department of Defense funding of basic research, for example, has only in the past 2 years returned to the level, measured in constant dollars, that it was in 1970. The Defense Department has traditionally played a vital role in supporting basic university research. A time of rapid expansion of the defense budget is no time to abandon that tradition.

Universities have had to compete with the national laboratories for the Department of Energy's research dollars. When research is funded at a university, not only does the research get done, but also students are trained, facilities are upgraded, faculty and students get more support, and thereby better faculty and students are attracted. Moreover, the students that go into industry help in the transition of advanced research into concepts for industrial innovation. When the same research is funded at a national laboratory, most of the educational dividends are lost.

Universities should not have to compete head on with national laboratories for mission agency funds. Unless the national laboratory will do a substantially better research job, the university should get the funds. The same holds for government funding of research in industry. Those funds that advocates of industrial policy propose to invest in government-directed industrial R & D would normally be much better spent in universities, unless there is a special reason why an industrial laboratory can do it much, much better.

I am not proposing that we simply throw money at universities. We need to be selective. To borrow a phrase from the industrial policy advocates, the government should stress the growth of "sunrise science and technology." Unlike the targeting of sunrise industries, the targeting of sunrise—that is, fast moving—areas of research can be done. We can identify these technologies, even if we cannot specify in advance precisely what products or industries they will generate. But we are not doing this as well as we can and should. In microelectronics, for example, a study by the Thomas Group, a Silicon Valley consulting firm, concludes that government support of university microelectronics programs totaled only about $100 million between 1980 and 1982. To put that into

Diurnal Variation of Stratospheric Chlorine Monoxide: A Critical Test of Chlorine Chemistry in the Ozone Layer

P. M. Solomon, R. de Zafra, A. Parrish, J. W. Barrett

Abstract. *This article reports measurements of the column density of stratospheric chlorine monoxide and presents a complete diurnal record of its variation (with 2-hour resolution) obtained from ground-based observations of a millimeter-wave spectral line at 278 gigahertz. Observations were carried out during October and December 1982 from Mauna Kea, Hawaii. The results reported here indicate that the mixing ratio and column density of chlorine monoxide above 30 kilometers during the daytime are ~ 20 percent lower than model predictions based on 2.1 parts per billion of total stratospheric chlorine. The observed day-to-night variation of chlorine monoxide is, however, in good agreement with recent model predictions, confirms the existence of a nighttime reservoir for chlorine, and verifies the predicted general rate of its storage and retrieval. From this evidence, it appears that the chlorine chemistry above 30 kilometers is close to being understood in current stratospheric models. Models based on this chemistry and measured reaction rates predict a reduction in the total stratospheric ozone content in the range of 3 to 5 percent in the final steady state for an otherwise unperturbed atmosphere, although the percentage decrease in the upper stratosphere is much higher.*

Chlorine monoxide (ClO) has for some years been recognized as a key tracer of the stratospheric ozone depletion cycle arising from natural and anthropogenic injection of chlorine-containing compounds, principally halocarbons, into the atmosphere (*1*, *2*). The reactions

$$O_3 + Cl \rightarrow ClO + O_2 \quad (1)$$

and

$$ClO + O \rightarrow Cl + O_2 \quad (2)$$

constitute the catalytic cycle by which chlorine atoms convert ozone, O_3, to diatomic O_2.

There is a strong diurnal variation expected in the concentration of ClO. After the recombination of atomic oxygen at sunset, reaction 2 ceases. At night, ClO is believed to combine in a three-body reaction with NO_2 to form chlorine nitrate,

$$ClO + NO_2 \xrightarrow{M} ClONO_2 \quad (3)$$

which is thought to be the dominant reservoir of chlorine in the absence of sunlight. During daylight hours, free chlorine is again produced from this reservoir by the photolysis of chlorine nitrate:

$$ClONO_2 + h\nu \rightarrow Cl + NO_3 \quad (4)$$

The rate of nighttime removal of ClO via reaction 3 is dependent on the NO_2 concentration and the total density, both of which decrease with altitude above 30 km: thus high-altitude ClO is expected to last through the night, while ClO at lower levels (altitude $\lesssim$ 35 km) disappears. Earlier measurements by in situ resonance fluorescence (*3*), infrared heterodyne spectroscopy (*4*), balloon-borne (*5*) and ground-based (*6*) millimeter-wave spectroscopy have established the presence, approximate quantity, and vertical distribution of daytime stratospheric ClO. A more critical test of the full complex of reactions of stratospheric chlorine may be obtained from measurements of the diurnal variation of ClO. Such observations avoid the complications and uncertainties introduced by vertical and lateral transport and long-term seasonal trends. Earlier balloon-based millimeter measurements over a limited portion of the diurnal cycle have shown a decrease in ClO at sunset and an increase after sunrise (*5*). In this article we present a complete diurnal record of ClO variation, with a time resolution of 2 hours, acquired by ground-based remote sensing of millimeter-wave line emission.

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Observations of Emission Lines

The ClO molecule has millimeter-wave rotational spectral lines spaced approximately every 37 GHz. We have reported measurement (*6*) of the line at 204.352 GHz from the $J = 11/2 \rightarrow 9/2$ levels. Our current measurements are based on the $J = 15/2 \rightarrow 13/2$ transition at 278.630 GHz. We use a cryogenically cooled millimeter-wave heterodyne mixer receiver with a noise temperature of 1100 K, approximately 2½ times more sensitive than our earlier detector (*6*). Use of this more sensitive detector, combined with an increase by a factor of 2.4 in the theoretical line intensity for the higher frequency 278-GHz line as compared with the 204-GHz line, has led to a sixfold increase in observational sensitivity. For a fixed signal-to-noise ratio, the required measurement duration is reduced by about a factor of 6^2 or 36, allowing a relatively high time resolution to be achieved. The "back-end" spectrometer consists of a filter bank with 256 channels, each with a bandwidth of 1 MHz. The measurement technique, calibration method, and instrumental configuration described earlier (*6*) remain unchanged.

Our observations were carried out at the summit of Mauna Kea, Hawaii (elevation, 4250 m; latitude, 19.5°N) during two periods, from 8 to 11 October and from 9 to 16 December 1982. The atmospheric water vapor content, which dominates the tropospheric absorption of stratospheric emission lines at millimeter-wave frequencies, was very low and generally stable around the clock during these observation periods (*7*).

In the following discussion, we present emission intensities as brightness temperatures in kelvins. This custom, commonly used in radio astronomy, is derived from the Rayleigh-Jeans approximation for blackbody radiation, in which emitted power per unit frequency is linearly proportional to temperature. All intensities represent the values that would be observed if one were looking through one stratospheric air mass toward the zenith after removing the effect of tropospheric attenuation.

In Fig. 1, we present a sample of midday (1230 to 1630) and nighttime tive) from that of 17 with small-cell lung carcinoma (15 positive) is striking (see Table 1). Both cancers have common ancestry, but the former is of comparatively low malignancy and the latter is extraordinarily malignant.

5) While patients with carcinoma generally showed cellular and humoral immune responses to carcinoma-associated T antigen, the humoral response was stimulated preferentially by tubular and early lobular breast carcinomas, which had T activity comparable to other carcinomas. Significantly, these carcinoma types have a favorable prognosis among breast carcinomas (*8*, *54*).

The Tn/anti-Tn system may complement the T/anti-T system in elucidating aspects of the pathogenesis of carcinoma and in early diagnosis. While the link between Tn and carcinoma has been known for a decade (*10*), this system has not been studied in the present context. Research is complicated by the usually low concentration of anti-Tn. Tn's immunodominant structure, GalNAc-α, is also the dominant part of the blood group A and Forssman haptens, which may prevent some anti-Tn immune responses. Furthermore, Tn antigen is not readily obtainable from healthy tissues (*7*). There are, however, some highly instructive experiments by nature herself that show not only how unmasked Tn arises in hematopoietic stem cells, usually persisting indefinitely without malignant change, but that Tn, the epigenetic sequela of a rare, benign, somatic mutation, occasionally precedes and then accompanies leukemia, disappears upon chemotherapy-induced remission, and reappears in relapse (*66*).

Conclusion and Prospects

The studies described here have revealed, in a large number of carcinoma patients, a close link between malignant transformation and early, persistent changes in common carcinomas: unmasked precursor antigens T and Tn, that allow the patient's immune system to qualitatively differentiate carcinoma from noncarcinoma.

On rare occasions, demonstrable T and Tn antigens occur in premalignant lesions, which may either remain that way permanently or progress to frank malignancy. Some tissues with such changes are accessible to longitudinal study and thus aid in determining the decisive point of malignant transformation. This approach may be facilitated by manipulation of immune responses, as well as by locating incipient carcinomas with labeled mono- and polyclonal anti-T and anti-Tn reagents (*25*, *26*, *67*) [but see the introduction and (*27*)]. Our monoclonal antibodies to T and Tn were generated by desialylized human O erythrocytes. We obtained three relevant specificities: anti-T, anti-Tn, as well as a specificity directed toward a moiety shared by T and Tn haptens (*67*). The three types of antibodies reacted strongly and specifically with carcinomas in immunohistochemical analyses of surgical specimens but less well in antibody absorption studies (*27*).

Our recent observation (*68*) in carcinoma patients, but not healthy persons, of a significant increase in lymphoid cell cytolytic activity against target cells with surface-exposed T and Tn antigens supports T and Tn's importance in the malignant process—especially since there was often a concomitant decrease in natural killer cell activity. The findings discussed here, although they are in an emerging phase, indicate that uncovered T and Tn antigens endow the carcinoma cells with a multitude of novel functions. These functions may be fundamental to the multistep processes of invasion and spread of carcinoma, and clearly have a profound, measurable effect on the tumor bearer's immune system. T antigen is likely to be a powerful probe in early carcinoma detection.

References and Notes

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