9.1/6

File
WASH. STAR Editorials
Nov. 8, 1975

Ralph Nader

'The Bigger, the Better?'

For over 100 years the slogan, "the bigger, the better" has guided the business community.

Even today, few executives would question the validity of such a slogan. Banks with assets exceeding $30 billion, oil companies with sales over $30 billion annually and insurance companies with millions of policyholders are believed to be big because they are better for consumers and the country.

ARE THEY? Let's look at the bigness issues a little more closely:

1. Smaller companies can do a better job for the consumer than the giants are doing in the same industry. This is true, for example, in the pricing of life insurance or servicing by truck companies. Small businesses, whose owners know they can win under fair competition, are unable to fight the political and predatory market practices of their opposing goliaths.

2. Companies can become so large that government cannot allow them to fail. While small business is perfectly free to go bankrupt, big business can go to Washington — for a bailout. Apart from the more sensational welfare case of the Penn Central, big corporations are in Washington all the time asking for handouts on the grounds that if they don't get them they will go broke and damage the economy.

3. Giant corporations very often mean giant monopolies or giant monopolistic practices, which fleece consumers out of billions of dollars, as detailed by the Senate anti-monopoly subcommittee over the years. Frequently big business forces small business to go along with their anti-monopoly violations.

4. BIG corporations, historically without much of an innovative record, just as historically have lunched off lone inventors or small firms. A Department of Commerce study in the mid-'60s showed that individuals were the source of most inventions that helped build the economy, not the fabled corporate laboratories.

In 1964, Donald Frey, vice president of Ford Motor Co., noted that auto suppliers, not the big auto companies, were the prime source of innovation.

5. Big corporations gravitate toward massive technologies because it is more profitable for them and more expensive for consumers. Recently, big technology is more likely to induce tax concessions or government subsidies.

In the quest for energy adequacy, why develop the abundant agricultural wastes and residues or other solar energies when there are more complex, expensive and government supported technologies like nuclear power around?

6. **BIG COMPANIES** can resist more strenuously the displacement of their existing technology by a more abundant form of new technology that is cheaper for the consumer. AT&T has preferred underseas cables at the expense of satellites; the three television networks long opposed cable TV development with its dozens of channels.

7. Big companies can control government and abuse significant political power more easily. Du Pont in Delaware, Union Camp in Savannah, Ga., and U.S. Steel in Gary, Ind., are only a few of the company states or company towns where bigness becomes virtual government. It is hard to think of small business overthrowing South American countries.

8. Conglomerate companies can afford to ignore one consumer sector if they can profitably shift to other consumer sectors, compared to firms rooted entirely in a smaller community. In such a case, only small business can fill the gap.

9. Large corporations encourage widespread community rootlessness by requiring constant moving of families between branch offices or plants.

10. Big companies are more likely to be inefficient than smaller-scale alternatives. Prof. Joe Bain has shown how, in several major industries, it is plant size, not company size, that determines efficiencies. The steel industry is a case study of that point. One giant publisher recently contracted for a series of books to a tiny publisher because it was cheaper than doing it in-house.

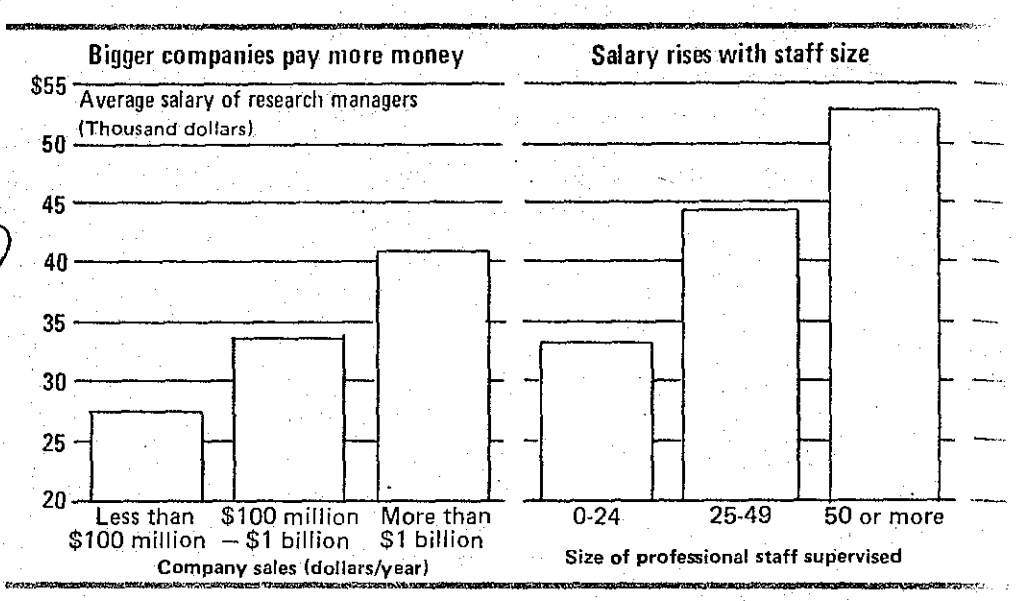
THE WHOLE question of efficiency needs a fresh review in other contexts as well, such as the side effects, maintenance costs, or injuries to consumers.

There need not be a reverse dogmatism in favor of all small enterprises to justify a critical examination of business bigness in our economy. Or to justify asking what such bigness is doing to our society's preferred values of individual initiative, responsibility and freedom from the giant organizations' conforming pressures.

CW Report
by Gordon M. Graff

File w/ editorials (see pgs. 30 & 33)

Researching the world of R&D managers



He is 47 years old and has been with the same company for the past 16 years. Since he left school with his highest degree in 1957, he has risen to direct a staff of 28 degreed chemists and chemical engineers. Last year he made a salary of $36,500, racked up a bonus of $4,800 and, more likely than not, took part in a stock-option plan. He finds it particularly hard to find qualified people for his organization, and he feels that excessive federal regulation has stymied creative and innovative research.

This is a profile of the research manager today, as revealed by a *Chemical Week* mail survey taken last month. It shows, by and large, a well-paid administrator who is hemmed in on several sides by internal and external constraints that make his job challenging and perplexing.

To avoid the pitfalls of comparing widely disparate sectors of the chemical process industries, *Chemical Week* sent out 117 survey questionnaires only to those readers identifying themselves as research and development managers in the "chemicals and allied products" segment of the CPI. Of the 63 questionnaires returned, 60 were used in the final tally. (Three were disqualified because the respondents no longer served in a managerial role.)

Wide Spectrum: As individuals, the respondents covered the age, salary and responsibility spectrum. The youngest manager was 27; the oldest, 72. The lowest salary reported was $20,000/year, while one manager received $75,000. The sizes of the professional staff (those with B.S., M.S. or Ph.D. degrees in chemistry or chemical engineering) supervised by the respondents ranged from one to 210.

As for degrees, 29 of the 58 managers who reported their educational background had Ph.D.s. Another 14 had only masters degrees; and surprisingly, 15 of the managers never went beyond bachelors degrees. Some of the respondents received their highest degree as long ago as 1938, while one graduated from school as recently as 1973.

Exactly twice as many of the managers (38) said they would be adding professionals to their staffs within the next year as those who responded that they would not (19). And of the 32 who listed the anticipated number of openings for professionals in their organizations this year, the average number of new openings reported was three.

It was anticipated that the current era of relative belt-tightening would be reflected in lower figures for the reported percentage of R&D funds alloted to new product and process development in 1977, compared with 1967. While this was indeed the case, the difference was not significant: 39.1% in 1977, as opposed to 41.5% in 1967.

The expected trend was more evident in

What's bugging research managers

"U.S. leadership in technological innovation is in trouble because U.S. business is managed by 'priority planning, selective investment, cash cows,' etc., which are really euphemisms for the old 'quick buck,' short-sighted management that has failed before."

"Top management is geared to short-range research at the expense of long-range, innovative research for which the immediate return is only a dream in someone's mind. A better balance is needed."

"Except for tax incentives, the federal government should be kept as far as possible from the operation of private industry."

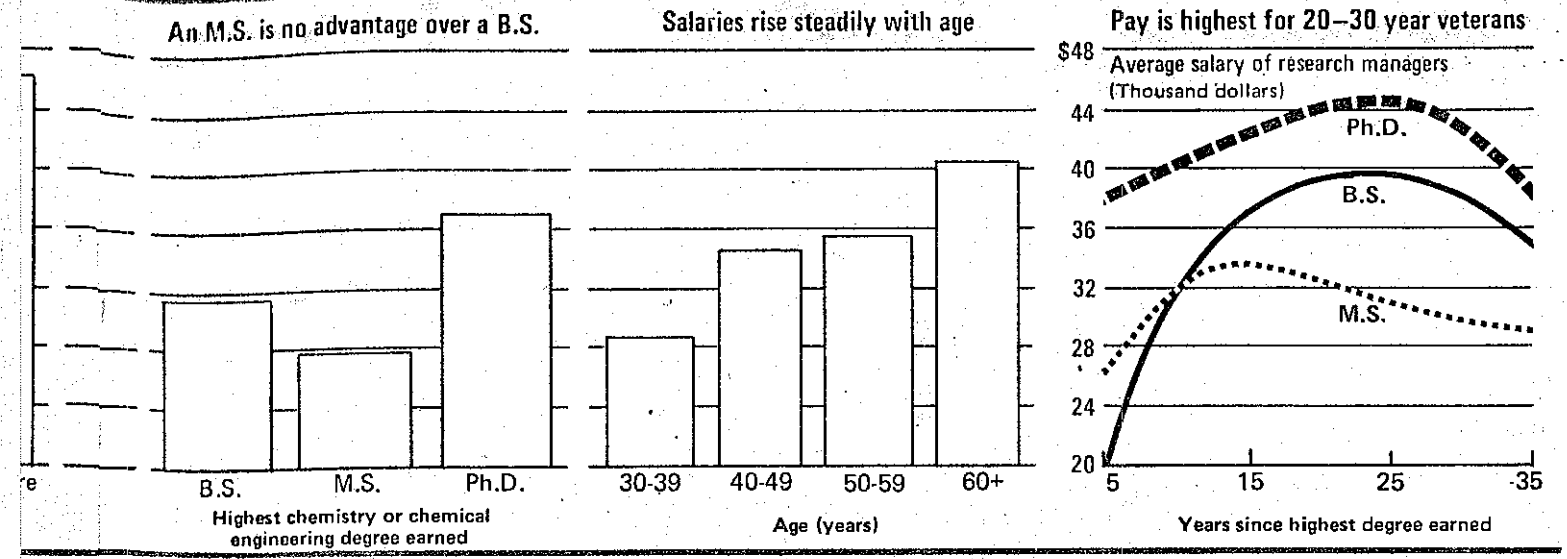
"Government regulations in the chemical industry are characterized by too much nit-picking and confusion."

"Industry needs to work more with government instead of confronting it."

'The chemical industry should stand up and respond more to the regulatory agencies, rather than letting them be swayed more and more by environmentalist groups."

"Shoot the Naderites and the anti-industry consumerists so that our value can be appreciated."

"The language and spelling of college graduates are atrocious. Their main problems are poor report writing and unclear recommendations. They tend to write reports like a mystery story."



responses to the question: "Is it easier or harder to obtain research funds in your company now than it was in 1967?" Among the respondents, 27 said it was now harder, 15 said it was easier, five said it was about the same, and nine said they didn't know.

Despite the key positions they hold, not all research managers are brought in on corporate decision making involving broad matters—for instance, major marketing or production decisions. While 38 of the managers responded that they were brought into decision making in these areas, 22 reported that they were not. And while 41 of the respondents thought there is adequate liaison between their departments and other departments in their firms (such as marketing and production), 19 felt there was insufficient communication within their firms.

Art vs. Science: How do research managers decide which projects to proceed with, considering the numerous available options? Surprisingly, only 25 of the managers who responded to this question said they used formal analytical tools such as risk analysis in determing which projects to undertake. The remaining 32 said they relied on "hunches," "intuition" and other nonobjective factors. Even in evaluating the success of their research programs, only 28 of the R&D directors said they used objective parameters, while another 26 reported the use of other indicators.

Eye on Education: By nearly a two-to-one margin, the R&D directors turned thumbs down on the effectiveness of U.S. chemical education today. Only 19 of the managers queried said they thought today's schools are preparing their chemistry and chemical engineering graduates adequately for careers in industrial research; 34 others rated the schools as inadequate in this respect.

For the question: "Do you feel industrial research can play a meaningful role in solving such national problems as energy and pollution?" the lion's share of the responses (55) were in the affirmative. Only one respondent felt otherwise. There was considerably more division, however, on the companion question: "If yes, is industry fulfilling that role as well as might be expected?" Among the responses received for this query, there were 21 in the yes column, 34 in the no column.

Asked to rate their problems from a list of choices, the managers put "a shortage of qualified people" and "no clear goals from top management" at the top of the list (*see table*).

Among external headaches, government regulations seemed to be the most vexing. A large chunk of respondents, 46, replied positively to the question: "Do you feel that rules and regulations of government agencies are seriously hindering new

"Most of the projects that graduate students work on have no connection with the real world. Most university research is a waste of money and time."

"Toxic data should be provided on all new products by their manufacturers."

"Excessive government regulation leads to less risk-taking and a sense of 'let's stop with what we already have.'"

"Companies should consider national needs as well as the current small effects of federal regulations on private industry."

"Intensive research is needed in recycling and to locate new sources of energy, with nonpollution of the environment paramount."

"Universities should be funded to do the basic research that is more difficult for industry to perform."

"Most new college graduates have zero idea of what R&D in industry does."

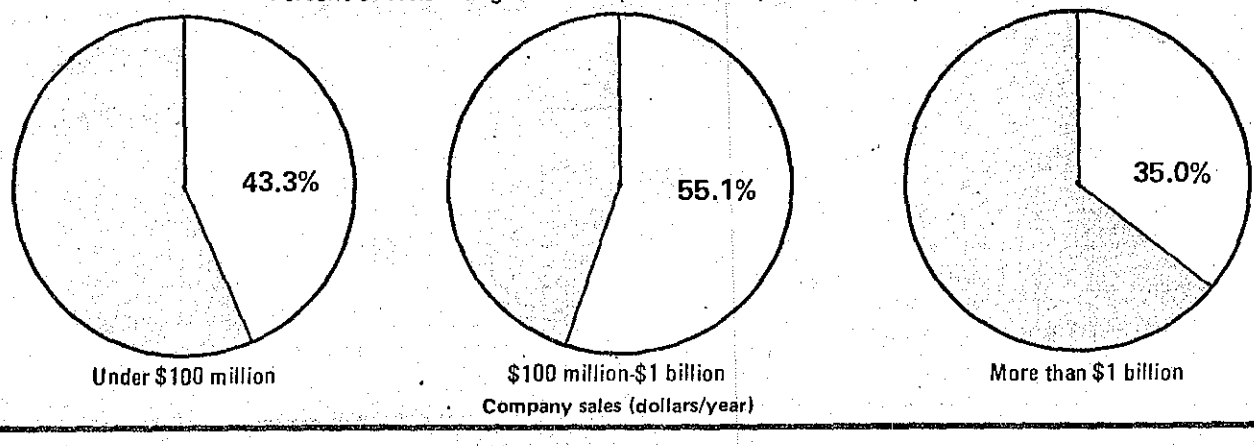
"New-product development has been slowed to a crawl by new and demanding carcinogen-mutagen testing requirements."

"Every researcher should have lots more projects and ideas than dollars. The problem is to determine the better ideas to work on."

"Industrial R&D can be aided by rigid exclusion of the media from news of research results until the results have been proved."

Big companies spend least fraction of R&D dollar on new product development

Percent of R&D budget for new product and process development



product and process development in the U.S. chemical industry?" Only 13 of the directors felt that the government presents no problems in this area.

When asked what the government can do to aid private R&D in risky and speculative areas, less than half the respondents chose any of four suggestions included in the questionnaire and few offered alternative proposals (*see table*).

The leading choices, however, were tax incentive plans, either for R&D in general or for research in specific high-priority areas. And research managers tend to look askance at quasi-public institutions which would sell technological discoveries to industrial bidders.

Taking a Closer Look: In order to obtain a clearer focus on the world of today's research manager, it helps to break down the raw data into more refined categories. For example, there is a clear relationship between the average salaries of research managers and the size of the company they work for (*see chart*). Frequently, group leaders in companies with annual sales in excess of $1 billion earn more than research directors for entire companies whose sales are less than $10 million.

Bonuses, like salaries, covered a wide range—from a low of 2.7% of annual salary to a high of 28.6%. Stock options are a less common feature than bonuses, but a significant number of R&D managers said they participate in such programs.

Salaries are strongly pegged to the size of the staff supervised by R&D managers (*see chart*). For example, those directors supervising a professional staff of fewer than 25 reported, on the average, a salary of $33,100/year. But the average annual compensation for those supervising a staff of 100 or more was $57,600.

An interesting exception to the general rule—higher degree means higher pay—was noted in the tabulation of the salary vs. degree data. While Ph.D.s, as expected, were on top of the heap in the salary department, compensation of those whose highest degree was an M.S. lagged behind that of managers who never received more than a B.S. (*see chart*).

One explanation for the difference might be found in the number of years that have elapsed since the degree was obtained. While B.S. and M.S. directors took their bachelor's degrees about the same number of years ago, the B.S. level managers tended to go immediately into corporate research, while the M.S. directors went to graduate school, spending anywhere from one to nine years there. During this time, their B.S. colleagues in industry got a jump on them in salary and promotions. And after the M.S. recipients got out of graduate school, their higher degrees did not offset the disadvantages of lost time spent pursuing those degrees.

But the experiences of M.S. directors in the survey are not typical of M.S. chemists as a whole. Numerous studies have shown that M.S. chemists tend to make, on the average, more money than B.S. chemists. In contrast, by 15 years after receiving their respective degrees, M.S. managers in the survey were found to earn less, as a group, than B.S. level directors.

It comes as little surprise that the salary of a research director rises with his age (*see chart*). The tally of salary vs. age shows a sharp upward leap from the mid-30s to the mid-40s, with a much more sluggish rise from the mid-40s to the mid-50s. The peak salary—$50,000—was recorded in the "65 or more" age category, but this is somewhat deceptive, since the ranks of research managers start to thin noticeably after age 60. This seems to be due either to voluntary or involuntary retirement.

For research managers under 60, the highest average salary—$40,200—was reported in the age 55-59 bracket. The message of these statistics seems to be that the few research directors who are allowed to remain active into their 60s and beyond can expect to make even more money than the already well-paid managers in their 50s, who, however, are present in much higher numbers.

There is no such steady rise in salary when it is tabulated as a function of years since the highest degree earned. The comparisons show the existence of definite salary peaks for all three degree levels (*see chart*). For B.S. and Ph.D. recipients, the peak pay tends to occur about 25 years after graduation. For M.S. directors, however, the peak is reached earlier—at about 15 years.

Those respondents who reported receiving their highest degrees 35 years ago earned less, as a group, than those who left school with a degree 25 years ago.

Stressing the Bottom Line: Turning away from the personal characteristics of research directors to their professional experiences, it is clear that finding funds for their projects is one of their key concerns. While the bountiful days of the 1960s have long since vanished, research funds are still widely available. And formulas for dividing up the research dollar by type of goal (new products and processes, for instance) have scarcely changed.

What has changed over the past 10 years is the ease of obtaining funds. Today's research director must make a good case for the money to initiate and continue work on his project—a much stronger case than 10 years ago. And increasingly, the criteria used by senior

corporate officials to dole out R&D funds involve the question: Will it produce a marketable product within the short term?

This hard-nosed policy has not met with everyone's satisfaction and sparked some pungent comments from a number of research managers (*see box*). When asked why they think it is harder to obtain R&D funds from top management now than it was 10 years ago, research managers cited a variety of reasons, but certain distinct patterns were evident.

One manager summed up his answer to this question succinctly: "Greater cost consciousness." Another respondent, who was echoed by many of his colleagues, said he believed management's somewhat tight-fisted R&D funding policy is due to "little concern for long-term (one year or more) programs, plus requirements of new government regulations" covering health and the environment.

"Management is too cautious," observed another director of research. "It is willing to fund process improvement projects more so than fundamental research." Wrote another: "Increased government red tape makes it more difficult and expensive to develop new products." One manager cited the Toxic Substances Control Act, noting that "we're doing more defensive research to defend our current products."

Not all the constraints on R&D funds were seen as originating outside. Some directors cited lower company earnings in recent years and increased operational costs in general as additional factors limiting the flow of funds.

Among the research directors who reported that it is now easier to get R&D funds than 10 years ago, the comment of one is typical: "Our company's present business plans are oriented toward growth." In short, firms striving for long-term growth have generally made R&D funds easier to obtain, while those seeking to improve next year's balance sheet are taking a coldly practical view of R&D funding.

Predicting Success: Many of the companies that are stressing short-term payout in their R&D programs are asking their research managers to come up with an objective way of assessing the probability of success for new projects. As a result, some research directors are applying various qualitative and quantitative yardsticks to their programs. Many of these assessments fall under the general category of "risk analysis."

When asked to be specific about just which methods they use to predict the likelihood of success for their projects, the R&D directors cited such currently fashionable techniques as management by objective, discounted cash flow, return on assets, and return on investment. Some claimed to have elaborate computer programs for taking into account the multiplicity of variables that go into the success equation. Others say their companies have internal numerical systems in which a research proposal must get a certain rating in order to get off the drawing board.

Some research managers claimed that their projects are reviewed by top management every year. ("We use annual technical audits of research projects," wrote one.) Others were willing to disclose their numerical criteria. Reported one director: "Our projects must be market driven with at least a 75% chance of success. The return on investment must be greater than 40%."

Among the respondents who said they did not use a formal system for deciding which projects to go ahead with, one reported that "attempts to employ risk analysis have not been too successful." Another candid director said R&D funding decisions in his firm are made as a result of "the basic whim of the president."

Evaluating the success of past projects is often a criterion for deciding whether to supply the cash for related ones in the future. Many directors reported that their projects are subjected to a formal review of results by senior management. One R&D manager said that the return on investment of a program is the main input management uses to evaluate its success. Wrote another: "We use post-audit computer analysis, break-even analysis and payback return" to gage a project's success ratio. Some of the evaluation techniques reported are long-term in nature. "We use the tracking of sales and net profits over the years attributable to our R&D efforts," wrote one respondent.

How Good Are Graduates? By and large, the research directors gave the universities and colleges low grades in preparing their chemistry and chemical engineering graduates for the real world. When asked how school curricula could be made more responsive to the needs of business, the managers responded over and over again: "greater emphasis on the practical, less on the theoretical."

Specifically, as one respondent wrote: "There should be solid courses for chemists in industrial chemistry and the economics of business." Another wrote that students "need to be taught the role and purpose of a business. I'm afraid many of the professors teaching technology overlook this."

There are some fields in particular where the respondents felt that today's graduates are insufficiently versed. For chemistry students, wrote one, "there should be more exposure to industrial chemistry such as polymer chemistry and practical chemical engineering, as well as an emphasis on problem solving." Some said they thought chemistry graduates don't know enough about chemical engineering, and vice versa. A number of the respondents again cited polymer chemistry as one area in which chemistry graduates are insufficiently trained.

Another theme that ran through the reponses dealing with problems of chemical education was the noticeable inability of many of today's graduates to write a logical, coherent and grammatical English sentence. Typically, one director suggested that school curricula should include "additional training of chemists and chemical engineers in effective oral and written communication."

As for the suggested means of bringing a greater awareness of business problems into chemical education, there were a variety of proposals.

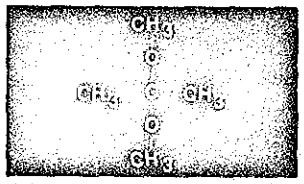
One manager said that graduate students planning industrial research careers should be required to attend special seminars on the nature of business, and of industrial R&D.

For undergraduates, suggested another manager, there should be an internship program in the senior year in which students would work in an industrial environment under a sponsor or supervisor. And one respondent said that industry should provide summer jobs for aspiring industrial researchers attending school, and the schools themselves should sponsor cooperative work-study programs as part of their curricula.

Tackling National Problems: While the vast majority of research managers said they feel private industry can play a meaningful role in solving such national problems as the energy shortage and pollution, most indicated that industry can hardly be expected to act out of pure altruism. They called for some form of economic incentive from government to make research in these areas worthwhile.

Typical of the comments on the role industry can play in tackling the energy shortage was the opinion of one R&D manager: "The benefits of alternative energy sources have not been elucidated from an economic standpoint. Industry could provide a workable and affordable

SODIUM SULPHATE
(Anhydrous)
SALT CAKE
PRIOR CHEMICAL CORPORATION
420 Lexington Avenue
Phone: 212-972-9811
New York, N.Y. 10017
Circle 32 on Mgt. Info. Service Card

Now Available....
2-2 DIMETHOXYPROPANE
Solvent dehydrating agent, intermediate in a wide variety of applications.

Now available again as min. 98% material to customer specifications from new production facility. For further information contact:
James Grier
Fisons Incorporated,
Muskegon, Michigan, U.S.A.
(616) 744-4711
or
David Kenworthy
Fisons Limited, Hauxton,
Cambridge, England
Cambridge 870312 (a c 0223)
FISONS INCORPORATED
Circle 33 on Mgt. Info. Service Card

CW Report

Shortage of qualified people tops managers' list of problems

Problem	Managers ranking problem as No. 1 concern	Percent
Shortage of qualified people	17	33.3%
No clear goals from top management	13	25.5
Lack of communication with marketing group	10	19.6
Shortage of funds	7	13.7
Other	4	7.8
Total managers responding	51	

solar heating and cooling system if given an incentive."

As for pollution, one director called for "emphasis on pollution problem solving through chemistry and engineering and not solely through compliance with government regulations."

There were frequent criticisms of the government's existing policies vis-à-vis industry. Wrote one R&D manager of public energy and pollution control policy: "The government is confused on where it is going, when, why and at what cost. It doesn't recognize the economics of industry. We need to get more industry people in Washington." Another respondent asserted that "government red tape stops a lot of work that could be done."

Repeatedly, the managers called for a working partnership between industry and government—but one that preserves the profit incentive for industry. For example, one director suggested that basic discoveries made at government agencies in the pollution and energy area could be developed by joint research programs at those agencies involving government and business. Another asserted that "tax incentives would help funnel additional funds to energy research. The end goal must be justified by economics."

At present, said many of the researchers, there is inadequate dialogue between government and industry on the energy and pollution problems. "We need to communicate better with government," wrote one. Specifically, another research director called for technical representatives from the business community to inform Congressional committees dealing with energy and pollution legislation about available problem-solving technology in industry. Congress would then be expected to provide the economic incentive for implementation of new proposals.

And industry should also try to get its message across to the public at large through a more vigorous public relations and advertising campaign, suggested another respondent.

Regardless of government actions, there are a number of things the business community can do unilaterally to alleviate the massive burdens of pollution and the energy shortage, asserted several of the researchers. "Companies should pool their resources to solve major problems" in the energy and pollution area affecting all of them, suggested one director.

One idea proposed by another manager was a national panel composed of representatives from government and industry. Its function would be to identify areas in energy and pollution where research input is needed and to make recommendations about how industry and government can work together to solve them.

Not all the researchers blamed the government for past lack of progress in solving national energy and pollution problems. For example, one research manager—distinctly in the minority—suggested that past efforts of business to tackle the industrial pollution problem have been less than sincere. "Companies need to make a more dedicated effort to reduce pollution than mere conformation to present standards," he wrote.

Bucking Bureaucracy: While a hefty margin of the research directors agreed that excessive government regulations are hindering development of new products and processes in the chemical industry, their reasons for this situation and their proposed solutions differed widely.

Such comments as "ambiguous rules, too much paperwork, needless delays," and "too rigid and often unreal" characterize the attitude of many toward the current maze of federal, state and local regulations controlling everything from worker safety and waste dumping in streams to development of new cosmetics and drugs.

"Compliance with many regulations makes some processes uneconomical. Higher management has become more concerned with not offending OSHA, EEOC, etc., than with innovative research to develop new long-range processes,"

The Chemistributors®
Subsidiaries of
Central Solvents & Chemicals Company

Atlanta (404) 448-7123
Atlanta Solvents & Chemical Company
Buffalo (716) 874-1600
Buffalo Solvents & Chemicals Corporation
Chicago (312) 594-7000
Central Solvents & Chemicals Company
Cincinnati (513) 242-7700
Amsco Solvents & Chemicals Company
Cleveland (216) 252-1100
Ohio Solvents & Chemicals Company
Dallas (214) 637-3450
Texas Solvents & Chemicals Company
Detroit (313) 941-4800
Western Eaton Solvents & Chemicals Company
Ft. Wayne (219) 749-5153
Hoosier Solvents & Chemicals Corporation
Grand Rapids (616) 245-9111
Wolverine Solvents & Chemicals Company
Greensboro (919) 454-1161
Southland Solvents & Chemical Company
Houston (713) 675-5241
Texas Solvents & Chemicals Company
Indianapolis (317) 638-1361
Hoosier Solvents & Chemicals Corporation
Kansas City (816) 241-3223
Missouri Solvents & Chemicals Company
Los Angeles (213) 773-3471
Central Solvents & Chemicals Co.
Louisville (502) 448-5111
Dixie Solvents & Chemicals Company
Milwaukee (414) 784-2400
Wisconsin Solvents & Chemicals Corporation
Minneapolis (612) 529-9236
Wisconsin Solvents & Chemicals Corporation
New Orleans (504) 837-8585
Southern Solvents & Chemicals Corporation
Oklahoma City (405) 232-2964
Oklahoma Solvents & Chemicals Company
Pittsburgh (412) 923-2570
Allegheny Solvents & Chemicals Company
Portland, Ore. (503) 286-5821
Central Solvents & Chemicals Co.
St. Louis (314) 421-3495
Missouri Solvents & Chemicals Company
Salt Lake City (801) 292-0437
Central Solvents & Chemicals Co.
San Antonio (512) 533-0123
Texas Solvents & Chemicals Company
San Francisco (415) 471-5420
Central Solvents & Chemicals Co.
Seattle (206) 226-8000
Central Solvents & Chemicals Co.
Spokane (509) 534-0519
Central Solvents & Chemicals Co.
Toledo (419) 536-3771
Toledo Solvents & Chemicals Company
Toronto, Ontario (416) 749-1591
Western Solvents & Chemicals (Can.) Ltd.
Vancouver, B.C. (604) 525-1651
Western Solvents & Chemicals (Can.) Ltd.
Windsor, Ontario (519) 252-5776
Western Solvents & Chemicals (Can.) Ltd.

Prove Quim S A de C V
Guadalajara, Jal., Mex. 12-16-00
Leon, Gto., Mex. 3 69 52
Los Mochis, Sin., 2-54-00
Mexico City, D. F. (905) 567-01-55
Monterrey, N.L., Mex. 52-47-90
Puebla, Pue., Mex. 2-86-12
Torreon, Coah., Mex. 3-38 73

THE SOLVENTS & CHEMICALS COMPANIES
7050 W. 71st. Street, Chicago, Illinois 60638

Research managers see tax incentives as spur to private R&D

Type of government incentive	Number who favor proposal*	Percent
Direct tax incentives for all industrial R&D	27	45.0%
Tax incentives for certain types of research (e.g., energy and pollution control)	26	43.3
Changes in antitrust laws that would allow cooperative research programs between different companies	22	36.7
Quasi-public institutions to carry out research in such areas as solar and fusion energy and medical technology. Developments would be sold to industrial bidders.	12	20.0
All of the above.	4	6.7
None of the above.	2	3.3
Other.	4	6.7

*60 questioned

complained one director. Wrote another: "OSHA, NIOSH, TSCA 'overkill' regulations are taking too much effort from constructive R&D. Everything points to a severe cutback in R&D output as TSCA implementation gets underway in 1978."

Regulations of federal agencies, wrote one manager, are "making it extremely difficult for small companies to survive. . . . The government keeps changing the rules and/or interpretations of them." Another echoed the complaint of ambiguous rules: "They contain cluttered language, with no clear guidelines to interpretation or intended objective." Still another researcher referred to "overlapping regulations between agencies."

Seeking Incentives: What can be done to enable industry and government to work together, instead of at loggerheads? Of the nearly half of the respondents who felt that the government should provide some incentives to private industry to engage in new and speculative research (such as novel energy sources, environmental management and basic medical sciences), most favored some form of tax relief for industry (*see table*).

Several researchers took the trouble to write a big "No!" next to the proposal for quasi-public institutions that would license discoveries to industrial bidders. "Definitely not!" wrote one researcher next to the proposal. "Private corporations use money and manpower more effectively." Wrote another respondent next to the suggestion: "They're too expensive, bureaucratic and nonproductive."

Many of the respondents offered suggestions of their own for government incentives to encourage private R&D in risky areas. "The government should stick to funding research at academic and medical research centers," wrote one R&D manager. "Government-controlled energy research will cost much more than it will ever return," he added.

One unusual proposal came from another research director: "Let the government help sponsor research by buying shares in newly formed businesses, thereby allowing for industry management and control."

Another manager called for a "change in most government agency policies towards patent licenses" in favor of "allowing exclusive licenses or significant lead time to justify development cost." One researcher went so far as to suggest that all basic research be done only in universities under government sponsorship.

Finally, one director probably reflected the thoughts of many of his colleagues when he suggested the ideal spur to private R&D: "Removal of unnecessary government regulations would do more than anything!" He didn't define "unnecessary," however. And some of the most hard-boiled critics of government indicated that some public regulation of industry is probably desirable.

Desirable or not, government rules and regulations will continue to be a fact of life for the research manager. And coping with them will likely be a major outlet for a research director's ingenuity and resourcefulness in the future. Just as in the past, R&D managers have withstood such ordeals as staff cutbacks, budget squeezes and soaring development costs, most seem to feel that they will be able to rise to this latest challenge.

File w/ editorials

other views

The world has a future—a great future

Perhaps one thing that has helped me has been an abiding sense of optimism. History teaches that it's been the optimists who have adjusted best to the changing tide of events—even though, paraphrasing Browning: "The reach has often been longer than the grasp."

What disappoints me most about today is that a distasteful spirit of "negativism" seems to permeate much of our society and the world we live in. . . .

It is not my nature to embrace such a depressing, fatalistic philosophy. So, if I may, I would like to leave with you the notion that all is not lost. . . . The problems we see today are not unlike the ones seen by those that have gone before us. The challenge to solution was just as great to them as our challenge to solution is to us today.

You would think that nearly four centuries of life in America has been no more than a series of alternating wars and panics. But let's stop and think. What did each of our past calamities have in common? Simple. We survived them all, and life in America has kept improving, generation after generation.

But let's come back to today. The Cassandras of 1977 are saying that all is lost; the end is near; after all, stocks have gone nowhere but down for a decade; we have inflation, capital shortages, unemployment, international competition, dwindling raw-material resources, industrial poisoning, declining growth, an energy crisis and other man-made problems. Uncertainty has been created in the minds of businessmen, investors and most of society as well. A return to the 1930s, we are told, is just around the corner.

Worldwide, our 1977 Cassandras are even more apocalyptic. And to all this, I say, "hold it." Let's step back and look things over from another vantage point.

Sure, in the United States, the unemployment rate is the highest since World War II; but since 1973, we have put well over 6 million additional people to work.

Sure there is a growth dilemma. We need growth. Some say we can't live with it and pay the penalty. Others say we can't live without it. The fact is that the cost of stopping growth would be disastrous. What we must do, and can do, is guide growth and, if necessary, control it.

There is an almost universally held belief in this country that industry and its products are major causes for a growing endangered species list.

The point to note, I think, is that man, with his institutions such as business and industry, is a recent visitor to this planet and had nothing to do with the extinction of the millions of species that preceded him. Nature is still a prime determining factor. In fact, man has not to date been successful in eliminating one single insect species. . . .

It is obvious that many of our problems today would not have existed in a primitive society, but neither would our present levels of accomplishments and well-being. . . . Up until recently, the predominate efforts and incentives of our nation were clearly directed toward the fulfillment of our basic requirements. . . . Was it bad that our society would be the first to reach freedom from materialistic wants? And is it bad that we are the only nation in the world which can completely feed its people and do so with only a small fraction of its resources? Aside from the obvious benefits to us, we have built a model to show the world what can be done with technology and free enterprise.

We do have problems that are not cyclical. Of these, our biggest are energy, raw materials and food. These are longer-term problems and so much the better because we'll need time to solve them. And solve them, we will.

In the final analysis, I have to conclude that there are no absolute shortages of resources—whether they be energy, raw materials, food or water. The shortage that does exist, if we allow it, is faith in ourselves and our ability to meet change; and above all, an optimism that keeps us going forward to cope with adversity and overcome it.

In closing, I would like to leave you with the feeling that all is not lost. The world has a future—a great future—as it always has had.

—Werner C. Brown
Chairman of the Board
Hercules Inc.

(Excerpts from remarks at the Palladium Medal Dinner, American Section, Société de Chimie Industrielle, Nov. 16, 1977)

Editor-in-Chief.....Patrick P. McCurdy

Executive Editor.....Donald P. Burke
Managing Editor.....Meyer Lurie
Director, CW News Center.... Anthony J. Piombino

Assistant Managing Editor..... John W. Price, Jr.
Assistant Managing Editor..... Herbert C. Short

Senior Editor.....Kenneth Brooks
Senior Editor..... Irvin Schwartz
Senior Editor..... Homer Starr
Senior Editor..... John M. Winton

Art Director..... Robert T. Martinott
Copy Chief..... William Mullinack

DEPARTMENTS
Environment..... Irvin Schwartz
International.....Albert H. Kislin
Management..... W. David Gibson
Markets..... John Rivoire
Production.....Kenneth Brooks
Research..... Gordon M. Graff
Specialties.....Patricia L. Layman
Top of the News..... Alan Hall, editor; Joseph F. Dunphy, Liz Forrestal

Art..... J. Bruce Haag, associate director; Sybil Collins

Copy..... James Gannon, Patricia Knowles
Reprints.....Frances Regan

CW NEWSWIRE..... Richard B. Roberts

McGRAW-HILL SERVICES
Economics..... Douglas Greenwald
News Bureaus..... Ralph R. Schulz, director Michael Johnson, editor

Atlanta, Stan Fisher; **Chicago,** Denis Chase; **Cleveland,** Arthur Zimmerman; **Detroit,** David Cook; **Houston,** Robin Neesham; **Los Angeles,** Michael Murphy; **San Francisco,** Margaret Ralston Drossel; **Washington,** Robert E. Farrell.

European Economic Correspondent, Robert Dorang (based in Paris); **Bonn,** Robert Ingersoll; **Brussels,** James Smith; **London,** James Trotter; **Madrid,** Jules Stewart; **Milan,** Andrew Heath; **Moscow,** Peter J. Hann; **Paris,** Michael Kolbenschlag; **Sao Paulo,** Ernest McCrary; **Singapore,** Peter Rutledge; **Stockholm,** Robert Skole; **Tokyo,** Robert E. Lee; **Zurich,** Laura Pilarski.

BUSINESS DEPARTMENT
Director of Business..... Beatrice Grove
Director of Production..... Verna M. Retzlaff
Advertising Service Mgr...... Astrid Chahmirian

BUYERS' GUIDE
Manager..... Joseph A. Callahan
Assistant.....Mildred Rimondi

MARKETING COMMUNICATIONS
Director of Services..... Raymond F. Fremed
Mktg. Research Mgr...... Bertha Chase
Marketing Services..... Lorraine Balutianski

Circulation Manager..... Paul W. Erb

Advertising Sales Manager..... Howard M. Mager

Publisher.....**H. John Sweger, Jr.**

You meant to get Washington moving,

By James A. Perkins
and Robert E. Sessions

This article — a 1951 publication which rings as true today as it did then — shows that the frustrations of government service are one of the eternal things of this world.

James Perkins, then with the Carnegie Corporation, now is chairman of the International Council for Educational Development. Robert Sessions was then a marketing and management consultant.

Adapted from "Public Administration Review," with permission of the American Society for Public Administration.

So you went to Washington, and took a job with the government? Stout fellow! You've been here nearly a year now, so let's compare your experience with that of others who have been "through the mill." How do you stand on the four inevitable steps of your development?

We will start with this question. Did you have a program of your own, perhaps not spelled out in detail but at least an idea of what you planned to accomplish during your Washington assignment? You did? Splendid! Now, did you believe that you have sufficient savvy to put it across? You did? Excellent! Did you believe that others in Washington have failed because they didn't or don't really understand the right way to get things done, or because they have not been able to state their mission with sufficient clarity and precision? You did? Ah, yes.

You obviously went through stage number one, which is called

The Eager Neophyte

The Eager Neophyte is a man with a mission, who believes that success only requires a rational explanation to essentially rational people, and that he was called none too soon to unravel the tangle or to get the program off dead center or to lend the encouragement of contagious enthusiasm to those who are jaded and frustrated by many small and petty failures.

Why are you blushing? How on earth did I read your mind so well? Let's recall how it went. The first week you, the Eager Neophyte, started your job, you were full of enthusiasm, breathing the exhilarating air of a place where things happen. You had a variety of conversations with your superior, your colleagues, and your staff, if any. As you went to bed your first night, two impressions were uppermost in your mind: it was ridiculously easy to see what needs to be done, and you were the man to do it. Fresh blood was all that was needed — a new approach, free from the rigmarole of red tape and bureaucratic inertia. With a sense of high resolve, you drifted off into a peaceful sleep.

Some eight weeks later your head was once more on the pillow. The same bed, the same pillow, but the frame of mind was hardly recognizable. Anger, frustration and despair had replaced the high resolve. Your sensible ideas had met with opposition. Your memorandums that so clearly state what needs to be done had no discernible effect whatsoever. Indeed, as the days passed, you became aware of evil influences at work — unreasonable people who push alternative programs that are based on entirely different and erroneous ideas of what is good for the country. And, what is worse, it is these other programs that secured the attention, and you rapidly became a voice crying in the wilderness of the Washington bureaucracy.

Indeed, as the days passed, you became aware of evil influences at work — unreasonable people who push alternative programs based on entirely different and erroneous ideas of what is good for the country. And, what is worse, these other programs are the ones that secured the attention, and you rapidly became a voice crying in the wilderness of the Washington bureaucracy.

After a night of fitful sleep you would wake up saying to yourself — what on earth am I getting so excited about? After all, my agency is only one of a great many in Washington, and I am in only one of the six bureaus of this agency. Furthermore, I'm in one of the six divisions of this bureau and, if the miserable truth must be told, I'm a subunit chief in one section.

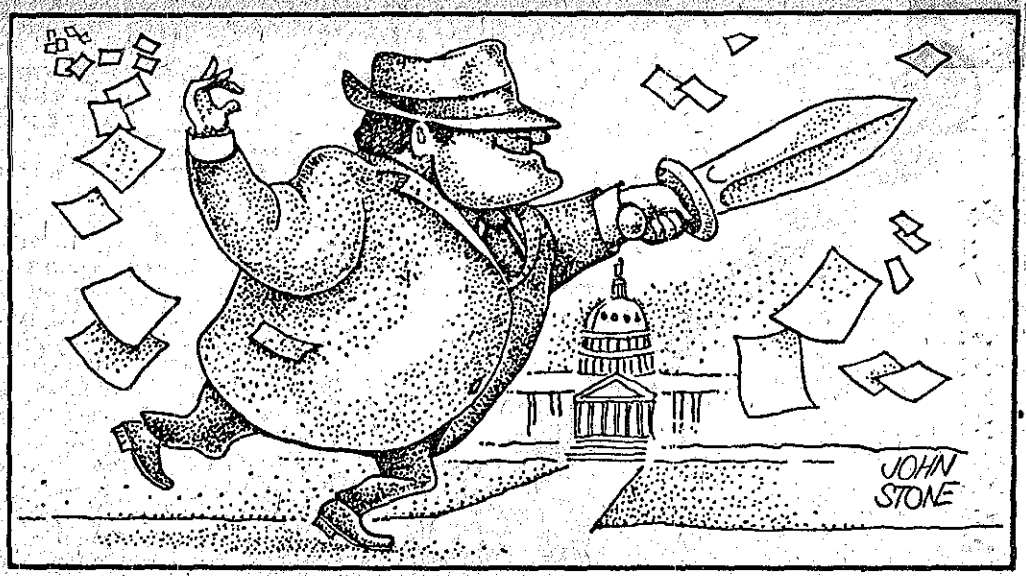
OK, so I'll do my little job as best I can, write my memorandums and reports, and make my recommendations. If my colleagues and superiors don't see the merits of my ideas, it's no skin off my nose. It's just their tough luck for being so stupid.

When you arrived at this happy state of mind, you moved into stage two —

The Polyp

The polyp, you know, is that very small animal that produces a grain of coral as a

but the change is in yourself!



full day's work. And you, too, were happy to produce your little grain of coral, neither asking nor caring where your effort fit into the total scheme of things — nor even worrying too much if there is a scheme at all.

You look annoyed and unbelieving! Yet I tell you that as sure as day follows night, the Polyp follows the Eager Neophyte. But you are a vigorous young man in the best of health with red blood in your arteries and your quota of blue blood in your veins, I should judge that you would have been likely to remain a Polyp for about six weeks.

Then one day, quite out of the blue, you erupted, violently. The eruption, in all probability, took place in some committee meeting where you suddenly realized that the discussion had once more reached a dead end. Before you knew it, the words came pouring from your mouth. You accused the committee members of stupidity and cowardice, of lack of patriotism and party loyalty, and generally of behaving in an appalling manner. You ended by declaring that a decision must be reached and promptly. You followed this up with a blistering memorandum to your superior, and you said to yourself, "All right, if you have to play rough to get anything done, I was not left wing on the ice hockey team for nothing. If they want to play dirty, so can I."

In this frame of mind you delivered yourself of a series of sulphurous letters, you became the terror of committee meetings, you would shout and bang the table, and you would leak information to the right columnists so that the public could hear the obstructionism (i.e., the opposition) with which you were faced.

In short, you were well into stage number three —

The Baited Bull

The frustrations you had nursed to your bosom as a Polyp came surging forward and you had yourself one whale of a time. But the human body and nervous system cannot stand this pace indefinitely. Depending on your metabolism, you at some point may have begun to slow down. You ran out of lurid language. Your fist became sore from pounding the table. You discovered that you were only shocking the Eager Neophytes and entertaining the Polyps and that your voice was getting rough and rasping from trying to drown out the other Baited Bulls. You were tired out.

But you did not become a Polyp again. Instead, you more likely became detached and objective about it all. You even became objective about yourself, and suddenly one day you may have, or perhaps you will yet, fit the different steps of your evolution into a concept of strategy. You will see the desirability of faith that is the essence of the Eager Neophyte. You will realize that the Polyp contributes the concept of the art of the possible. And you will understand that the Baited Bull has shown the necessity of fighting hard on some carefully selected fronts.

You will try to incorporate the best of each of these stages into a pattern, and when you succeed you will have arrived, my friend, at the last and final stage, that of

The Elder Statesman

No, no one can go directly there. Sorry. It is necessary for everyone actually to experience each stage in proper sequence — only then can one attain the proper objectivity and comprehension of the [illegible]

Patent Rights Provide Vital University Funds

Los Angeles Daily Journal 9/16/77

Inventions produced by medical researchers at Stanford provide an important source of income used to support academic functions.

According to Niels Reimers, manager of the Office of Technology Licensing, license and patent royalty payments exceeded $1 million last year. Most of the money, he said, is used in support of research and "to reduce the ever-increasing cost of education."

Reimers and his associate, John Poitras, are responsible for determining the marketability and patentability of inventions, negotiating licenses, and securing patent rights.

Research comprises a vital part of the University's functions. Within the medical school alone the volume of government-sponsored research was $28.6 million for fiscal year 1976. The University's operating budget for that year was $80 million.

Inventions in medical fields, such as the Optacon reading device, which translates printed matter into the tactile stimuli of Braille code, have had significant impact on medicine and have garnered for the University nationwide attention. But the benefits of medical research cannot be realized unless inventions make it to market. Since the University is an educational and research institution, it can publicize its inventions, but it can not produce or sell them. The transfer of technology from the clinical laboratory to the marketplace must be done by outside sources such as the government or private industry. This process is detailed in the current issue of Stanford MD, the journal of the Medical Alumni Association.

Government grants constitute a major portion of research development and funding, but actual production is usually handled by industry. The University gives companies the right to make, use, and sell its inventions by granting licenses in return for royalties which are determined as a percentage of sales. Often the negotiated license is exclusive for a period long enough to enable the company to recover its investment.

The Office of Technology Licensing has negotiated nearly 50 agreements for developing and marketing its inventions since its inception in 1970. Six inventions related to the medical field are now producing earned royalties. For example, Stanford has arranged an exclusive license with the Hewlett-Packard Corporation to develop and produce a coronary care unit (CCU) monitoring system.

This systm provides a continuous computerized monitoring of electrocardiograms (ECGs) of up to 16 patients. It analyzes the ECGs and alerts the staff to abnormalities

patent rights. Patents provide an additional competitive advantage by ensuring exclusivity in development and production for 17 years. Patents also provide an additional source of income for the University. Last year patent royalties totaled $300,000. The government has realized the importance of patents, not only in furthering research but also in protecting its own inventions.

According to Clive Liston, patent and copyright manager in the University's Sponsored Projects Office, the government's policy is one of "defensive patenting." The SPO is responsible for disclosing inventions to the government and determining the rights and obligations of inventors.

One result of the government's defensive patenting policy is the institutional agreements which Stanford has with the Department of Health, Education, and Welfare (HEW) and the National Science Foundation. These agreements ensure that Stanford has the first option on any invention which results from agency supported research.

"HEW has one of the best patent policies," says Reimers. "They really want to see that research gets out."

The strongest earned royalty income source from the Medical Center at present is the fluorescence activated cell sorter (FACS). Developed in 1971 by Dr. Leonard Herzenberg, professor of genetics, and his associates, the FACS separates cells on the basis of the fluorescent label they carry by passing a liquid stream of cells through a laser beam. The device has been patented, and is used primarily as a research tool.

Patents rarely create monopoly situations. "A good patent stimulates further research," says Reimers. "It is simply one way of accomplishing an objective."

Patents are not suitable for every project. Many inventions are not patented because they would not make enough in royalties to cover the time and expense of filing (an average of $2,000 is now required to file and follow a patent through to issuance) or because they fail to meet patent criteria.

Patents do not guarantee production. Sometimes a company which has been developing an invention will decide to let its exclusive license lapse, even though the patents on it by then have been secured.

Reimers estimates 1 project in 100 survives the development phase to enter production, and those that do often take years to reach the market.

File Editorials

Science and law

Howard T. Markey, Chief Judge of the U.S. Court of Customs and Patent Appeals, gave an address earlier this summer on science and the law before the New Jersey Patent Law Association. Here, verbatim, is a small part of what he had to say. The full text of the address, which marked Markey's receipt of the Jefferson Medal, is published in the June 1977 issue of the Journal of the Patent Office Society.

Like all good marriages, that of science and law is not formed of identical partners but of different partners complementary to each other. The differences, though profound, are not fatal. Science seeks knowledge of facts; law seeks justice which may rise above and beyond the facts. Justice may be tempered with mercy; a fact may not. Science can tell us the amount of shoe leather consumed in a given march; law is the music we march by. Science is a metronome for the melody of the law.

Science rests on the material; law on the moral, ethical, and philosophical. Science teaches us what we can do; law tells us whether we should. Science seeks certainty; law deals with the uncertainty of the human will. Science emphasizes the general; law the particular. Scientific proof is standardized; legal proof varies with probabilities. Science determines; law compares. Science finds fixed relationships; law establishes rights and duties. Science analyzes and predicts phenomena; law clarifies and controls conduct. Science describes; law prescribes.

The things of science are only those which can be observed. The things of law, like justice and mercy and truthfulness and reasonableness and honesty and compassion and responsibility, cannot themselves be seen.

The laws of science, like gravitation or Newton's laws of motion, are inviolable. The laws of humanity can be broken. Hence we prosecute the outlaw and not the falling rock.

Science weighs, counts, and measures matter; law defines and protects the values a society holds dear.

Man has learned to build on knowledge and experience in the fields of science and the application of science we call technology. He has not yet learned to do so in morals and ethics, where every baby starts from scratch. Yet there is hope, for with every new baby our troubled race gets a new start. And to the extent that law rests on morals and ethics, not just on force, we may someday begin to build an ethical structure of grandeur and excitement equivalent to that of science. To do so requires an understanding of the relationship between law and science beyond their differences.

As in every good marriage, the partners need each other. The relationship of need finds law needing to employ the empiric methods of science, where they fit, in a lawyer's world so dependent on and infused with science. And science needs law to aid in determining the monumental ethical questions it now confronts and which it cannot answer empirically, like the use of experimental drugs and procedures on human beings, genetic experiments like those with recombinant DNA, modifications of the environment, the effects of "social engineering," treatment of laboratory animals, and the relationship of science to politics.

As in human marriages, each partner brings an influence on the other. Science and technology move the law toward new fields and the need to change and grow. The law tames, controls, and channels science and technology.

The blindfolded lady of justice, like many wives of dynamic men, has been a helpmate and a softening influence on her scientific partner from the time man crawled from the swamps until he walked on the moon. When the lady's counsel has been ignored, the purveyors of perverted science have ended by burning humans in furnaces and by making lampshades of human skin.

Only the law can deal with threats to life, liberty, and the pursuit of happiness, like those which lie in the technology of computer data banks and electronic surveillance devices. In a broader sense, unless law controls science, man will become, in Thoreau's phrase, "the tool of his tools."

Thus science and law must be treated as legitimate lovers, not as living in sin. □

C&EN editorials represent only the views of the author and aim at initiating intelligent discussion.

Wash. Post
10/10/77

A 23

Rowland Evans
And Robert Novak

A President Unlikely To Change

Jimmy Carter, the miracle worker of 1976, is now marked by critics as the political incompetent of 1977 whose compulsive industriousness has produced a swirl of confusing objectives and made him an easier prey for the vultures in Washington's power centers.

That a crisis now exists cannot be denied. The hope of Carter insiders that the President's popularity would survive in the countryside while his status fell in Washington was shattered by the NBC poll putting his approval rating at 46 per cent. What makes this descent alarmingly different from past presidential crises is that it comes from no war, no economic collapse and no major scandal.

Rather, its source is deep inside the methods and procedures of the Carter presidency. Although the President's popularity will surely rally, he is liable to stay in trouble so long as he conducts his office as he does now. Thus, the most distressing fact in Washington today is that there is no signal yet pointing to any significant changes in the way Jimmy Carter functions as President.

Although many Democrats blame Carter's problems on the profusion of leftist appointees pushing policies not compatible with his own, the criticism comes equally from left and right. Indeed, part of his troubles may derive from a deficit, not a surplus, of ideology. Not linked to a philosophy other than an obsessive work ethic, the President has forged ahead with overambitious programs, both domestic and international, many parts of which relate to no overall theme.

Voters expected a President bringing calm and stability. Instead, confides one middle-level administration official, "they got a Lyndon Johnson overachiever" just as the presidency was entering a dangerously weakened state induced by Vietnam and Watergate.

The inevitable defeats suffered in the collision between a massive program and an independent Congress with the bit in its teeth are compounded by the fact that Carter not only is an outsider but came here boasting about it. Lacking real friends in Congress intimately tied to his fortunes, the President was set upon by congressmen acting like vultures sniffing blood from 1600 Pennsylvania Ave.

There are also vultures in his own administration. No recent administration has evidenced less personal loyalty to the President within the departments. Officials at the assistant secretary level, picked by heads of departments in Carter's "Cabinet government," owe their loyalty to the Secretary rather than the President and show no hesitancy about criticizing the President. Lobbying on Capitol Hill, usually a source of White House power, is also diffused with the departments.

In this situation, the President himself—whose political assessments on the road to the White House seldom have been matched in shrewdness—might be expected to assess the situation and change it. Some senior aides believe the prodigious output of domestic and foreign initiatives must be slowed.

But like the sorcerer's apprentice, Carter is too busy to stop the process. A few insiders say his schedule is too fully booked to think seriously about his presidency. Aides proudly point to his appetite for official reading. He has devoted 26 full hours to studying the defense budget, and more such time is being set aside. He spent much of last week going over 200 pages packed with tax-reform data.

Such total immersion would be unimaginable for statesmen such as Otto von Bismarck, Winston Churchill or Charles de Gaulle. "Jimmy sees things that any assistant secretary shouldn't see," one administration official told us. Carter is so deep in details that he seems compelled to push forward, further overloading his circuits.

The answer by many friends is to broaden his staff—"to get some aides in there with a little gray in their hair," in the words of one Cabinet member. Yet it may be unrealistic to believe that newly recruited aides could succeed where old ones have failed in changing what very well may be Carter's set style.

The hard reality is that both the overambitious legislative program and the work habits are pure Jimmy Carter. The blunt assessment of one administration official—"he's not a statesman, he's an engineer"—may be too harsh, but it points to the problem.

Some of Carter's supporters outside the administration believe his first imperative is to slow the mad pace and offer voters the impression of calm and orderliness they had expected from

Backing Off Basics

Many Concerns Stress Product Development And Reduce Research

Vexed by Sharp Competition And Federal Regulation, Firms Seek Fast Payoffs

Will U.S. Exports Be Hurt?

By Mitchell C. Lynch
Staff Reporter of The Wall Street Journal

BOSTON — The "R" is slipping from R&D, and many scientists, economists and foreign-trade specialists figure that spells trouble.

They discern an ominous change in the nation's scientific posture: Industry is curbing slow-payoff, basic research aimed at finding new products and instead is favoring hard-nosed, quick-payoff development of existing technology.

If this trend continues, some experts fret, the U.S. eventually could lose its standing as both the world's most innovative country and the biggest exporter of high-technology goods. Others worry that scientists aren't getting the elbowroom to, say, come up with synthetic fuels to replace petroleum. The problem has spread even to universities, long considered the birthplace of basic research.

"I don't hear many of my industrial contemporaries talking about exciting new major discoveries that they think will shake the world," sighs N. B. Hannay, head of research at Bell Laboratories, an arm of American Telephone & Telegraph Co. Thomas A. Vanderslice, who oversees research at General Electric Co., also is concerned. "There are trends that, unless corrected, could lead to a rapidly maturing crisis," he says.

Real Outlays Stagnant

The switch in R&D emphasis has taken place at a time when the total of such spending in the U.S. has turned essentially stagnant. American companies are spending more money on R&D, of course; one private study found that industry expenditures on R&D last year rose more than 11% from 1975 to $16.2 billion. However, the higher outlays have barely kept pace with inflation. "Strip away the higher costs, and you don't have much of an increase in the real amount of R&D being done today," says Michael Boretsky, senior policy analyst at the Commerce Department. And Otto Eckstein, who heads an economic research firm near Boston, says spending is lagging behind the pace that would be expected during a rebound from the 1974-75 recession.

Perhaps even more ominously, R&D spending in the U.S. is beginning to slacken in comparison with the rest of the world. [illegible] study estimates that the

Raytheon Co. is blunt about it. "Very definitely we have gotten away from long-term general research," a spokesman for the big, diversified company says. "All the research we now are doing is applied research with well-defined goals, better focus on business objectives, and a promise of payback within a reasonable period of time."

Reasons for Switch

Executives and economists alike attribute the new, quick-payoff approach to R&D to the still-high rate of inflation, the shortage of capital funds during the current slump in the stock market, sharp competition here and abroad for existing high-technology markets, and uncertainty about government regulations and policies.

"During periods of uncertainty, companies aren't in any mood for high risks," says Alan Greenspan, a former chairman of the President's Council of Economic Advisers. "Uncertainty is plaguing the investment community, and it is far more pervasive than it was a decade ago." Under these circumstances, for example, "it is no wonder this country hasn't done much research into synthetic fuels," Mr. Greenspan says. "The payoff is too far down the road."

Richard E. Heckert, senior vice president who oversees R&D at Du Pont Co., specifically cites the impact that federal policies are having on coal-gasification proposals. "Who the hell is going to develop expensive coal processing when natural gas is selling at half its real market price?" he asks. With gas prices held down by federal regulations, Mr. Heckert says, industry is concerned about "whether it could even get a buyer for any higher-priced synthetic fuels." And George Gols, chief economist at Arthur D. Little Inc., a research and consulting firm, suggests that there is a deeper problem, "that industry, in the long run, doesn't really believe that fuel is going to be much more expensive or scarce."

Du Pont itself, whose $353 million R&D budget last year puts it among the biggest in industry, has realigned its program drastically. In recent years, the big chemical company has dropped about 22 of what it considers "new adventures" in R&D and is working on only two or three. Indeed, only 22% of Du Pont's R&D budget went to basic and new-venture research last year, compared with 38% in 1972. In the same four years, spending for what Du Pont calls "improvements for existing businesses" climbed to 78% from 62%.

This new policy means "much lower risks and much higher rewards," Mr. Heckert says. In a way, he adds, the company has given up "looking for another nylon or Dacron," two synthetic fibers that were developed by Du Pont researchers and marked major breakthroughs. Du Pont isn't searching for more extensions of plastics and synthetics because "there aren't any simple combinations left," Mr. Heckert says. "There are only so many ways you can mix around the basic molecules."

In the long run, companies like Du Pont might prefer to license technology developed by other companies, Mr. Heckert indicates.

Indeed, many companies clearly are irked because foreign manufacturers have proven adept at picking up U.S. technology through licensing agreements, improving it and then exporting high-technology products

Prof. Davidson adds that he wouldn't be surprised to see foreign manufacturers make big inroads in the U.S. markets for office copiers, electric typewriters, outboard motors and electric organs. (Using a Hammond Organ Co. license, Yamaha of Japan already has begun exporting a competitive electric organ, the professor says.)

Zenith's Layoffs

U.S. companies often lose their technological lead because, Prof. Davidson says, they are so preoccupied with keeping their share of the current-technology product market. Other observers say much research work merely involves a hunt for ways to make current products more cheaply or an attempt to accumulate so many patents in a given field as to hamper potential competitors.

A few days after Prof. Davidson was interviewed, Zenith Radio Corp.—almost as though on cue—announced that it is laying off 25% of its work force, including a large number of researchers. The reason: competition from Japanese TV-set makers. The Research Department is being brought into the Product Development Department, a Zenith spokesman said. Research projects that "aren't directly related to the immediate product line (color-television sets) are being eliminated," the spokesman added. "We're dropping some research projects where the payoff was 20 years from now. They weren't making a contribution to our needs now."

Many corporate executives, economists and academics also complain that government regulation and red tape are strangling basic research in the U.S. Foreign governments, in contrast, nurture industrial research, U.S. businessmen say.

These governments have less-stringent antitrust laws and, in fact, often urge domestic companies to share technology and production operations. For example, under pressure from Paris, the Peugeot S.A. auto maker last year acquired control of Citroen S.A., another French auto maker, which was in deep financial trouble. Peugeot's job was to bring Citroen under its wing and create one streamlined auto-making operation. The U.S. Justice Department's Antitrust Division, on the other hand, prohibits American auto makers from even exchanging information or knowhow, much less combining production operations.

Drug Regulations

Foreign governments also impose fewer regulations that slow the introduction of new products. This difference is most apparent in the pharmaceuticals field.

Du Pont's Mr. Heckert says that in this country the average corporate cost of bringing a new drug from the laboratory to the pharmacy is $10 million. "Think about introducing 50 of them," he says sardonically. To get Food and Drug Administration clearance for a muscle relaxant called Dantrium in 1972, the Norwick-Eaton Pharmaceuticals division of Morton-Norwich Products Inc. submitted to the agency 456 volumes of technical material, with each volume two inches thick—literally a ton of documents.

An FDA spokesman says the average new-drug application today takes up about 70 volumes of technical material. And the processing of such applications can take years. One reason is a bureaucratic problem: An FDA employe risks little by delaying an application, but he can get into [illegible] by clearing a drug that later is im-

Walter E. Goldblith, provost of the Massachusetts Institute of Technology, puts part of the blame on what he calls "a nightmare" federal funding system. Compared with the looser block grants of bygone years, money now is doled out only for tightly controlled projects, Mr. Goldblith says. By insisting on multifarious reports and other forms of accountability on basic-research projects, Washington has "fragmented the study of nature until it has become meaningless," he complains. "Scientists? Our people have had to become more like accountants," Mr. Goldblith snorts.

It is difficult to determine the extent to which this basic-research lag is hurting the nation's trade figures. However, technology clearly is important to U.S exports. The Commerce Department says that while the U.S. was incurring a $5.88 billion deficit in merchandise trade last year, its exports of technology-intensive manufactured goods were outrunning such imports by $26 billion.

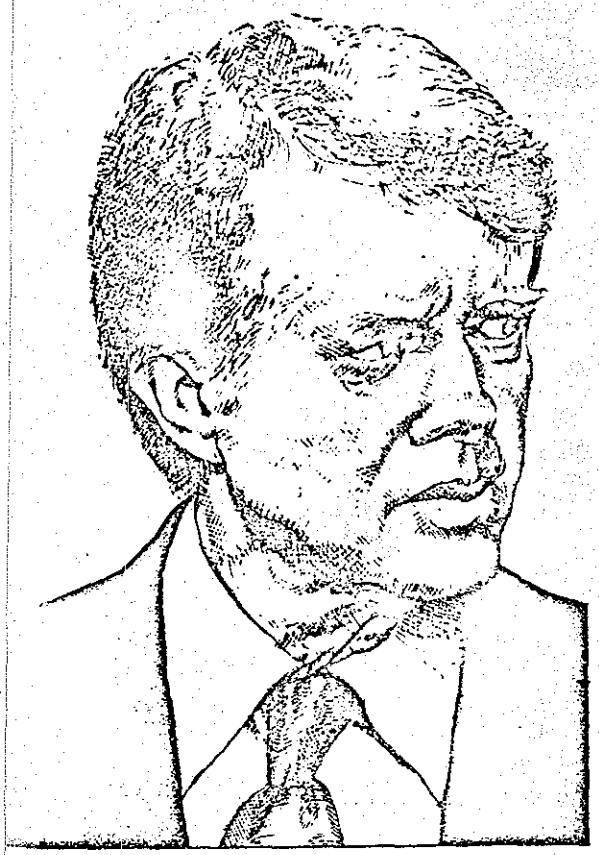
"What alarms me is the trend we're seeing now and what effect it may have on our trade picture later," says Edward M. Graham, a professor at MIT's Sloan School of Business. "Right now it's a problem not quite a crisis."

"Unfair" Comparisons

But not everyone is alarmed. Some economists, including Mr. Gols of Arthur D. Little, say research comparisons with, say, the late 1960s are "unfair" because the government and corporations then were spending huge amounts of money on research related to defense and the space program.

Frank Press, President Carter's science adviser, agrees. "A certain amount of deterioration is inevitable," Mr. Press says. "The first thing we have to realize is that the boom years of the 1960s have passed." Furthermore, he warns that the statistics are "still too imprecise; we need to break down the figures sector by sector to find out where the problems really are."

To Mr. Press, the answer isn't a flood of federal funds into basic research. "We have to be careful," he says. "We don't want to overload the system."



Carter and Ford detail their ideas on science and technology for C&EN

9.1/6

Where do the Democratic and Republican Presidential candidates stand on the vital issues affecting science and technology? Both candidates have a record of being supportive of science and technology: Jimmy Carter as governor of Georgia, Gerald Ford as President of the U.S. However, neither candidate has spoken out in much detail in the campaign so far on how science and technology would fare in his Administration.

C&EN believes the reader needs to be better informed on the candidates' positions. So, to determine the candidates' views and plans for science and technology, C&EN assistant managing editor and Washington bureau chief Fred H. Zerkel submitted the same set of questions to Gov. Carter and President Ford. Here are their unedited replies:



What level of research and development funding would your Administration recommend? How would it be divided among defense, space, and civilian sectors? Should national R&D funding be linked to some percentage of gross national product? And what is an appropriate balance of federal funding for basic research, applied research, and development?

FORD

I have stated repeatedly that I believe that a strong national effort in R&D is critically important to strengthen the economy and our defense and to improve the quality of life for all people. One measure of this belief is my 1977 budget, which included requests for $24.7 billion in federal funding for R&D. This represents an 11% increase over 1976 for R&D as compared to an overall budget increase of 5.5%.

I will continue to support vigorous, forward-looking federal R&D programs, but it is too early in the preparation of my 1978 program and budget to predict the levels of funding for R&D. It is important, in this connection, to recognize that the federal government does not have a separately determined "R&D budget," as such, and that the level and distribution of federal funding depend on many factors.

Applied research and development is carried out as a means to assist in achieving a variety of important federal and national goals and objectives; e.g., new weapons systems to deal with new threats to our security, or working with the private sector to develop new energy technologies to reduce our dependence on foreign oil.

The series of factors that must be considered in deciding on the level of funding for various applied research and development programs include: (a) the relative importance to the nation of a particular problem or objective, (b) the appropriate role of the government versus the private sector in dealing with the problem or achieving the objective, taking into account the nature of the private sector R&D effort under way or expected, and (c) the relative contributions expected from R&D and from other actions to achieve the desired ends.

In the case of basic research, there are insufficient incentives in many cases for private industry to invest enough to meet national needs. Thus, a strong federal effort is essential to assure that the nation will have the necessary new knowledge that underlies future advances in science and technology. There is no precise way to determine how much national investment there should be in basic research, but my Administration has examined trends in federal support of basic research and has undertaken to assess the potential impact of these trends on the



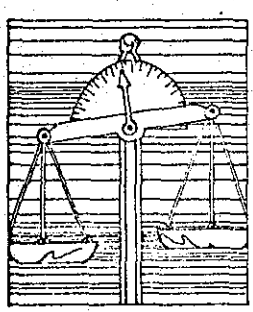
status of the U.S. effort. Based on our analysis, my 1977 budget proposed $2.6 billion for basic research—an increase of 11% over 1976 estimates. This level of funding would reverse the steady decline—in constant terms—in federal investment in basic research which has occurred since 1967.

It is not practicable to predetermine the spread of federal R&D funding among defense, space, and other civilian objectives; the spread among basic and applied research and development; or the appropriate percentage of the gross national product that should be invested by the nation in R&D. These can and should change with changes in national priorities or changes in the other factors, such as those cited earlier, which affect decisions on the level and distribution of federal funding for R&D.

CARTER

The federal budget for R&D should not be reduced, but is unlikely to be expanded dramatically because of resource constraints. Nevertheless, there is a great opportunity to rebalance expenditures in such a way as to stabilize the long-term commitment to the basic research foundations on which all technology rests, to increase the priority given to research in fields likely to be of long-term economic importance, and to give proper attention to environmental, health, and other civil concerns, including applied research important in global problems. This can be done at the expense of some development and demonstration programs and other direct federal operations that should better be carried out with private funds.

The level of national R&D effort, public and private, should be growing with the economy. In recent years it has in fact been falling, as economic growth has sagged and the federal government's R&D strategy has fallen into disarray. This trend must be reversed. But it is wrong to tie R&D expenditures to a fixed fraction of any macroeconomic indicator, for R&D is a microeconomic activity. It is a means to an end, and the level of investment follows the ability of organizations to use it effectively. Thus, at the national level attention must be given to creating the conditions that encourage high-risk, high-payoff industrial activity, and that motivate both public and private sector institutions to do the research that will best protect the long-term future of the country.



What specific areas of R&D would your Administration emphasize? De-emphasize? And how would you rank in priority R&D efforts needed to solve national problems such as energy, environment, and health?

FORD

I will continue to emphasize basic research and those areas of applied research and development that (a) can make a significant contribution in achieving important national objectives or solving critical national problems, and (b) are appropriate for federal R&D investment—either alone, such as defense, or in partnership with the private sector, such as in energy technology development.

This approach to determining relative emphasis is reflected in my 1977 budget proposal wherein I identified a number of high-priority areas for increased federal investment—including energy, defense, basic research, agriculture, and health—while continuing major R&D efforts in space, environment, natural resources, transportation, urban development, and other areas.

As indicated in my response to question No. 1, future funding levels will be determined in relationship to national priorities and the other factors cited.

I will continue to give priority attention to energy, environ-

ment, health, defense, and other areas of national importance, but each area must be examined separately to see how and to what extent R&D can make a contribution and what the appropriate roles of the government and private sectors are.

I also would like to point out that the relative level of funding for a particular R&D program does not necessarily reflect the relative importance of the objective or problem, or the contribution ultimately expected from R&D. For example, the funds required to build a large demonstration-scale plant for a particular technology (e.g., synthetic fuels plant or nuclear reactor) are much larger than the funds that can be spent usefully in pursuing in an orderly fashion R&D on a concept that has not advanced to a large demonstration phase (e.g., solar electric power generation).

CARTER

As indicated above, R&D emphasis is of two kinds: policies and incentives for private R&D and direct investment by the federal government. The federal government should use both approaches to providing a stronger economy and national capability to manage risks, protect the environment, and accomplish the other needed goals. In some areas of federal R&D investment the problem is not inadequate funds, but poorly managed programs. Internal priority shifts are necessary.

There are a number of areas in which specific R&D efforts need strengthening. Examples include earthquake prediction, arms control research, and research to provide a more quantitative basis for determining risk to human health and well-being from substances and environments (such as noise) of many types. In many areas of federal regulatory activity, there are lacking the kind of hard quantitative data on the basis of which to make sound regulatory policy.

A few areas of science and technology need a new commitment of national attention. One example is the scientific basis for the enhancement and improvement of nutritional quality of food supplies for all the world's people. Here the primary need is to share what we know. In defense and space R&D we must ensure that our efforts are of very high quality, and sustain the levels of technical leadership that are essential.



What programs or policies would your Administration recommend to ensure continuity of funding for science and technology to prevent peaks and valleys in technical training and employment as well as a sustained real growth in the nation's science and technology effort? Should such programs be different for the industrial and academic communities?

FORD

The most important factor in ensuring continuity of national funding for science and technology and preventing peaks and valleys in training and employment is the maintenance of a strong and growing economy—an objective to which I am very firmly committed. This will provide an environment for real and sustained growth in the U.S. science and technology effort so that the research and the inventiveness of our scientists and engineers can be translated into new knowledge, and new goods and services for the benefit of all.

With regard to federal investments in R&D—which investments play a critical role in the national scientific and technological effort, I will make a special effort to avoid sharp changes that can contribute to peaks and valleys in employment. I appreciate fully the need to minimize or avoid major dislocations that can result from federal actions in scientific and technological activities and in other sectors of the economy.

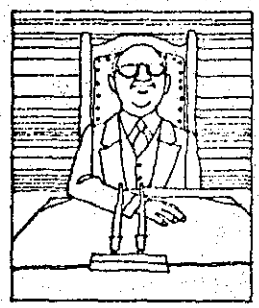
R&D funded through mission agency programs such as Defense and the Energy Research & Development Administration, together with actions to sustain economic growth, should provide strong stimulus for R&D efforts in the industrial sector.

With respect to the academic community, I believe the federal government has a special role to play in ensuring adequate support of basic research—the largest portion of which is conducted in the nation's colleges and universities. My concerns both for basic science and for ensuring the continued vitality of research in universities is reflected in my 1977 budget, which proposed an increase of 11% above 1976 estimates for federal support of basic research. This included an increase in basic research funds of about 25% for the National Science Foundation, which has long had a primary role in providing funds for basic research in academic institutions.

CARTER

Rapid fluctuations in demand for R&D are particularly difficult to accommodate. Such fluctuations are wasteful of a priceless national human resource. On the industrial side the essential requirement is a stable economy with low unemployment. R&D is a risk investment, and is made when companies have confidence in the future. Incentives for private investment in R&D should emphasize the power of R&D to permit innovation. When a business downturn occurs, countercyclical encouragement to innovation can help provide the basis for long-term strength in the economy.

In academic research, fluctuations in support result from the impact of economic cycles on government revenues, and thus on resources for public investment, and changes in the program content of federal agencies funding research. Since the federal government has direct or indirect responsibilities in both areas, federal leadership is needed to stabilize the research base in universities. The director of OSTP [Office of Science & Technology Policy] must work with OMB [Office of Management & Budget] to ensure that the aggregate impact of all federal R&D programs is well managed.



Should the U.S. have a coherent overall science and technology policy? Should there be a Cabinet-level department of science and technology in addition to the new White House Office of Science & Technology Policy to provide centralized funding and management of the federal end of the national R&D effort? Or is the existing federal science apparatus adequate?

FORD

As a general rule, coherent overall policies for particular areas of activity are desirable, but the specific meaning of the phrase is very important in the case of science and technology.

To illustrate, I would be very concerned and strongly opposed if a coherent overall policy implied that we should have some centrally developed master plan by which we would attempt to set priorities and funding levels for our nation's many-faceted scientific and technological effort.

I believe that the unsurpassed strength and accomplishments of the U.S. scientific and engineering communities can be attributed in large part to the pluralism and the flexibility that have been achieved through a decentralized approach. We look primarily to the private sector for the innovation that carries our new knowledge and inventions forward to useful products and services. The successful innovation we bave enjoyed could not possibly have resulted if we had centralized planning.

I understand most experts agree that the U.S. achieves much more for its R&D dollars than many foreign countries—such as the Soviet Union, which has centralized R&D planning—even though other countries spend larger percentages of their GNP on R&D.

Particularly because of the advantages of diversity, pluralism, and flexibility, I have serious reservations about the idea of a department of science and technology. Furthermore, many of our mission agencies such as the Department of Defense, Health, Education & Welfare, and the Department of Transportation must be able to use R&D as one means to achieve their assigned missions. It would be unrealistic and unprofitable to have a single centralized agency manage these agencies' R&D efforts. There may, however, be some areas of federal R&D that could benefit from consolidation.

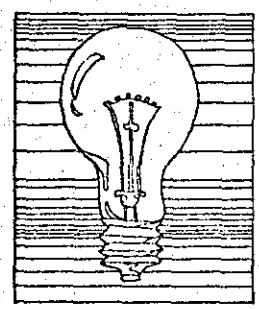
The same law that establishes the Office of Science & Technology Policy in the White House, as I proposed in June 1975, also establishes a President's Committee on Science & Technology. The committee is charged with studying and reporting on the overall context of the federal scientific and technological effort, and it is specifically charged with studying the concept of a department of science and technology. I look forward to the results of that study and I will consider seriously any recommendations made in the area of science and technology organization. Any organizational changes in this area would, of course, need to be examined in the broader context of overall government organization.

CARTER

Certainly, the U.S. government should have a coherent overall science and technology policy. The lack of a mechanism for generating such a policy in the past four years has sown waste and confusion across the national scientific scene.

The question is, how much pulling together of technical agency activities is desirable? The "mission-oriented" agencies should certainly continue to operate laboratories and fund or cost-share R&D outside government as the prudent, efficient, and responsible way to carry out their missions. Such technical programs should not be separated from their end purposes and drawn together.

It also may be desirable to give more central authority and resources to agencies concerned with the health and vigor of the national scientific and technological enterprise. Finally, there are some glaring weaknesses in the present structure, for example in the ability of the federal agencies to contribute to the civil economy, or to carry out commitments that derive from foreign policy.



In what ways do you see the federal government able to play a role in technological innovation? Further, what role, in terms of tax incentives, patent policy, and the like, should the federal government play in relation to R&D in private industry?

FORD

The federal role should be to further technological innovation in sectors of the economy in which private developments are inadequate to meet special needs. For example, there are overriding national benefits from a strong defense system and from attaining additional security against the potential disruption from energy embargoes.

If privately financed R&D is not sufficient to provide the new technologies needed for a higher level of security, or for the achievement of broad national goals then federally funded programs should be put in place. But where the private sector is producing new goods and services at a rapid rate for consumer use and for national needs, there is little or no justification for federally supported R&D.

This is not to deny a role for tax incentives and patents.

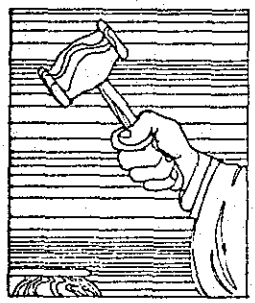
Where there are serious market imperfections, such as inability to obtain ownership rights to one's own inventions, then taxes and patents can be used to provide necessary corrections. These should be used as supplements to make markets work better, not as substitutes for private initiatives.

CARTER

First, the federal government should set a good example, by using its own purchasing power to encourage innovative products and services that can increase the efficiency of government. The small program on Experimental Technology Incentives (ETIP) in the National Bureau of Standards has demonstrated the power of this approach.

Next, attention must be given to the special circumstances surrounding the most fertile ground for innovation, the small, technologically oriented firm financed with venture capital. It has been over a decade since the "Charpie Report" looked into this question, and still many of its recommendations lie unimplemented. The area should be looked at again to see what must be done in the present business and technology climate.

Another area requiring attention is federal patent policy, which all too often either reduces the incentive of private investors to attempt to exploit the results of federal R&D in commercial markets, or simply prevents the firms with the most technical capability from wishing to participate in federal programs. Finally, tax, trade, and antitrust policy must be managed so they encourage R&D and innovation.



Should a sort of "science court" be set up to adjudicate scientific and technological issues? Further, what should (should not) be the role of the federal government in the setting up and perpetuation of such an apparatus?

FORD

I understand that the "science court" concept has been suggested as a means for establishing scientific facts, or lack of facts, in the case of issues of national concern that become very controversial.

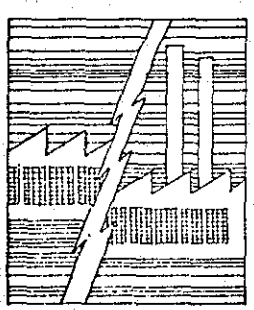
The concept was reviewed by the two scientific and technical advisory groups (led by Dr. Simon Ramo and Dr. William O. Baker) that I established to help prepare for the new Office of Science & Technology Policy. Those groups recommended that the concept be considered further and that an experiment with the science court be pursued. Recently, the concept of a science court also was considered during a two-day meeting sponsored by the Commerce Department, National Science Foundation, and the American Association for the Advancement of Science, which was attended by some 250 concerned citizens representing a wide range of viewpoints. This meeting also led to a recommendation that the concept receive further consideration.

Whether a "science court" will provide a better basis in fact than the means currently used is yet to be demonstrated. The National Science Foundation and the Department of Commerce now are seeking ways of assisting in a test of the concept on an experimental basis.

CARTER

If by "science court" we mean competent institutions that make objective evaluations of scientific evidence, uncertainty and risk, undertaken in the open for public view, I would support the idea.

There is a clear need for better and more public policy determinations and the development of institutions for making the basis of such determinations clear.



Should individual chemical companies or other corporate entities be permitted under the antitrust statutes to cooperate and coordinate their R&D programs in the solving of national problems such as energy or environment?

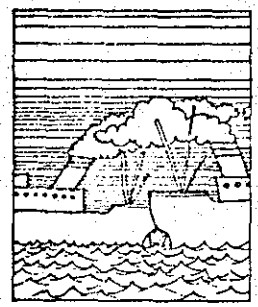
FORD

Under existing pollution control laws and antitrust laws, it is possible for two or more firms to join together to do certain kinds of cooperative research. The Department of Justice reviews proposals for such cooperative efforts on a case-by-case basis and where it finds no anticompetitive purposes or effects will provide the companies involved with its conclusion not to bring any federal antitrust action.

I would favor such cooperative research efforts in nonproprietary areas where it is approved by the Justice Department and where it increases the chances of hastening the finding of solutions to common problems, improves the utilization of resources, and does not interfere with the innovation that sometimes requires multiple approaches to the same research objective before a solution is likely.

CARTER

This would have to be considered on a case-by-case basis. In nonproprietary research, if cooperation is necessary and would have a beneficial effect on competition I would consider it. However, in no case would I approve of this approach if it had the effect of eliminating or decreasing competition in the private sector.



What role do you see U.S. R&D playing in solutions to U.S. balance of trade problems? Should there be close government control over export and licensing of U.S. science and technology, in general, and in sensitive areas such as nuclear equipment and technology, in particular?

FORD

For a number of decades now, an important part of U.S. trade exports has been based on the technical superiority of our products. Aviation sales and products using advanced solid-state circuitry such as computers are examples. In addition, we lead in agricultural exports.

The "R&D content" of our exports has been higher than those of most other industrialized nations. Indeed, to continue to expand our trade with other countries, U.S. industry must develop new and better products each year and put these products into exports. But this has to be done without giving away new technology to be used by others in weapons systems. The licensing procedure of the Export Administration (Department of Commerce) is designed to prevent this, without at the same time holding back legitimate commercial exports. A Presidential task force with an assignment to improve Export Administration procedures has been examining the agency's operations and will report to me soon.

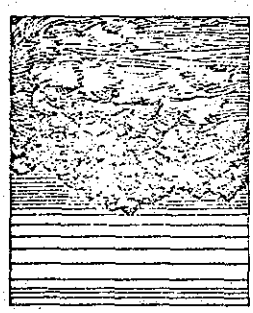
In the case of sensitive areas such as nuclear equipment, technology, and fuel, we must take special precautions and have close government control. Our objective is to control the international spread of the capability to develop nuclear explosives. I recently have directed that a thorough review be undertaken of our nuclear policies and options, particularly with respect to exports, reprocessing, and waste management.

CARTER

U.S. foreign trade performance is, above all, a measure of the internal strength of the U.S. economy in comparison with the economies of our main trading partners. In this comparison the figures since 1968 are serious cause for concern. U.S. improvements in productivity lag the rates in Japan and many European countries. The percentage of the work force engaged in R&D continues to rise in those countries; it has been declining in the U.S. since 1969.

More and more frequently we have seen major inroads by foreign competitors in areas of traditional strength in the U.S. (But the right policy for the U.S. is not to copy the policies of foreign governments, but is to take steps to strengthen the competitiveness of the domestic U.S. economy.) This strength is greatest in the areas of most rapid technical progress. Agriculture, civil aviation, and computers are all examples.

There are circumstances, especially in technology of military significance and in critical materials areas, in which a government policy concerning exports and imports is justified. Our government should react with appropriate firmness to other governments that intervene to our disadvantage. What we should do is adopt those domestic policies—in education, science, economic policy—that are most likely to keep U.S. industry ahead, and give careful attention to the dislocation of the labor force that accompanies rapid technological change.



There is a growing feeling that some of the current legislation and regulations to implement enacted legislation aimed at curbing pollution, safeguarding the environment, and so forth, is either too heavy-handed or cast in such broad terms as to be either meaningless or too subject to arbitrary interpretation. What is your view?

FORD

I believe that we can go a long way toward achieving our environmental, energy, and economic development goals at the same time, if we proceed deliberately and carefully.

However, I agree with the view that some current environmental laws and regulations have lacked a reasonable balance, and I have acted to achieve a better balance. For example, I have urged Congress to extend the Clean Air Act deadlines for meeting automobile emission standards so that we can have a better balance among our clean air, energy, economic, and consumer price objectives.

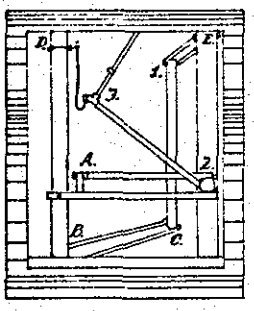
I also have been concerned about the impact of environmental regulations but, in some cases, the regulations have been issued by the regulatory and enforcement agencies in direct response to explicit provisions of the law or to comply with court interpretations of the law. Many of the environmental laws were put in place quickly and with good intentions. Now that better information is available, the laws and the regulations should be corrected for the long-term benefit of all our society. As illustrated above, I am seeking such corrections.

In general, our pollution control programs should achieve a balance among the benefits and costs of improving environmental quality and benefits and costs of industrial and commercial development. In the past two years, we have come closer to striking a socially acceptable balance than before. At my direction, the Environmental Protection Agency (EPA) first initiated "Economic Impact Statements" and then I ordered "Inflation Impact Statements," to provide a basis for assessing social benefits and costs of each particular rule-making. In some cases, EPA was prevented by law from basing decisions on these assessments. But where possible, EPA has gone a long way in making decisions that reflect a balance between the benefits of improved environmental quality and costs to the economy.

CARTER

There is no doubt that a few federal regulatory programs produce few real benefits to the public while exacting a cost to the economy. However, properly managed and structured, regulation not only should meet its purpose of protecting the public interests but also provide incentives to innovation.

Too often the rules are hard to interpret, government policy is too unpredictable and unstable, compliance is indifferently enforced. The most serious shortcoming of regulation is that it often fails to relate the social and economic costs of the goals to objective measures of benefit. Indeed, often the reduction of risk in one area is achieved at the expense of enhanced risk in another. Improvements in the regulatory process would come from reorganization. Above all, more objective scientific fact determination is needed, so policies can be soundly based.



What views do you have on reform of the U.S. patent system, particularly as it affects individual inventors or wider licensing of U.S. technology? Are existing federal programs to transfer technology developed at government expense to private industry or other sectors of the economy adequate? What further efforts in this area might you propose? And how would your Administration view exclusive licensing to industry of federally owned patents? Should there be some form of compensation to the government and should government-employed inventors of such licensed technology receive some form of compensation?

FORD

The U.S. patent system on the whole is working positively toward the rapid development of new technologies. However, the changing nature of applied research has raised questions about the adequacy of the patent system, which has changed only slightly since early in the 19th century.

My Administration has submitted comprehensive legislation that would rid the patent system of many of its existing problems without sacrificing the indispensable stimulus to invention now afforded by that system. The proposals are designed to assure that the patents issued are more valid and contain greater disclosure of the technology involved. Also, the proposals seek to improve the administrative procedures in the patent and trademark office so as to permit a simple and straightforward search for new patents.

This and other patent reform measures have been under consideration in Congress for some time, but none has been enacted.

The number of government-owned patents that have been licensed for use in the private sector is less than 5% of the total. Measured against the performance of the university community, whose licensing rate exceeds 30%, the federal technology-transfer record is poor. Although this situation has existed for decades, my Administration is doing something about it. First, a high-level patent-policy task force has now reported to me and to Congress on sweeping recommendations for making optimum use of government-funded innovations. Second, we already have begun (with encouraging results) to *market* government-owned inventions, instead of letting them sit idly on the shelf while waiting for someone to ask about them.

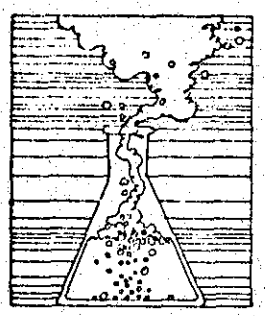
Government-owned inventions which are licensed for use in the U.S. stimulate employment and create revenue in the form of tax receipts. In some cases it may be appropriate to charge a royalty for such domestic licenses. Foreign licenses, on the other hand, generally should be issued on a royalty basis.

The principal goal of federal investment in R&D should be to maximize the benefits to the public of the new technology that results. In some circumstances, this end may be served best by giving exclusive rights to those in the private sector who will take the necessary steps, make the required investments, and exercise the required diligence to disseminate the benefits of the technology expeditiously and effectively. The university experience indicates that this is a valuable and often indispensable tool for actually transferring technology into the market place.

CARTER

I realize that the present U.S. patent system has some severe difficulties in regard to inventors, users, and recipients of technology. I have not yet made a detailed study of the system, but I plan to do so in the near future. Until that time, I would like to withhold any judgment on this matter.

Your suggestion on private licensing of government-owned patents is provocative. If it can be determined that such a system would encourage and increase competition in the private sector, I would be willing to consider it. I would have to study the matter of consideration for government-employed inventors from a personnel management perspective.



How do you view the current level of effort in the Environmental Protection Agency and the Occupational Safety & Health Administration to regulate toxic chemicals? Should the effort be increased and, if so, in what fashion?

FORD

The Toxic Substances Control Act, recently passed by Congress, establishes a new framework for much of the government's activities with respect to toxic chemicals. I have supported enactment of such legislation, although I continually urged that unduly burdensome premarket notification requirements be eliminated from the bills because they were overrestrictive and of little value in protecting the public health.

As in the case of all new laws such as this one, we will have to proceed carefully and seek to assure that the costs of complying with it do not exceed the benefits gained.

CARTER

We must do more to guarantee each and every American the right to a safe and healthy place of work. More than 600 toxic chemicals are introduced into our workplace annually. There are currently more than 13,000 already listed. Nearly 100,000 working people die each year from occupational illnesses and accidents. More than 17,000 disabling injuries have occurred in our nation's mines. This terrible toll cannot be tolerated.

I believe the basic concept behind OSHA is excellent. We should continue to clarify and expand the state role in the implementation of health and safety. OSHA must he strengthened to ensure tbat those who earn their living by personal labor can work in safe and healthy environments.

The Occupational Safety & Health Act of 1970 should cover all employees and be enforced as intended when the law was enacted. However, early and periodic review of the act's provisions should be made to ensure that they are reasonable and workable. I would look favorably on developing means to provide technical assistance and information to employers to encourage compliance with the act.

The control of occupational hazards can save many workers each year who die prematurely because they are exposed to toxic chemicals, dust, pesticides, unsafe machinery, and other dangerous conditions. Nationwide efforts in this area should continue until our working citizens are safe in their jobs.

Federal Alert— *new regulations*

This listing covers regulations appearing in the Federal Register *from Sept. 8 through Oct. 7. Page numbers refer to those issues.*

PROPOSED

Food & Drug Administration—Changes status of 10 ingredients that are used in cold remedies from requiring a prescription to over-the-counter sales; comments by Dec. 8 (Sept. 9, page 38312).

Allows use of Red Dye No. 4 in externally applied drugs and cosmetics; comments by Oct. 26 (Sept. 23, page 41854). Continues provisional approval of 52 color additives, including ferric ferrocyanide, zinc oxide, and bismuth citrate; comments by Nov. 22 (Sept. 23, page 41860).

Allows use of triglyceride mixture of caprylic and capric acids to be used as surface finishing agent, formulation aid, lubricant, and in dietary foods; comments by Dec. 3 (Oct. 4, page 43754).

Requires new labeling for estrogens, to include account of cancer risks associated with estrogen use; comments by Nov. 29 (Sept. 29, page 43108).

Nuclear Regulatory Commission—Phases out over the next 10 years the government's program to compensate the public in the event of a serious reactor accident; comments by Oct. 20 (Sept. 20, page 40511).

Patent & Trademark Office—Strengthens patent examining and appeal procedures: permits patent owners to bring new prior art to the office through reissue apolications, assist examiners by providing them with patentability statements in all applications, modify appeal procedures to authorize oral arguments by examiners; comments by and hearing on Dec. 7, in Arlington, Va. (Oct. 4, page 43729).

FINAL

All agencies—Spells out plans to involve consumers in their decision-making processes; effective immediately (Sept. 28, page 42761).

Department of Transportation—Sets forth packaging, labeling, and placarding requirements for air, water, and surface transportation of hazardous materials; effective immediately (Sept. 20, page 40613).

Environmental Protection Agency—Designates for five years the Gulf of Mexico as ocean dumping site for incineration of chemical wastes; effective immediately (Sept. 15, page 39319).

Postpones implementation of its program to phase out use of lead additives in gasoline; effective immediately (Sept. 28, page 42675).

Food & Drug Administration—Bans use of Red Dye No. 4 in maraschino cherries and ingested drugs; effective immediately (Sept. 23, page 41853).
Bans use in cosmetics of aluminum stearate, bentonite, calcium silicate, calcium stearate, gold, kaolin, lithium stearate, magnesium aluminum silicate, magnesium stearate, and zinc stearate; effective Oct. 26 (Sept. 23, page 41855).

Bans use of carbon black in foods, drugs, and cosmetics; effective immediately (Sept. 23, page 41857).

Denies Abbott's petition to reinstate use of cyclamates in food; effective Oct. 4, objections by Nov. 3 (Oct. 4, page 43754).

NOTICES

Environmental Protection Agency—Announces availability of draft environmental impact statement on proposed cancellation of chlordane and heptachlor pesticides (Sept. 9, page 38206).

Asks public input on what sort of information should go into toxicology test reports that are submitted in support of pesticide registration applications; for example, should the director of the laboratory performing the tests sign and approve all reports; comments by Dec. 6 (Oct. 5, page 43921).

Federal Energy Administration—Requests expressions of interest and comments on private sector participation in commercial energy projects under the International Energy Agency; projects can include pilot plants for oil shale or tar sand development, and natural uranium exploration; comments by Oct. 15 (Sept. 13, page 38818).

Nuclear Regulatory Commission—Sets forth safety and environmental aspects of using mixed uranium-plutonium fuels in light-water reactors; comments by Nov. 4 (Sept. 20, page 40506).

Levine thinks we also need to focus on the "third party problem." While the company that made the know-how sale might use the proceeds to regenerate its own technology, other companies in the same industry might be adversely affected by sales of products made with the know-how. If these companies, he observed, had patent protection, they could enforce their patents. But, with no patent protection available, "technology owners in an industry who are not at the bargaining table in a negotiation with the Soviets" may have their technology invalidated without payment.

Consequently, Levine feels strongly that the U.S. Government should take the initiative in negotiations with the Soviets to protect American technology interests.

Levine concluded:

[Text] If the businesses of the United States engage in a series of one-shot technology know-how sales, our economy will very quickly have traded all it has to trade in the way of high technology. If this occurs, where will the benefit to our economy be? Its leadership will have disappeared and we will move closer toward fulfilling Lenin's forecasts for capitalism.

We will not be left with a good feeling toward East-West trade, or trade with developing nations, but instead the feeling of disappointment which comes from knowing you have made a bad bargain.

If, on the other hand, we have exchanged our technology for some form of market share, for some ongoing participation in the Soviet and Eastern European and developing country markets, we will have a continuing economic exchange which is beneficial for continued, long term trade and technology exchange.

The U.S. Government must play a leading role and can and must take action on this issue. The potential consequences are momentous for the future of high technology industry in the U.S. as well as for vigorous and successful international trade. [End Text]

Innovation

John A. Welsh, Director of the Caruth Institute of Owner-Manager Business of the School of Business Administration, Southern Methodist University, described "Conditions for the Successful Exploitation of a New Idea."

Patent lawyers, Welsh said, are in the unique position to meet with the people in our world who have new ideas of sufficient quality and novelty to be worth protecting. Attorneys may be better equipped to advise and counsel these inventors if they have a coherent picture of the complexity of exploiting a new concept.

There are three major components to the milieu of entrepreneurship, Welsh said. Principal among these is the individual, the entrepreneur, who makes it happen. The other components, he continued, are a viable business concept and capital. A viable business concept, he noted, is described in terms of the consumer's perceived values in the new concept or idea. There are many forms of capital, including sweat, credit, good wishes and favorable comments. Sooner or later, however, some class "A" capital is required, "the kind which we use to buy groceries."

Welsh thinks the successful entrepreneus is a particular kind of a person traveling along a time-line. There is a segment of this time-line which is conducive to entrepreneurial success. Only the right person at a particular segment along his career path (e.g., when confronted with a special job opportunity, or some major disappointment that motivates him to change his plans) is likely to create and sustain a new business enterprise.

Copyright © 1977 by THE BUREAU OF NATIONAL AFFAIRS, INC., Washington, D.C. 20037

While some inventors may deserve the label "entrepreneur," some clearly do not. Welsh suggests the profile of the successful entrepreneur looks like this:

1. GOOD PHYSICAL HEALTH

In a small business there is no depth of management. The leader must be there.

2. A BASIC NEED TO CONTROL AND DIRECT

Entrepreneurs typically are unable to deal with authority over them. They would rather direct their own structure poorly than be part of anyone else's structure. They are frequently unable to function in traditional situations and structures.

3. SUFFICIENT EMOTIONAL STABILITY

Successful entrepreneurs are able to handle their anxieties and bear up under the pressures of the business and their personal problems.

4. MODERATE INTERPERSONAL SKILLS

Entrepreneurs drive themselves and their organization, think clearly, are usually mentally ahead of their associates, are impatient, and aren't built to have the tolerance and the empathy necessary for team-building interpersonal behavior. They run their own show and delegate very few key decisions. They are more concerned about accomplishments than feelings.

5. SELF-CONFIDENCE

Entrepreneurs have bountiful self-confidence in what they believe to be possible when they are in a position to control and direct. Conversely, their self-confidence fades to uncertainty and insecurity when they are not in control.

6. STRONG DRIVE

Entrepreneurs seem to have a never-ending sense of urgency to get things done. Inactivity makes them impatient, tense and uneasy.

7. SUPERIOR CONCEPTUAL ABILITY

Entrepreneurs have the raw intellectual ability to identify relationships among functions and things in complex situations. They see clearly what has to be done more quickly than most of their associates.

8. BROAD THINKING OF A GENERALIST

Entrepreneurs are constantly aware of the general overview. This broad view and breadth of knowledge tends to enhance their superior conceptual ability.

9. VERY REALISTIC

Entrepreneurs accept things as they are and deal with them that way. They may or may not be idealistic, but, they are seldom unrealistic. They want to know the status of things at all times.

Copyright © 1977 by THE BUREAU OF NATIONAL AFFAIRS, INC., Washington, D.C. 20037

10. LOW NEED FOR STATUS

Entrepreneurs are concerned with the achievement of functions and things of a productive nature. They seem to have a high tolerance for confusion and chaos while striving toward achievement. The symbols of success are usually relegated to the lower end of their list of priorities while building their organization.

11. MODERATE RISKING

Entrepreneurs are often thought of in terms of the risk they assume. Like any prudent businessman, however, they know that high risking is gambling, not business. They are not gamblers.

Welsh believes that when the successful entrepreneur has been found to be weak in one or more of these characteristics, another individual can be identified who is strong in the entrepreneur's weak characteristics and who occupies a position of significant influence with the entrepreneur.

In summary, he noted, the composite profile of the successful entrepreneur and those who influence his or her behavior has a large measure of each of the characteristics listed here.

Counselors, consultants, and advisors should realize that the entrepreneurial client has difficulty adapting to structore or diverting any significant degree of control, said Welsh. While the entrepreneur respects experts for their achievements, their advice and lecturing may very likely be viewed as substantiated information. Counselors would be wise to couch their advice and guidance in forms which the entrepreneur perceives to be self-discovery. If counselors need to receive recognition or credit for their efforts, they may be happier dealing with non-entrepreneurial individuals.

Duty of Disclosure

John F. Lynch, of Houston, provided some perspective on "Living With the Duty of Disclosure."

Culpability for improper conduct in patent prosecution arose out of equitable principles, Lynch observed. Early cases did not attempt to define a standard of conduct, but treated allegations of impropriety in the context of "unclean hands." It was not until 1944, beginning with Hazel-Atlas Glass Co. v. Hartford Empire Co., 322 U.S. 238, 61 USPQ 241 (1944), that the courts expressed concern that patents be free from fraud and inequitable conduct and attempted to define a standard of conduct.

In 1945 Precision Instrument Mfg. Co. v. Automotive Maintenance and Machinery Co., 324 U.S. 806, 65 USPQ 133, expressed the "uncompromising duty" standard and in 1949 Kingsland v. Dorsey, 338 U.S. 318, 83 USPQ 330 imposed on attorneys a duty to act with the highest degree of candor and good faith.

For many years, he noted, while some cases surfaced, essentially the issue of inequitable conduct remained dormant. However, Walker Process heralded the "inequitable conduct explosion." That case (Walker Process Equipment, Inc. v. Food Machinery and Chemical Corp., 382 U.S. 172, 147 USPQ 404, 1965), he said, held that fraudulently obtained patents would form the basis of a Section 2 Sherman Act violation.

Copyright © 1977 by THE BUREAU OF NATIONAL AFFAIRS, INC., Washington, D.C. 20037

1876 1976

Biomedical sciences: the past 100 years

Alfred Burger, University of Virginia

It has been just over 100 years since the first instructional laboratory of physiological chemistry was established in the United States. Russell H. Chittenden, who had studied at the University of Heidelberg under Prof. Willy Kühne, took charge of the new laboratory, established at the Sheffield Scientific School at Yale University in 1874. "They were very modest quarters at first," Chittenden later wrote, "for the movement was an experiment and the authorities obviously felt it unwise to risk much in a venture that might prove unsuccessful."

Contrary to this early fear, physiological chemistry blossomed in the U.S. and throughout the world. With atomic, thermodynamic, and kinetic theories essentially in hand by the turn of the century, scientists could discard the nebulous, mystical descriptions of vitalism, and conceptualize the molecules of life in the same terms as inanimate matter. Out of physiological chemistry grew what we today call biochemistry—a dynamic discipline bent on explaining the nature and interactions of men, microbes, and plants. Contributing to the mushrooming nature of the science have been improving experimental techniques in analytical, physical, and organic chemistry which continue to provide the tools needed for probing biomolecules.

For example, the study of photosynthesis goes back at least as far as the 1770's when Joseph Priestley observed that green plants could improve the air spoiled by animals and flames. But an understanding of the complex biochemical pathways involved in photosynthesis did not come until the 1940's when the use of nuclear reactors made artificial radioisotopes available for tracer studies. The development of chromatographic techniques greatly facilitated following and isolating the tagged molecules participating in the photosynthetic process. Similarly, increasingly sophisticated spectroscopic techniques are helping to unravel the scheme by which light quanta are absorbed by chlorophyll and converted into potential chemical energy.

Following the fate of molecules participating in photosynthesis has been one of the exercises characteristic of biochemistry. Biochemists have not been satisfied with merely describing the chemical and physical properties of isolated molecules. Instead, the nature of their science has required that they constantly ask, "Where did the molecules originate? To what are they transformed?" And, "How and why are they transformed?"

In seeking answers to these questions over the past century, biochemists have come to understand many of the principles involved with energy transfer in the cell, the role of cellular structures such as membranes and ribosomes in cellular function, the importance of stereochemistry in life processes, and the basic mechanism by which hereditary information is coded. Greater insight has been gained into processes such as the Krebs cycle, glycolysis, electron transport and oxidative phosphorylation, biosynthesis, contraction and movement, and the maintenance of concentration gradients across membranes.

Central to the study of many of these processes, and to the general growth of biochemistry, has been the elucidation of protein chemistry. Early investigators probing the molecules of life were confronted with not only determining the units of protein structure, but understanding how these units were linked together, and then applying



Squibb chemist synthesizes a central nervous system agent for subsequent preclinical testing at the drug firm's animal research farm

this knowledge to explaining biological activity. Emil Fischer and Franz Hofmeister proposed as early as 1902 that proteins were polypeptides. However, it was not until the 1930's that incontrovertible evidence proved this belief to be true.

In 1938 Max Bergmann and Joseph Fruton showed that the enzyme pepsin could catalyze the hydrolysis of synthetic peptides, thus implicating the peptide bond in protein structure. And in 1953 Frederick Sanger announced the amino acid sequence of the protein hormone, insulin. Sanger's work offered definite proof of the peptide theory. Since this landmark effort, many amino acids have been sequenced. Moreover, x-ray data have offered insight into the three-dimensional structure of proteins. By 1958, John Kendrew was able to report the crystal structure of whale myoglobin, and in 1969 Dorothy Hodgkin and her colleagues solved the structure of insulin.

Much of the impetus for studying protein chemistry has arisen from the recognition of the importance of enzymes in life processes. John H. Northrup conclusively established the protein nature of enzymes in his work with pepsin and trypsin between 1930 and 1935. Yet, only a century ago the term "enzyme" did not exist. Willy Kühne coined the word in 1877 to distinguish soluble ferments from the microorganisms associated with fermentation.

Today scientists routinely try to explain the functions of enzymes in terms of molecular structure. The understanding of enzyme action and procedures for isolating and handling these proteins have developed to the point that enzymes are used regularly in food processing, medical applications, analytical instruments for testing substances such as glucose, and in preparing drugs, amino acids, sweeteners, and other materials. New techniques for stabilizing enzymes outside their cellular environment and allowing their re-use promise to open up even more practical applications for these biological catalysts.

Certainly, of the various areas upon which biochemistry impinges, some of the greatest advances have been made in the field of nutrition, particularly in vitamin studies. In 1926 the Polish biochemist Casimir Funk concluded that deficiencies of certain nonamino acid nitrogen compounds in yeast and rice polishings were responsible for beriberi. Funk took the Latin word for "life" and suggested that these chemicals be called "vitamines."

One by one, an impressive array of vitamins came to be recognized, including vitamins A, D, E, K, C, B_1, B_2, B_6, niacin, biotin, folic acid, and B_{12}. And in many cases, especially with the water-soluble B vitamins, an understanding of their chemical function also appeared. Even before its discovery as a vitamin in 1937, nicotinamide was recognized as being important in an enzymic conversion of glucose. By 1948, the participation of several other vitamins in enzymic reactions also was recognized.

Undoubtedly, much of the enthusiasm surrounding biochemical investigations has involved the possibility of applying research results to improving health. To a great extent, biochemistry had its origins in medical schools, and it is through the interplay of medicine and chemistry that a good deal of biochemical history can be traced.

Indeed, the past third of a century has witnessed a glistening parade of miracle drugs and an unparalleled revolution in the treatment of many major diseases. Some of these advances arose from the development of improved therapeutic methodology, diagnosis, and technique, but by far the greatest saving of life and renewal of healthy living has been achieved by the use of chemicals to prevent, treat, and cure diseases. Numerous contagious and infectious diseases and parasitic infestations have lost their historic hopelessness and epidemiological horror. Many functional disorders that could either not be cured at all or required surgical intervention now can be treated and often cured by medication. Surgery itself, a dirty art a hundred years ago, has become a reliable and aseptic science through the use of anesthesia and antibiotics. Hospitals for mental and behavioral diseases have become true treatment facilities after emerging only 25 years ago from a medieval state of restrictive centers. Many mental patients have been stabilized by drugs and returned to active life as productive members of society. Infant mortality has been reduced spectacularly all over the world; in fact, this reduction has become one of the principal factors in the increased average life span of mankind.

About 30 frequently encountered inherited errors of metabolism have been recognized as molecular diseases and several of them have become treatable by enriching or depleting the diet's chemical that is at fault. Beyond that, many functional diseases now are regarded as chemical aberrations due to decreases or sometimes rate increases of enzymically catalyzed bioreactions. If cofactors of the decisive enzymes are involved, manipulation of these conditions can heal the biochemical lesion. Missing enzymes cannot yet be replaced directly in disease and aging, but the restoration of their biosynthesis offers a possibility for future therapeutic repairs.

These triumphs constitute the most positive applied results of chemistry in our lives. Although many sciences have contributed to the discoveries made so far, the real miracles in the growth of medicine have occurred through medicinal chemistry, biochemistry, and pharmacology.

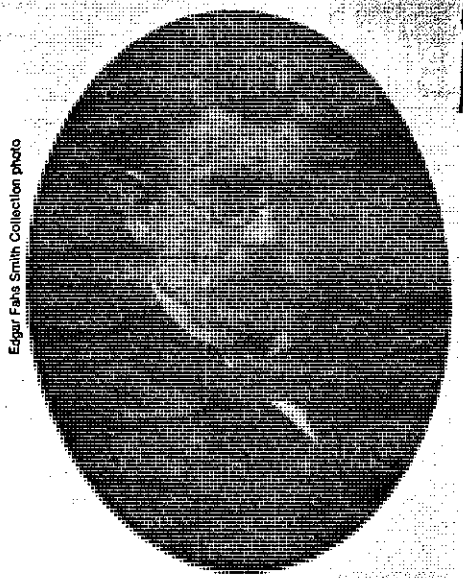
One glance at the mushrooming volumes of *Chemical Abstracts* devoted to biochemistry and the medicinal and genetic sciences offers convincing proof that the search for new roles of chemistry in medical theory and practice has not abated. Many old problems still go begging. The action of salicylate was discovered by Stricker and MacLagan in 1876, the year the American Chemical Society was founded. Together with the perennially favorite acetylsalicylic acid, sodium salicylate is still used to suppress the clinical signs and improve the histological picture of rheumatic fever, although the salicylates do not cure the disease and are beset with frequent side effects. The first plausible explanation of the biochemical mechanism of the anti-inflammatory action of salicylates had to wait until J. R. Vane, only five years ago, postulated that they inhibit the biosynthesis of the inflammatory prostaglandins PGE_2 and $PGE_{2\alpha}$ (*1*). This is only one of hundreds of examples of unsolved or poorly understood problems that haunt chemists and biologists and worry physicians who must make do with available drugs, although they are obviously far from the best.

From superstition to drug synthesis

Even today one can find primitive peoples in remote areas of Central and South America, in Mexico, parts of Siberia, and Haiti where the healing of the sick is still based on botanical brews. The recipes range from salads of sacred mushrooms to less savory stews of roots, leaves, barks, and fruits of diverse plants and trees that were venerated for their generation of vital forces. The same experimentation that liberated organic chemistry from the vital force concepts of previous centuries has shed light on the therapeutic folklore of primitive and medieval herbal legends (*2*).

Many ancient therapeutic plants were extracted in the laboratories of apothecaries, and pure active principles were greeted with the same enthusiasm that is still accorded pretty crystals at the end of a chemical operation. The pure drugs afforded pharmacologists their first opportunity to study homogeneous substances in biological test systems. Structure elucidation by piecing together bits of evidence from degradation studies took one or several lifetimes. Ultraviolet, infrared, and nuclear magnetic resonance spectroscopy were a century away. Mixtures were separated by countless manual fractionations; chromatography and mass spectrometry were daydreams. Melting and boiling points were ultimate criteria of purity. Yet these primitive and inexpensive methods led by tortuous paths, through decades of work, to some of the triumphs of determination of complicated structures. Today, one may mourn the expenditure of talent and time in these studies. With modern instrumentation, decades of effort could have been saved and accuracy improved by several magnitudes.

As synthetic organic compounds became more abundant, active drugs were discovered among all structural types, both of natural and synthetic origin. Hormones and vitamins joined botanical products among natural substances. The last lingering shreds of teleological philosophical views were torn when synthetic analogs of many natural products were found to be more active and often more specific than their natural prototypes. This discovery was extended even to several hormones that had been held sacrosanct as the most active materials one could encounter for a given physiological purpose. With the discovery that nature was not as perfect or purposeful as had been assumed, extensive series of molecular modifications of every interesting "lead" compound were undertaken. In complex structures with a given spectrum of biological activity, the barest structural segments that would still possess all or some of this activity were elaborated and modified further.



Edgar Fahs Smith Collection photo

Paul Ehrlich

Emergence of medicinal science

As tens of thousands of new compounds were tested and hundreds introduced into medicine, the quest arose for unified concepts to explain their mode of action and perhaps to take some of the empiricism out of drug design. A 50-kg woman or a 70-kg man can be affected profoundly by 5 to 7 mg of some drugs, that is by amounts of only 10^{-7} of their body weight. Such drugs must react with biochemicals of similar low concentrations—that is, with primary biocatalysts that act at these and greater dilutions. The most ubiquitous of these biocatalysts are the enzymes, and at an early date many drugs were recognized as enzyme inhibitors by in vitro confirmation. Since diseases may be caused by derangements of multiple complex enzyme systems, it is not always easy to invoke inhibition of one enzyme as the cause of a drug's action in vivo. Moreover, many drugs have been viewed as competitors of substrate molecules at the enzymes' catalytically active domains, but drug molecules do not often resemble known substrates. In such cases, allosteric modification of the enzyme, with the drug molecule bonding to a region not concerned with the substrate, has been hypothesized. Such attachments unrelated to the active site are supposed to deform the substrate-specific site and make it unavailable for reaction with the substrate. Similar views have been suggested for drug receptors, some of which are believed to be enzymelike proteins, perhaps integral components of definite cellular locations (*3*).

Nucleic acids also have been identified as targets of primary drug bonding, the drug molecule intercalating with their helical portions or affecting nonhelical segments in such a way that transcription to protein and enzyme assembly is impeded.

Great ideas arise almost always in the mind of one gifted individual who can synthesize basic concepts from the interpretation of facts in converging doctrines. That is what Paul Ehrlich (1854–1915) did for medicinal science. Starting as a practicing immunologist, he translated the ideas of his field into the language of chemistry and microbiology. He erected the biochemical, metabolic, and toxicological explanations of the mechanism of action of drugs in such a measure that they needed only to be modernized and expanded to incorporate current knowledge. In a structurally relatively limited series of aromatic arsenicals and dyes, and with a sometimes naive picture language, Ehrlich and his associate, Alfred Bertheim, developed the principles of biomedicinal chemistry, briefly expressed in today's terminology as follows (*4*).

A chemical must reach its target (the receptor) and must not be absorbed prematurely on serum proteins or at tissue membranes (sites of loss). It must not be metaholized and excreted prematurely, but should disappear from the body after its mission has been fulfilled. At the receptor, a drug molecule should fit snugly enough sterically to withstand competitive and metabolic removal until its inhibitory task has been accomplished. If a chemical administered for therapeutic purposes is not in the right molecular or ionic state for such action, it must be changed to the active state by enzymic alteration or by ionization before reaching its target. A drug must have a large therapeutic ratio—that is, its maximum tolerated or minimum toxic dose must be an acceptably large multiple of its minimum effective dose; in other words, it must be relatively safe.

However, Ehrlich recognized that absolute safety was unattainable, although he expressed the hope that some day a drug like a "magic bullet" without systemic toxicity would be found. But as soon as magic is invoked, one calls on unreasonable dreams, and it is not surprising that no 100% safe drug ever has been encountered. Ehrlich also found that one cannot rely on beginner's luck and that the first prototype compound for a given biological activity rarely is the optimal drug in a series of structural congeners. Of the 1000 to 1100 compounds synthesized and tested in his research, only about six reached clinical utility. In more recent times, only one out of 5000 to 20,000 has become a clinically use-

ful agent, and the rate of attrition of drugs is faster than it used to be. Few major drugs retain their full use for more than 15 to 20 years.

During the first decade of this century, several other significant medicinal experiments took place that also were to become prototypes for most drug discoveries to this day. They were the degradative examination of the structure of cocaine which resulted in the aminoalkyl ester-type local anesthetics such as procaine (*5*), and the determination of the essential structural features of the adrenal medullary hormone, epinephrine (Adrenalin, *6*). The elaboration of the ester-type local anesthetics opened the way for the contemporary amide-type drugs for the same purpose, and for the similar derivation of synthetic anticholinergics (antispasmodics, antiulcer drugs, mydriatics) from the solanaceous plant alkaloid, atropine. The epinephrine studies heralded the introduction of adrenergic (sympathomimetic) drugs such as ephedrine (*7*), amphetamine (*8*), and isoproterenol (*9*), to name just a few. With the identification of acetylcholine (*10*) as the neurohormone of parasympathetic (cholinergic) nervous transmission, it became possible to synthesize both cholinergic drugs and inhibitors of acetylcholine-sterase, the enzyme that destroys excess acetylcholine by hydrolysis. Some of these inhibitors have become valuable insecticides, and others are used in the maintenance therapy of neuromuscular disorders, especially myasthenia gravis.

Screening for "lead" compounds

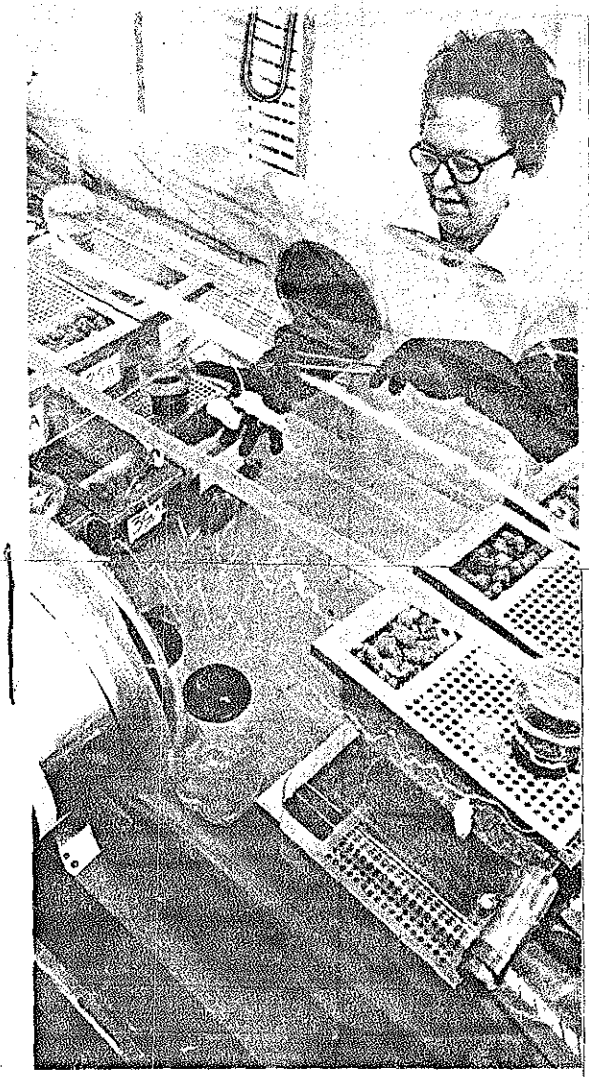
The success of biologically screening potential drugs depends not only on simple, rapidly reproducible methods, but on the significance of the method for estimating the value of the test substance in a therapeutic situation. That means the test method must be sophisticated enough to represent the clinical conditions as much as possible. In retrospect, many screening programs should not have been undertaken because the test methods did not fulfill the conditions just mentioned. Unfortunately, the current state of biological science fails to provide background and practice for such methods; yet, medical urgency spurs crash programs not having an adequate experimental foundation.

The chemical contribution to screening projects used to be uninspiring. If an ethyl ester of an acid was found to have a desirable biological activity, the methyl, propyl, isopropyl, butyl, *sec*-butyl, amyl, etc. esters were prepared and tested duly and dully. The venturesome would try a thioester or -ether, or exchange one azaheterocycle for another, provided synthetic expediency permitted such a luxury. A group leader in the pharmaceutical industry used to supervise rows of technicians as they performed condensations of amines with every accessible acyl chloride to form amides for biological screening. When young organic chemists decided to join medicinal-chemical laboratories, their theoretically oriented professors asked them whether they would not prefer to dig ditches. Nevertheless, screening has uncovered so many unexpected and often unexplainable "leads" that one would be loath to abandon the process, despite its wastefulness and the inherent lack of reason behind it.

Serendipitous drug discoveries have been diethylcarbamazine and isoniazid. The piperazine derivative, diethylcarbamazine, was designed purposefully as an analog of the analgetic meperidine by chemists at the Lederle Laboratories of American Cyanamid. Because a relatively large research sample of the compound had been prepared, the drug was screened in other tests which interested Lederle biologists at that time. Anthelmintic activity especially was examined since piperazine is active against worm infestations. Diethylcarbamazine turned out to be an active filaricide, killing filarial worms at drug concentrations well tolerated by the infested human host (*11*).

The second example, isoniazid, was studied by chemists and biologists at Hoffmann-La Roche, E. R. Squibb, and in Germany around 1950. Isoniazid has been credited with emptying tuberculosis sanitaria and putting an end to tuberculosis as a classical epidemic disease ("consumption"). Isoniazid had not been intended as a drug but was only an intermediate in the synthesis of 4-pyridinealdehyde thiosemicarbazone, which had exhibited a measure of antituberculous activity in experimental infections. When the delivery of this compound was delayed, synthetic intermediates containing 4-pyridinecarbonyl groups were tested and isoniazid was found to possess superior activity (*12*).

A much more effective plan for screening is based on keen biological observation. Sometimes a compound tested for a given activity elicits side effects unrelated to the test at hand. For example, an antiinfectious drug might lower the blood pressure or blood sugar of test animals. By suitable molecular manipulation, one may be able to develop drugs for lowering blood pressure, or that are active in diabetes, without any of the original antiinfectious activity. This amounts to the discovery of a "lead" in such unexpected conditions.



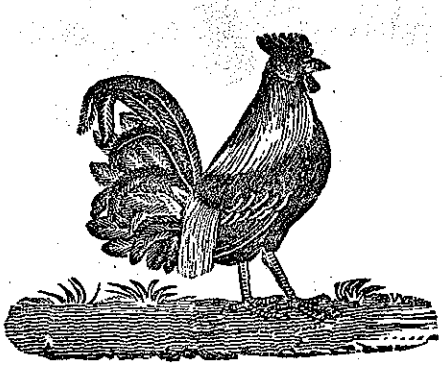
Eli Lilly worker uses white mice to screen activity of new compounds

Drug design by molecular modification

From 1920 to 1930, perhaps 6000 compounds were examined as potential antimalarials in an experimental avian plasmodial infection. This effort yielded quinacrine (Atebrin), a clinically effective and useful agent. Quinacrine was derived vaguely from quinine, the oldest antimalarial agent known. A few years later, 10,000 commercial and experimental dyes from collections of the fiber and chemical industry were screened as antibacterial chemotherapeutics. It was reasoned that

Agricultural research a boon to all Americans, not just farmers

Few individuals, even the farmer himself, realize the many contributions that agricultural research, mostly carried out at agricultural research stations, has made to the daily activities of all Americans. Although the farmer has benefited tremendously from this agricultural research work, its impact has been much broader than just the farm. Today's chicken, for example, is a far cry from its counterpart a hundred years ago. Just in the past 30 years, agricultural research has shown how to produce a pound of chicken with half the necessary feed required earlier and to grow the chicken to maturity in only



about half the time. And a vaccine developed in the Virginia Agricultural Experiment Station to protect poultry against Newcastle disease is estimated to have a worldwide value of about $1 billion.

Agricultural experiment station scientists discovered the role of minor elements, such as zinc, copper, cobalt, and molybdenum, in plant and animal nutrition. They discovered Dicumarol (bishydroxycoumarin) to control blood clotting in humans and streptomycin to treat tuberculosis and other diseases. They defined the significance of amino acids in our diets—they discovered vitamins.

In two agricultural experiment stations—the first one in the U.S. in Connecticut and in the Wisconsin Experiment Station—scientists and chemists were studying animal feeds. These studies, first carried out on cows and hogs, had moved to rats, which were traditionally the farmer's worst enemy. In fact, at the Wisconsin Experiment Station, researcher Elmer V. McCollum had to battle the station's administration before he could continue his studies. Just two years after McCollum started his work in 1907, the Connecticut Agricultural Experiment Station independently started its own studies. Chemist and station director Thomas B. Osborne, son-in-law of Samuel Johnson (see page 159), carried out his research with Lafayette B. Mendel of Yale, whom he had invited to join him.

Osborne and Mendel started out with a pure protein, starch, lard, and salt mixture, but were unsuccessful until they included whole milk powder and finally just the milk's sugar lactose and minerals. Further experiments pinned down the essential role in growth played by the amino acid lysine. Continuing experiments showed that "a substance [in butter] exerted a marked influence on growth." These words reported the discovery of what would later be called vitamin A. Independently, McCollum and his associate, Marguerite Davis, at Wisconsin were making the same discovery.

Further investigations by Osborne and Mendel showed that their "substance" was also present in cod liver oil, which found wide use in Europe after World War I to save the eyesight of thousands of children. In Wisconsin, meanwhile, Davis and McCollum were determining a second type of essential nutritive factor, which turned out to be vitamin B. It was this factor, present as a contaminant in Osborne and Mendel's earlier protein-free milk diet, that was responsible for the success of that diet in their earlier feeding tests. This work of Osborne, Mendel, Davis, and McCollum would develop in just a few years into the vitamin theory of nutrition.

dyes with high affinity for fibers might stain and thereby affect bacterial cells, hopefully without acting on the cells of the host. Azo dyes containing a sulfamyl group para to the azo linkage appeared to fulfill this requirement (*14*). Actually, the host organism reductively cleaves the azo group to sulfanilamide, which in turn became the "lead" compound for thousands of experimental and the few clinically useful systemic antibacterial sulfa drugs.

In 1932 Hans Erlenmeyer of the University of Basel began his classical studies to put molecular modification on a scientific basis (*15*). Realizing that chemical, physical, and biological manifestations of a compound are different expressions of the inherent molecular properties of the material, he introduced Irving Langmuir's (1919) concept of isosterism into medicinal thinking. This idea referred to the outer shell electrons of a compound, and for organic molecules took on an overtone of steric shape. Two compounds that had virtually identical physical properties such as melting and boiling points when mixed with each other were termed isosteric. Such compounds often exhibit a similar biological behavior.

Here, then, was a way of predicting the likelihood of biological analogy on the basis of physical properties. Soon the boundaries for drug design imposed by similarities of outer shell electrons became too narrow if one wanted to branch out beyond these classical confines. Therefore the "same type of biological activity" was incorporated into the definition of isosterism, but this introduced many biological variables as soon as compounds were compared by gross pharmacological observations.

The concept of nonclassical bioisosteres (*15*) tried to adapt predictability of biological response based on chemical structure with varying success. The nonclassical bioisosteres did take account of analogous molecular orbitals and analogous biochemical responses in definable reactions, preferably in vitro. The latest definition by Corwin Hansch of Pomona College (*16*) regards bioisosteres "as compounds causing identical biochemical or pharmacological responses in a standard test system. The system might be an enzyme, membrane, mouse, or man." This definition disregards chemical structure altogether, and even if compounds act alike in "mouse or man," totally different biological responses might be involved with a similar overall symptomatology. In vitro or in simple isolated cell and organ preparations, compounds with quite simple structures indeed become comparable. In a few cases, compounds with irreconcilable differences in outer electron shells act alike in a biological test and here their biological similarity has been based on isolipophilicity.

As Hansch points out, "We must break away from heavy reliance on the traditional symbols of organic chemistry. These have served the synthetic chemist well, but they are a terrible hindrance to progress in relating structure to activity. They convey a static message with meaning for architects; there is no dynamic message for those who are interested in rate processes." This is not quite true because a structural formula tells an experienced chemist a good deal about reactivity, even near-quantitatively, although not quantitatively enough for a kineticist.

If we measure biological activity first, and then ask what makes different compounds act alike in a definable biochemical or at best very simple biological test, we find lipophilicity a major factor. But except to prove a scientific point, who wants to prepare a drug with exactly the same activity as the one in hand? The whole purpose of molecular modification is to produce more potent, more selective, and less toxic compounds, or drugs with a wider spectrum of useful activity. Hansch focused attention on partition coefficients of a compound between 1-octanol and water as a model for distribution between lipids and blood serum.

A much earlier model for the same property had been the distribution between oil and water, studied by E. Overton and by K. H. Meyer before 1900 during attempts to explain anesthetic potency on the basis of proper transport of a drug into the nervous system, where anesthetic action takes place. By inserting Hammet substituent constants into equations in regression analysis, Hansch could use a dozen or so existing compounds in a given related structural series to predict active analogs that had not yet been prepared or tested.

Spencer M. Free and James W. Wilson of SmithKline Corp. (*17*) derived de novo substituent constants not from tables in textbooks on physical-organic chemistry, but directly from the biological activities of a set of congeners. Combinations of the two methods also have been considered (*18*), but in polyfunctional compounds which can combine with a biomacromolecule in many different ways; mathematical prediction of the optimal congeners to be tested may only furnish a nonpreferential selection of too large a number of possible candidate compounds. In such cases, experience and judgment still must supplement forecasts made by computerized regression analysis, but at least some semblance of predictable constraint on unlimited numbers of potentially active congeners can be attained.

Some prototype compounds are chosen from among biosynthetic intermediates of proteins, nucleotides, and cofactors. Gradual alteration of their structure yields analogs that may still have a biochemical activity similar to that of the prototype, but more often they inhibit enzymic reactions and compete with the natural substrate for an active site of the enzyme (*19*).

Another approach is to examine compounds for their behavior toward biochemically essential metal ions. Recently, metal inclusion complexes have become known, the best studied being the potassium derivatives of the antibiotics gramicidin-A, enniatin-B, and others. The antibiotic activity of valinomycin appears to depend on this ability to enclose and extract specific metal atoms. Many other examples have been suggested, the most interesting being compounds that help in transporting sodium, potassium, calcium, and other ions across neuronal membranes during the transmission of nervous impulses. In other types of chemistry, the "crown" ethers also can have such ion enclosures, and therefore have been contemplated as candidates for a variety of biological tests based on this common denominator.

Drug metabolism

Chemicals may pass through the body unchanged but more often are metabolized. Many kinds of reactions have been observed during drug metabolism, the most frequent ones being oxidations (including hydroxylations), reductions, O-, N-, and S-alkylations, and dehydrogenations (*20*). Most metabolic reactions change a drug to less toxic and more diffusible, soluble, ionizable derivatives or conjugates that may be excreted more easily, and thereby rid the body of the toxic foreign agent. In a few instances, the drug's metabolites are more active or more toxic than the administered substance; that is, the original compound has been activated. Such activations reveal new insights into novel prototype compounds. For example, the early bacteriostatic azo dyes of the Prontosil type are cleaved reductively to sulfanilamide, the active component of the dye molecule. The local anesthetic lidocaine and the antidepressant imipramine, which are traditional tertiary amines, are N-dealkylated to secondary amines of greater activity. The phenylbiguanide antimalarial chlorguanide owes its activity to a metabolite with a cyclized triazine structure. Molecular modification of such activated metabolites with unexpected structures has been a fruitful activity in developing series of potent and selective analogs.

Age of medicinal biochemistry

The task of biochemistry is to describe, study, and explain the chemical syntheses and reactions in living cells or those of chemicals isolated from animate tissues. The baseline of such studies is normal cellular metabolism and emphasis has been placed on this all-important phase.

The animal body is a conglomerate of thousands of inorganic and organic chemical reactions many of which proceed simultaneously in a highly organized and compartmentalized manner. Some of these reactions occur freely in circulating body liquids and therefore affect each others' rates, course, and choice of substrates. Other biochemical reactions take place within cells or subcellular particles, occasionally across polymeric macromolecular membranes of such units or their higher aggregates, the tissues. Some of the reagents reach their transition states, and do complex and proceed to end products without special help. Others need considerable activation, and this is provided by a variety of biochemicals of which the high-energy phosphates are the best known. In turn, the high-energy phosphates are resynthesized, the bioenergy input for these syntheses being provided by the oxidative metabolism of dietary nutrients. The monomeric constituents of such nutrients (monosaccharides, amino acids, fatty acids, nucleosides, etc.) are oxidized in many coupled and sequential stages which are mediated by coenzymes and other electron acceptors, and under conditions that permit gradual dissipation of the energy created. These hundreds of steps comprise intermediary metabolism, the core of biochemistry.

The coenzymes, in many cases, are degradable to smaller units including numerous vitamin molecules from which the normal organism can reconstitute the essential biocatalysts. Some animal species can biosynthesize certain vitamins which thereby take on the role of hormones in these species.

The bewildering variety of ac-



Erwin Chargaff

tions of vitamins, hormones, coenzymes, and their synthetic congeners, as well as the frequent overlapping of their activities, has found a suggestion of a common denominator through the discovery of secondary hormones of the cyclic nucleotide type. These compounds, and enzymic reactions needed for their formation, were described by Earl W. Sutherland and his associates (*21*) and have given us an indication that the incredible diversity of biological phenomena might be reduced some day to a few fundamental concepts through chemistry. Analytical, organic, and biological chemistry has come close to this goal in genetics where the genes could be equated with deoxyribonucleic acids. Now that levels of thought, emotion, behavior, and mood are on the verge of being based on concentrations of biogenic amines in the brain, the most mysterious characteristics of human life and striving may also yield to biochemical methods and explanations.

Diseases result from the breakdown of normal biochemical pathways; such deviations are investigated best in their extreme pathological manifestations, where overlapping with pre-existing normal reactions and reagents is minimized. Medicinal chemists who must understand the causes of pathological changes have taken up at least in vitro examinations of such pathways. By the same token, pharmacologists had to branch out into biochemistry in an effort to refine gross observations of tissue pathologies. The mixture of these converging efforts has been labeled molecular biology, molecular pharmacology, and medicinal biochemistry, depending on slight differences of emphasis and the earlier training of the investigators.

Cancer and viruses

Molecular biology took a turn toward organic chemistry when the structure and at least part of the conformation of nucleic acids (DNA and RNA) were elucidated by Erwin Chargaff, Linus Pauling, James Watson, Francis Crick, and Maurice Wilkins in the 1950's (*22*). These discoveries were followed by the recognition of the chemical details of the genetic code (H. G. Khorana) by which nucleic acids transcribe genetic information for the alignment of amino acids activated by phosphorylation in the biosynthesis of proteins, enzymes, and other polypeptides. The individual stages of the coded transmission from DNA via RNA's of various lengths (messenger RNA, short RNA, transfer RNA, etc.) and the essential features of various aggregates such as ribosomes and polysomes also are understood, although many details still need to be filled in. These findings converted genetics, previously a descriptive biological doctrine, into a science based on accurate chemical data.

This work led to much unexpected fallout of value to medicine. For example, both the nucleic acid core and the protein capsid (coat) of small viruses became amenable to detailed study, and the process of viral reproduction at the expense of normal host cells could be pictured.

James Watson



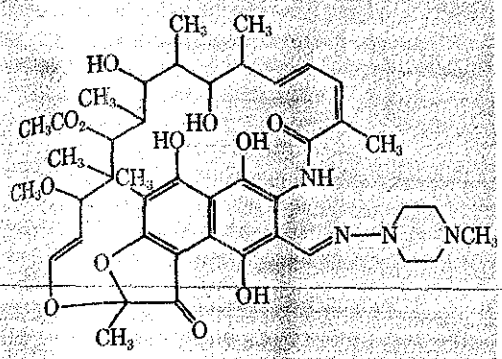
Moreover, a theoretical basis was provided for the old speculations that some malignancies of vertebrates are associated with RNA viruses—that is, viruses whose whole or predominant nucleic acid core is RNA. In all oncogenic (cancer-forming) RNA tumor viruses, the customary flow of information from DNA to RNA is reversed by the enzyme RNA-dependent DNA polymerase (reverse transcriptase), which catalyzes the synthesis of DNA from RNA by a pathway first proposed by Howard M. Temin (*23*). A similar enzyme has been extracted from white blood cells (leukocytes) of some patients with acute leukemia, and particles containing a reverse transcriptase have been found in human milk, particularly from patients with breast cancer and from inbred populations with a high incidence of this disease.



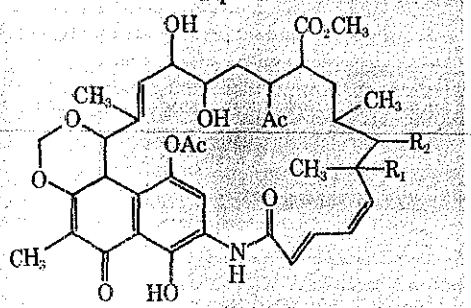
Howard M. Temin

The role of reverse transcriptase in the transformation of normal cells into malignant tumor cells is by no means clear. However, some derivatives of the antibiotics rifampicin and streptovaricin inhibit both the viral and the leukemic cell enzyme and kill leukemic cells at pharmacologically acceptable concentrations (Figure 1). Other inhibitors of the enzyme potentially useful in cancer chemotherapy also have been observed (*24*).

Cancer chemotherapy is one of the best examples of the impact of biochemical thinking on drug design, medical treatment, and cures. Its intertwining with virology, genetics, and immunology, and with the yet unsolved riddle of carcino-

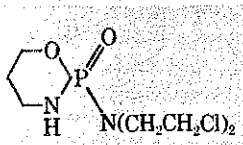


Rifampicin

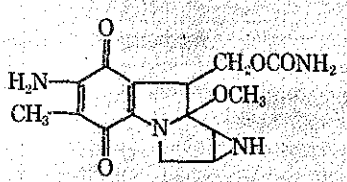


Streptovaricins
A: $R_1 = R_2 = OH$
B: $R_1 = H$, $R_2 = OH$

Figure 1



Cyclophosphamide



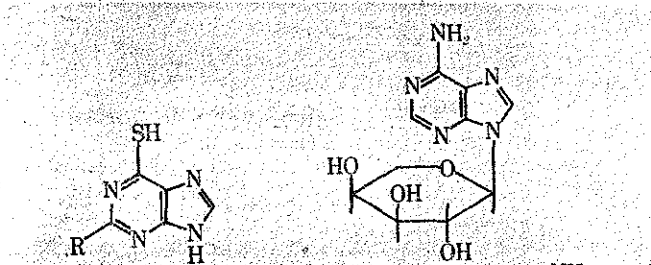
Mitamycin C

Figure 2

genesis, has made cancer chemotherapy one of the most active—and recently best funded—fields of biomedical research.

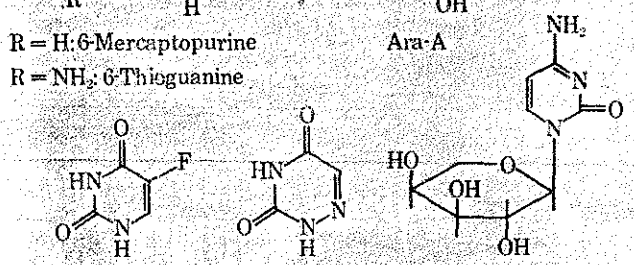
The nitrogen mustards, among them cyclophosphamide, and other alkylating agents, including the *Streptomyces caespitosus* antibiotic mitamycin C with its ethylenimine group, act primarily by way of nucleophilic reactions (Figure 2). They alkylate DNA at the 7-position of the purine base, guanine, cross-linking opposed guanine molecules on the two strands of DNA where a twist in the helix puts them in the best steric apposition for this reaction.

Other biochemically based anticancer drugs such as methotrexate are structural analogs (antagonists) of tetrahydrofolic acid. *N*-Formyltetrahydrofolic acid furnishes a one-carbon segment for the ring closure of a purine nucleotide; methotrexate inhibits this enzymic cyclization, and thereby DNA biosynthesis. Hundreds of analogs of purine and pyrimidine bases have been tested as antagonists of purine and pyrimidine biosynthesis. Only a few have a reasonable chemotherapeutic index and therefore are acceptable for cancer chemotherapy. Among these are 6-mercaptopurine and its 2-amino derivative (6-thioguanine), 5-fluorouracil, 6-azauracil, and the arabinosides of adenine and cytosine—Ara-A and Ara-C (Figure 3) (*25*). Some of these drugs also decrease the immune response and thereby are of value—albeit temporary—in suppressing rejection of organ transplants. Some others are active against herpes viruses—for example, 5-iodouridine in eye infections and Ara-A in infections of the nervous system by the virus.



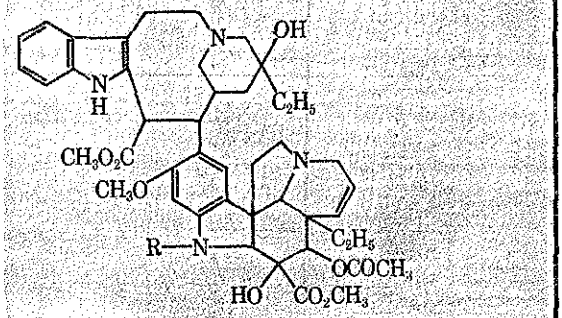
R = H: 6-Mercaptopurine
R = NH_2: 6-Thioguanine

Ara-A



5-Fluorouracil 6-Azauracil Ara-C

Figure 3

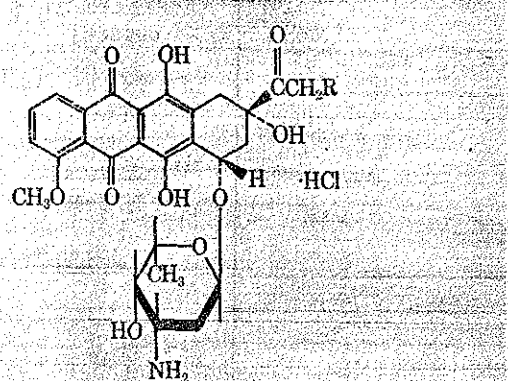


R = CH_3: Vinblastine
R = CHO: Vincristine

Figure 4

These "faulty metabolites" compete with natural substrates for active sites of enzymes that control the biosynthesis of purine and pyrimidine nucleotides. However, compounds whose action is anticipated less easily sometimes do as well as medicinal agents. For example, two periwinkle alkaloids with a long medical folklore to recommend the plant *Vinca rosea* Linn. as a drug for diabetes are used widely in the treatment of acute childhood leukemia and other neoplasms (Figure 4). These alkaloids, vinblastine and vincristine, interfere with the synthesis of soluble or transfer RNA and also may act as acylating agents in vivo (*26*).

Only an arbitrary semantic distinction separates a chemotherapeutically active alkaloid from an antibiotic. A number of Streptomyces antibiotics are useful in cancer chemotherapy, notably daunomycin (*27*) and adriamycin (*28*) (Figure 5). These compounds apparently act through intercalation with DNA (*29*).



R = H: Daunomycin
R = OH: Adriamycin

Figure 5

One of the many probable causes of hypertension is the accumulation of excessive amounts of biogenic amines (phenethylamine, tyramine, dopamine, norepinephrine, serotonin) in the central nervous system, sometimes combined with peripheral vasoconstriction by epinephrine and perhaps by other biogenic amines. Of these, dopamine, norepinephrine, and epinephrine appear as the principal culprits—at least they have been most thoroughly investigated, together with serotonin (5-hydroxytryptamine, 5-HT), which also may be involved. If the action of a biochemical is to be prevented, two routes are open to the medicinal chemist: Block its action at its receptor site, or cut down its biosynthetic supply. For the latter route, deactivation of a critical enzyme in the biosynthesis could be envisaged. One of these steps is the decarboxylation of dopa (3,4-dihydroxyphenylalanine) to dopamine under the influence of a rather unspecific enzyme, aromatic amino acid decarboxylase (dopa decarboxylase).

It appeared possible that replacement of the group, $-CH_2-CH(NH_2)CO_2H$, in the substrates by a sterically hindered group, $-CH_2C(CH_3)(NH_2)CO_2H$, would produce compounds that would inhibit the decarboxylase. This turned out to be the case; the α-methyl homolog of dopa, called methyldopa, indeed inhibits dopa decarboxylase activity. That means less dopamine is produced, and since dopamine is the biosynthetic precursor of norepinephrine and epinephrine, less of these two catecholamines also is formed (Figure 6). Methyldopa, after due testing, was introduced as an effective antihypertensive agent (*30*). Later an additional mode of action emerged from further studies. Methyldopa is not only a decarboxylase inhibitor, but also a (rather poor) substrate of this enzyme. That means some methyldopa is decarboxylated to α-methyldopamine, which, in turn, is bioconverted further to α-methylnorepinephrine. This compound antagonizes the action of norepinephrine at its receptor; this antagonism may be one of the reasons why the body's blood pressure is lowered.

Dopa for Parkinsonism

Dopamine has been identified as an important neurotransmitter. It is found in relatively high concentrations in the substantia nigra and the corpus striatum in the brain. When its concentration falls below a critical threshold, extrapyramidal motor system deficiency symptoms are observed in mammals, corresponding to the syndrome of Parkinsonism in man. Dopamine administered to such patients cannot cross the blood-brain barrier because it is too polar. Its biosynthetic precursor amino acid, L-dopa, is less polar, enough is taken up and concentrated in the corpus striatum to be decarboxylated there to dopamine. Thus dopamine concentrations are brought up to par and dramatic alleviation of the symptoms of Parkinsonism follows (*31*).

Throughout every phase of DNA synthesis in the life of each organism, and in the course of inheritance from one generation to another, there are many chances of isolated errors in assembling the nucleotide bases and probably other structural units of the DNA molecules. Some of these errors in molecular structure can be corrected, but others cannot and lead to mutations. Each faulty sequence of the nucleotides of DNA alters the genetic information, and therefore the type of proteins and enzymes biosynthesized by the organism. Every cell is programed by a copy of the individual's DNA, and every cell can mutate. Only germ cells that produce ovum and sperm can transmit a mutation to the offspring without having an effect on the individual.

The biosynthesis of catecholamines and a pathway for its inhibition

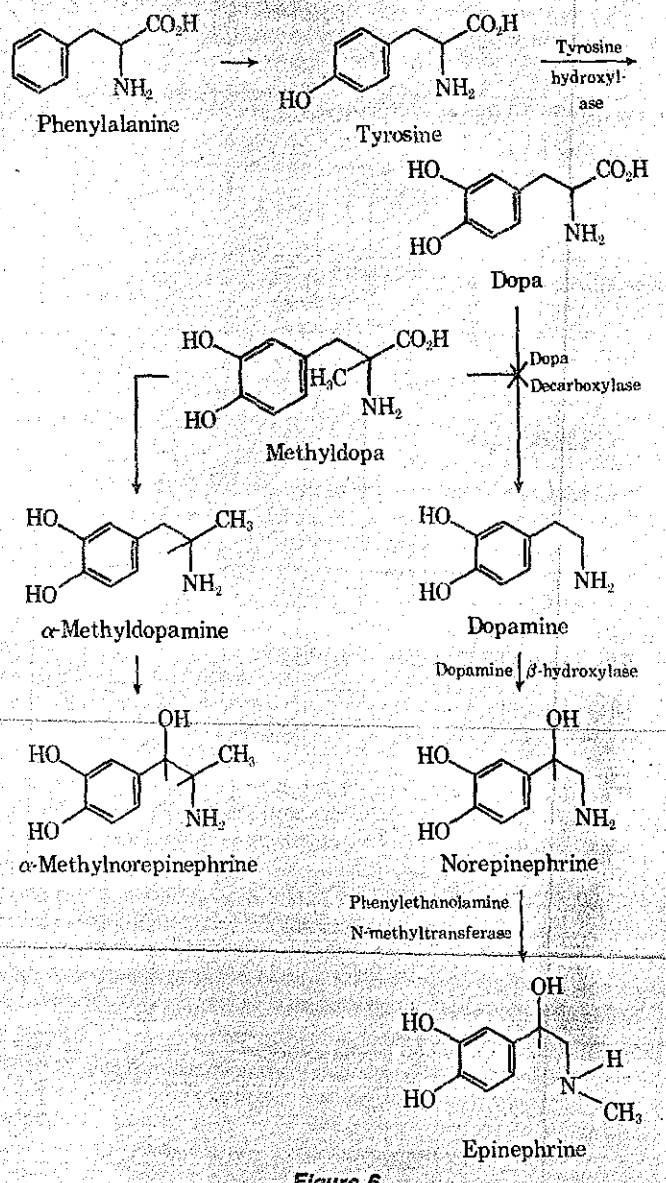


Figure 6

Agricultural research station patterned after German concept



Samuel Johnson in 1901

The first agricultural research station actually predates the founding of the American Chemical Society by something less than a year—it started its work on Oct. 1, 1875. The driving force behind its inception was an agricultural chemist named Samuel W. Johnson. He was one of a small group of farsighted individuals who felt that science and chemistry could play a valuable role in agriculture, and he felt this could best he done through agricultural research stations modeled after those already in existence in Germany.

Samuel Johnson was the son of a New York farmer and, after graduation from Lowville Academy, had later entered Yale Scientific School to study agricultural chemistry. Like many other scientists and chemists in those days, he studied for a couple of years in Germany, and it was while there that he got a first-hand look at the operations of the German station at Moeckern, which itself was the first of its kind. Literally translated, the German name for this institute was "Agricultural Experiment Station."

From Germany, Johnson returned to New Haven, Conn., and the position of chief assistant in the Yale Scientific School chemistry laboratory. A year later, in 1856, he was appointed to the chair in agricultural chemistry. It was during these days that Johnson started his campaign that would later culminate in the first agricultural station in the U.S. It was in an address, in fact, in 1856 before the New York Agricultural Society that Johnson defined what the American counterpart to the German experiment station should be and the role it could play in translating science into the field of agriculture—just one minor part of which could be the evaluation of fertilizers purchased and used by farmers.

Shortly after this, Johnson resumed his practice of analyzing and evaluating fertilizers, and this led to his being hired by the Connecticut Agricultural Society to perform the same function for them and to issue reports on his findings for the use of farmers in Connecticut. The start of the Civil War brought an end to the Agricultural Society, but the end of that conflict found the start of a State Board of Agriculture in Connecticut and Samuel Johnson back in the thick of things as its first chemist. He was to hold that position until 1898.

Johnson, of course, was still campaigning for a research station and wound up at one point as the Board of Agriculture committee chairman for the group which was evaluating just such a station. Needless to say, the unanimous decision of the committee was wholeheartedly in favor of such an installation. After meeting all over the state pushing the idea, a bill proposing it was entered into the state legislature in 1874, but it was tabled without action. With greater backing it was taken up again in 1875 and, with the help of the offer of a laboratory at Wesleyan University and a $1000 starting grant, the Connecticut legislature approved the formation of an Agricultural Experiment Station July 20, 1875, and appropriated $2800 for its first two years of operation. Shortly thereafter, a new bill moved the station to New Haven and made it a permanent part of the Connecticut agricultural scene. Not unexpectedly, Samuel W. Johnson was appointed to the position of station director.

Mutations occurring in body cells have no effect on later generations but are suspected of causing cancer-like diseases and possibly playing a role in the aging of the organism. Inheritable (germ cell) mutations may affect physical or emotional characteristics, appearance, or intellectual capacity, and cause deformities or handicaps. The mutation may be dominant (immediately expressed in the next generation) or recessive, that is, it may appear in posterity when an egg and sperm carrying the same defect are united.

Factors that cause increased mutations are radiation and carcinogenic and mutagenic chemicals. Among such chemicals are some compounds in our environment, and certain food additives and drugs. Some of them may induce inheritable mutations, whereas others (teratogens like thalidomide) may cause direct bodily deformations of a growing fetus, but are not transmitted to further generations. For drugs and food additives, tests in animal model systems for carcinogenicity and teratogenicity are mandatory before approval by the Food & Drug Administration for their use in foods and in medicine.

The medical significance of germ cell mutations is the surfacing of hereditary diseases caused by deficiencies of pivotal enzymes. Many of the known inherited diseases involve the absence of a crucial enzyme. Genetic enzyme deficiencies are transmitted from parents to children, usually as autosomal recessive traits, both parents being carriers of the gene for the disease. The carriers themselves are not affected by the deficiency since they have about one half of the normal concentration of the enzyme—enough to keep them well and unaware of their condition. The affected child, however, usually has so little of the enzyme that he or she succumbs to the disease.

In some cases, dietary nutrients and foods that contain substrates requiring the missing enzyme for chemical transformation can be avoided by the patient. For example, infants suffering from phenylketonuria (PKU), an inability to oxidize the aromatic ring of the essential amino acid phenylalanine, can be placed on a diet low in phenylalanine and thus develop normally. Milk with its content of milk sugar (lactose) can be eliminated from the diet of children suffering from a deficiency of galactosidase as in galactosemia. Such deficiencies can be diagnosed by chemical tests of the newborn, but in most genetic chromosomal aberrations the physician

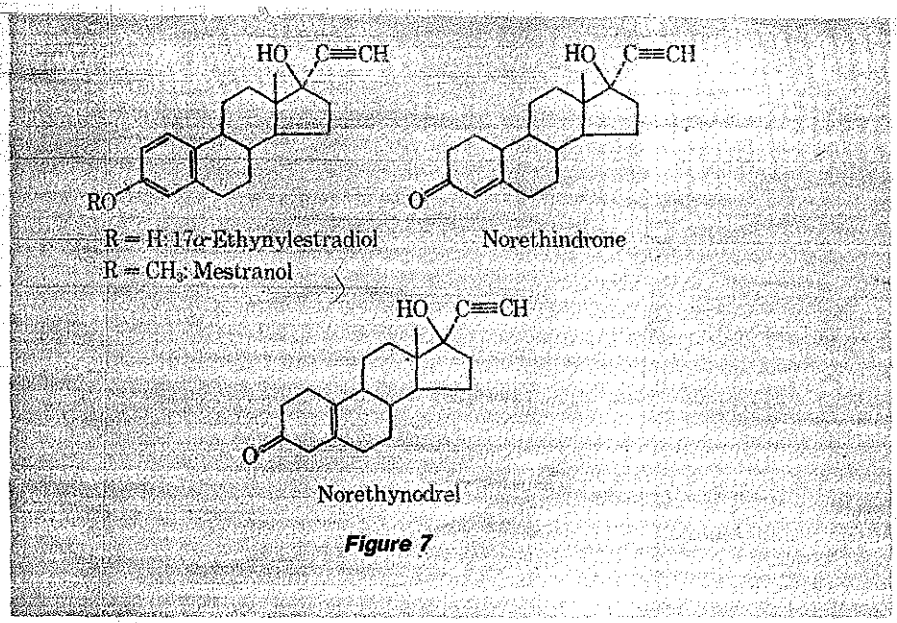


Figure 7

is helpless. To be sure, once a genetic enzyme deficiency has been diagnosed in a family, carriers of the defective gene can be detected by biochemical assays and other measures.

One of the most thoroughly investigated molecular diseases is sickle cell anemia, which results from a deformation (sickling) of red blood cells with a concomitant deficiency of oxygen transport by the abnormal hemoglobin in such cells. This inherited disease is caused by one variant amino acid group in globin. The abnormal hemoglobin S can be separated by electrophoresis. Sickle cells are of genetic advantage in regions in which *Plasmodium falciparum*, the parasite of malignant malaria, is prevalent. Individuals with a sickle cell trait which also involves zinc deficiency have an enhanced resistance to this blood cell infection. Sickle cell disease now can be treated with cyanate ion, although, as a side effect, this therapy may lead to nerve conduction abnormalities.

Hormonal therapy

The problems of replacement also plague the use of many polypeptide hormones. Securing adequate amounts of hormones at affordable prices from animal sources with a minimum of allergenicity has been achieved only in a few cases. Synthetic attempts to simplify and modify the structure of hormonal peptides indicate that more specific analogs can undoubtedly be made, but a lack of interest in the pharmaceutical industry has not let these searches come to clinical fruition, perhaps because massive uses for such hormones have not developed. The synthesis of insulin (51 amino acids), calcitonin (32 amino acids), and human growth hormone (Choh Hao Li, 1971; 190 amino acids) has demonstrated that there is no real barrier left to the small-scale and presumably the large-scale synthesis of such peptides if the need should arise. The fascinating biological properties of the hypothalamic neurohormones which release thyrotropin, corticotropin, growth hormone, prolactin, luteinizing hormone, etc. make it seem most likely that these and other polypeptide hormones will find a place in therapy soon.

The case is quite different for the modified steroid hormones which have revolutionized the control of female fertility by methods of contraception. Last year, more than 50 million women worldwide, and 11 million in the U.S., relied on the "pill" or, less frequently, on injectable contraceptive agents to prevent unwanted pregnancy.

The pill is usually a combination of a progestational agent and an estrogen, in varying ratios, and blocks ovulation in the normally cycling woman, thereby preventing conception without suppressing withdrawal bleeding (32). This medication was conceived by the endocrinologist-biologist Gregory Pincus, and the gynecologist John Rock, and their coworkers in Massachusetts. Their combined medication became possible through the development of the orally active estrogen, 17α-ethynylestradiol (Hans H. Inhoffen, 1938) and its 3-methyl ether (mestranol), followed by the orally active progestational hormones, 17α-ethynyl-19-nortestosterone (norethindrone) and its $\Delta^{5(10)}$ isomer (norethynodrel) synthesized 25 years ago by Carl Djerassi at Syntex and Frank B. Colton at G. D. Searle (Figure 7). Combinations of norethynodrel and mestranol and of norethindrone and mestranol are examples of widely used oral contraceptives.

Many modifications of these agents have been proposed and tested. Especially the progestational components have been varied with the intention of eliminating the estrogen altogether. This has been realized in injectable preparations that block ovulation up to six months. (Amenorrhea is, however, a common side effect.) Another application of progestational agents alone is the minipill, an orally active means of altering the cervical mucus and making it impassable to sperm.

The contribution of chemistry to this important field of medication has been to provide a long series of steroids that exhibit minimal or virtually no side effects on administration over several decades. Since the oral contraceptives do not fulfill a therapeutic purpose in disease but are taken voluntarily by normal, healthy women, the restrictions on their benefit-to-risk ratio imposed by regulatory agencies have been particularly severe.

Dilemma of pharmacological selectivity

When drugs are administered, nobody wants to add insult to injury and expose a suffering patient to additional discomfort, pain, poisoning, or even danger to life. Yet it is inherent in the concept of pharmacotherapy that the drug interrupts some damaging, unwanted, pain-producing, or disease-forming process, thereby bringing relief. It is unlikely, based on accumulated experience, that a drug will be found that will do this without ever spilling over into other vital or unrelated bodily reactions. The hope for absolute pharmacologic specificity appears to be an unattainable myth.

In every phase of our lives we have to make value judgments between competing courses of action. These lead to choices between options. Such often vexing and crucial questions force us into compromises and send us for help to consultants, counselors, and confidants. With drugs, the counselor is the physician. He must weigh the odds, decide on the risks, estimate the benefits, and then take a chance on exposing the patient to foreign and not always selective chemicals. Although the ultimate decision about what drug, what dosage, and what regimen to use rests with the physi-

cian, he and the patient can learn from preclinical and extensive clinical trials before the drug has been made available. Most importantly, the Food & Drug Administration has evaluated the drug's advantages and disadvantages before it—always hesitatingly—puts its stamp of approval on the use of the drug.

Life-saving drugs for acute and lethal infections, for leukemias and other malignancies, and for catastrophic diseases of vital organs will be allotted lower margins of safety and a measure of nonselectivity if no better agent is available. This concession disappears almost completely for therapeutic agents of general value—those that ameliorate a nonlethal disorder or provide relief from tolerable pain. The vast majority of prescription and over-the-counter drugs fall into this category. Demands for absolute safety are raised for medicines that are taken voluntarily as prophylactics, such as vaccines and contraceptives. The hurdles to be overcome by a new contraceptive agent consist of clinical tests for efficacy, side effects, and absence of chronic toxicity extending over a decade or more and costing an estimated $18 million, calculated before the 1973 inflation (*33, 34*).

Projections into the future

Forecasting scientific progress without proper experimental data is not rewarding. But in a profession where intuition, imagination, and beating the odds are conditions for success, it is not unusual to encounter discussions of therapeutic problems whose solution appears intangible at the moment. The impetus for such occasions usually is provided by a clinical inquiry, when the symptomatology of a given disease suggests a biochemical cause. What do we know about applicable biochemical metabolites and reactions? Is there an indication that some metabolites have gone astray and that a resupply might do some good? Or should one block the supply of some biochemicals; perhaps their metabolism could be at fault? If indeed there is a biochemical derangement, should it be corrected by medication or by other means?

There is a temptation to program computer memory with such multiple questions and extract some composite answer. But that activity cannot yet replace human intuition in drug design (*16*).

Some important practical constraints loom in the background of such discussions. Like it or not, somebody has to pay for research projects. In the pharmaceutical industry, market analysts will have a voice in the choice of such programs. That means that the number of patients with a given disease will be a persuasive argument to risk research capital. One suggestion that incorporates very large patient populations concerns the field of tropical diseases. The figures in these areas run in the hundreds of millions of patients for malaria, schistosomiasis, filariasis, amebiasis, leishmaniasis, and others (*35*). Although we have "leads" to compounds with such badly needed activity spectra, only a few developmental studies are going on in these areas, mostly because of the depressed economic conditions of the affected nations.

It is not surprising that many speculations about unorthodox approaches to new drugs center on the role of the immune system and on agents and conditions that suppress or enhance autoimmune responses. These phenomena are involved in so many poorly understood pathologies that compounds affecting the immune response should radiate into diverse therapeutic missions. Some of them have already been touched upon, in the discussion of antitumor drugs and compounds that prevent the rejection of homografts. Other diseases in which immune responses are implicated include allergies, immunizations to infection, natural resistance to infection in a given animal species (including man, who cannot be infected by numerous mammalian or avian pathogens), and bone marrow depression. Delayed hypersensitivity or cell-mediated immunity, such as the tuberculin PPD skin reaction, may be mentioned in a long list of autoimmune phenomena. The continuing keen interest in these subjects points to the probability that medicinal research in coming years will deal heavily with such topics. □

References

1. Vane, J. R., *Nature New Biol.*, **231**, 235 (1971); Ferreira, S. H., Moncada, S., Vane, J. R., *ibid.*, p. 237.
2. Burger, A., "Medicinal Chemistry," 3rd ed., Ed. Burger, A., Chapter 2, Wiley-Interscience, New York, 1970.
3. For a review, see Gourley, D. R. H., *Prog. Drug Res.*, **20** (1976).
4. Burger, A., "Paul Ehrlich," *Chem. Eng. News*, **32**, 4172 (1954).
5. Einhorn, E., Pfeifelder, E., *Ann. Chem.*, **371**, 131 (1909).
6. Barger, G., Dale, H. H., *J. Physiol.*, **41**, 19 (1910).
7. Chen, K. K., Schmidt, C. F., *J. Pharmacol. Exp. Ther.*, **24**, 339 (1933).
8. Alles, G. A., *J. Pharmacol. Exp. Ther.*, **32**, 121 (1927); **47**, 339 (1933).
9. Siegmund, O. H., Granger, H. R., Lands, A. M., *J. Pharmacol. Exp. Ther.*, **90**, 254 (1947).
10. Loewi, O., *Arch. Gesamte Physiol. Menschen Tiere*, **189**, 239 (1921).
11. Kushner, S. L., Brancone, L. M., Hewitt, R., McEwen, W. L., Subbarow, Y., Stewart, H. W., Turner, R. J., Denton, J. J., *Ann. N. Y. Acad. Sci.*, **50**, 120 (1948).
12. Fox, H. H., *J. Org. Chem.*, **17**, 542, 547, 555 (1952); Fox, H. H., Gibas, J. T., *ibid.*, p. 1653.
13. "Molecular Modification in Drug Design," Gould, R. F., Ed., *Advan. Chem. Ser.*, 45, American Chemical Society, Washington, D.C., 1964.
14. Domagk, G., *Deut. Med. Wochenschr.*, **61**, 250 (1935); Mietzsch, F., Klarer, J., German Patent 607,537 (1935).
15. For a review, see Burger, A., Bioisosterism in Molecular Modification, in "Medicinal Chemistry," 3rd ed., Ed. Burger, A., pp. 72–80, Wiley-Interscience, New York, 1970.
16. Hansch, C., *Bioisosterism, Intra-Science Chem. Rept.*, **8**, No. 3, 17 (1973); *J. Med. Chem.*, **19**, 1 (1976).
17. Free, S. M., Jr., Wilson, J. W., *J. Med. Chem.*, **7**, 395 (1964).
18. Hansch, C., Silipo, C., Steller, E. C., *J. Pharm. Sci.*, **64**, 1186 (1975).
19. Baker, B. R., in "Medicinal Chemistry," 3rd ed., Ed. Burger, A., Chapter 12, Wiley-Interscience, New York, 1970.
20. For a review, see McMahon, R. E., in "Medicinal Chemistry," 3rd ed., Ed. Burger, A., Chapter 5, Wiley-Interscience, New York, 1970.
21. Sutherland, E. W., *Science*, **177**, 401 (1972).
22. Watson, J. D., "The Double Helix," Atheneum, New York, 1968.
23. Temin, H. M., Mizutani, S., *Nature*, **226**, 1211 (1970).
24. For a review, see Apple, M. A., *Ann. Rep. Med. Chem.*, **8**, 251 (1973).
25. For a review, see Montgomery, J. A., Johnston, T. P., Shealy, Y. F., in "Medicinal Chemistry," 3rd ed., Ed. Burger, A., Chapter 28, Wiley-Interscience, New York, 1970.
26. Creasey, W. A., Markiw, M. D., *Biochim. Biophys. Acta.*, **87**, 601 (1964); Moncrief, J. W., Heller, K. S., *Cancer Res.*, **27**, 1500 (1967).
27. Arcamone, F., Cassinelli, G., Franceschi, G., Mondelli, R., Orezzi, P., Penco, S., *Gazz. Chim. Ital.*, **100**, 949 (1970).
28. Ross, W. J., Jamieson, W. B., McCowen, M. C., *J. Med. Chem.*, **15**, 1035 (1972).
29. Karnaky, K. J., *Southwest Med.*, **53**, 10 (1972).
30. Sourkes, T. L., *Arch. Biochem. Biophys.*, **51**, 444 (1954); Oates, J. A., Gillespie, L. Jr., Udenfriend, S., Sjoerdsma, A., *Science*, **131**, 1890 (1960).
31. Yahr, M. D., Duvoisin, R. C., Hoehn, M. H., Schear, M. J., Barrett, R. E., *Trans. Amer. Neurol. Ass.*, **93**, 56 (1968).
32. For a review, see Deghenghi, R., Mason, A. J., in "Medicinal Chemistry," 3rd ed., Ed. Burger, A., Chapter 35, Wiley-Interscience, New York, 1970.
33. Djerassi, C., *Science*, **168**, 941 (1970).
34. Burger, A., *Chem. Eng. News*, **53**, No. 38, 37 (1975).
35. See the collection of pertinent papers in *Prog. Drug Res.*, **18** (1974); **19** (1975).

deals with the toxic effects of chemicals on individual organisms.

Another topic treated by the report is environmental management, including monitoring, simulation modeling, establishment of standards, and risk estimation. The panel emphasizes the need for more knowledge in all environmental areas. "It is difficult to see how best to improve the environment without first establishing fundamental facts; such facts will also serve to offset the interminable speculation frequently passing for knowledge."

However, the report notes, a comprehensive global environmental monitoring system, endorsed by the UN Conference on the Human Environment in 1972, is still not being set up. The delay may be caused by deficient understanding of how to go about monitoring in practice, SCOPE says, and it suggests ways of remedying such deficiencies.

One of the panel's key points is that when scientists gain knowledge about the environment and its possible threats, they must be willing and able to communicate their knowledge in an understandable fashion to scientists in other disciplines, policy makers, and the public, including use of the mass media. "They must not ponder this knowledge in the detached and rarified atmosphere of the intellectual ivory tower," notes Holdgate. "This kind of science is not just addressed to scientists." Indeed, SCOPE has an ongoing research project bringing together scientists and policy makers to examine the difficulties of actual use of scientific evidence in environmental decisions.

The tone of the SCOPE report is one of "cautious optimism," despite the many environmental threats. "No other attitude is sensible," says Holdgate, "unless we doubt our own powers and understanding so much that we are left with no other recourse but despair." There are already many success stories of wise management of natural resources, he points out. And the impacts of human activities "will certainly not all continue to grow at [an] exponential rate."

What about implementation of the report's recommendations? Highest priority for further research "should clearly be given to those problems whose solution is being impeded by lack of scientific knowledge" rather than by deficient social or political will, Holdgate stresses, and a multidisciplinary approach must be taken. ICSU and its unions and committees are already working in some areas discussed, and may undertake cooperative research efforts in additional ones.

"I'm optimistic," concludes Kovda. "But you have to pressure governments, you have to create social opinion" in order to get a comprehensive network of global monitoring stations, exploratory research, modeling, environmental legislation, and other efforts. "What is the point? Action is the point. Action, action, and action."

Richard J. Seltzer, C&EN Washington

Scientists called to action on world problems

A "call to action"—urging scientists and engineers to help move the world away from awesome threats to its future—was sounded at the final session of the symposium held in Washington, D.C., in conjunction with the General Assembly of the International Council of Scientific Unions. Prepared at a meeting in Bellagio, Italy, by a panel of 17 prominent and "concerned" scientists from eight countries, the appeal focuses with "guarded optimism" on the possibilities of solving over the next 25 years such major science- and technology-related world problems as food supply, environmental control, materials and energy supply, and arms control and nuclear proliferation. The panel was chaired by Dr. Lewis M. Branscomb, vice president and chief scientist of IBM and former director of the National Bureau of Standards.

The report, according to the panel, "is not a view of impending doom, but neither is it a view that justifies complacency or procrastination. Rather, it is a sobering view of a great challenge, together with an assertion that the world *can* reach the goal of a better life for all humankind, if it can chart a prudent course through troubled times." Success, the panel adds, will depend not on a single dramatic effort or institutional invention, but rather on "a long sequence of small, correct decisions," with science and technology as "necessary agents" in making these decisions and in carrying them out.

Much of the scientific knowledge and technological tools for improving living conditions worldwide are already available, the report notes, but their application is often frustrated by political, economic, and social constraints. Scientific and technical skills must be much better distributed globally to deal with world problems, for example. And many uses of science and technology contribute short-term benefits, but do so at the expense of future resilience—"leaving an ominous legacy for future generations."

Nevertheless, the panel's recommendations assume no major changes in world institutions and attitudes, "however much such changes might be welcome." But the report does strongly urge revamping of the traditional roles of scientists and scientific institutions, to do far more than just contribute new knowledge.

Successful management of human affairs will "depend strongly on the involvement of scientists and engineers with the social and political institutions that determine the use of technology," stresses Branscomb (himself a leading science adviser to Presidential candidate Jimmy Carter). And the panel emphasizes "the responsibility of the engineer to be alert to consequences of his technological contributions." Indeed, it says, "failure of the world's technical community to commit itself" and to insist on "development of needed policies . . . and cooperative activities could make the pessimistic view of doomsayers a self-fulfilling prophecy."

The panel thus urges creation of new problem-oriented institutions for scientific and policy research to provide facts and analysis enabling "anticipatory decisions" and contingency planning before hazards become critical. Such institutions, together with scientific societies, international scientific unions, and academic institutions, will have to learn to deal credibly and as rigorously as possible with incomplete information and problems "so riddled with uncertainties that hypothetical situations must be modeled as the basis for public decisions."

And it is urgent that scientists learn to communicate their conclusions relevant to policy making to the general public, because "the public's sense of priorities and values limits the decision options of its leaders," the panel points out. "The public must understand the alternatives before it is asked to forego a near-term benefit" for the sake of later gain or safety, Branscomb stresses. "In the past, the scientific community has sometimes taken an elitist view of its role."

Antimalarial research proposals sought

As part of its antimalarial drug development program, the Army is seeking research proposals for synthesis of new antimalarial agents. Proposals, the Army says, should be supported by a compelling chemical, biochemical, biological, or pharmacological rationale. Proposals that request support for basic chemical research not related to the antimalarial program, it notes, will not be supported.

Proposals should include a title page, organizational and administrative information; a budget sheet; a technical presentation, including methods of approach; résumés for key personnel; and a description of facilities. The Army says that proposals may be written to cover research for more than one year but that contracts are funded on a yearly basis. Also, all proposals are subjected to peer review by a study group.

Proposals should include an original and two copies and should be sent to: Commanding General, U.S. Army Medical Research & Development Command, Attn: SGRD-SSL, Washington, D.C. 20314. Inquiries on technical matters can be sent to: Division of Medicinal Chemistry, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D.C. 20012. □

Chemical & Engineering News
1155 16th St., N.W., Washington, D.C. 20036

Editor: Albert F. Plant
Managing Editor: Michael Heylin
Assistant Managing Editors: William F. Fallwell, David M. Kiefer, James H. Krieger, Donald J. Soisson, Fred H. Zerkel
Senior Editor: Earl V. Anderson (New York)
Senior Associate Editor: Howard J. Sanders
Associate Editor: Ernest L. Carpenter
Assistant Editors: P. Christopher Murray, Rebecca L. Rawls, Richard J. Seltzer, Karen Joy Skinner
Editorial Assistant: Theresa L. Rome
Editing Services: Joyce A. Richards (Head)
Editorial Reference: Barbara A. Gallagher (Head)
Graphics and Production: Basil Guiley (Head), Leroy Corcoran (Manager), John V. Sinnett (Art Director), Norman W. Favin (Designer). Staff Artists: Linda Mattingly, Diane J. Reich
NEWS BUREAUS: New York: William F. Fallwell (Head). Chicago: Ward Worthy (Head), Joseph Haggin (Staff Writer). Houston: Bruce F. Greek (Head). Washington: Fred H. Zerkel (Head), Ling-yee C. Gibney, Janice R. Long (Assistant Editors)
FOREIGN BUREAU: London: Dermot A. O'Sullivan (Head)
ADVISORY BOARD: Alfred E. Brown, Mary Carter, Theodore L. Cairns, Marcia Coleman, Arthur W. Galston, Derek P. Gregory, James D. Idol Jr., Gerald D. Laubach, Richard D. Mullineaux, Paul F. Oreffice, Rustum Roy, Edward R. Thornton, Herbert L. Toor, M. Kent Wilson

Published by
AMERICAN CHEMICAL SOCIETY
(202)-872-4600
Robert W. Cairns, Executive Director
Arthur Poulos, Editorial Promotion
Marion Gurfein, Circulation Development

EDITORIAL BOARD: Mary L. Good *(Chairman)*, Herman S. Bloch, Bryce Crawford Jr., Anna J. Harrison, Robert W. Parry, Glenn T. Seaborg, B. R. Stanerson, *President-Elect:* Henry A. Hill; *Representative Council Publications Committee:* Ernest L. Eliel; *Past-President:* William J. Bailey
© Copyright 1976, American Chemical Society

Subscription Service: Send all new and renewal subscriptions with payment to: Office of the Controller, ACS, 1155—16th St., N.W., Washington, D.C. 20036. All correspondence and telephone calls regarding changes of address, claims for missing issues, subscription service, status of records and accounts should be directed to: Manager, Membership and Subscription Services, ACS, P.O. Box 3337, Columbus, Ohio 43210; telephone 614-421-7230.
On changes of address, include both old and new addresses with ZIP code numbers, accompanied by mailing label from a recent issue. Allow four weeks for change to become effective.
Claims for missing numbers will not be allowed if loss was due to failure of notice of change of address to be received in the time specified; if claim is dated (a) North America: more than 90 days beyond issue date, (b) all other foreign: more than one year beyond issue date; or if the reason given is "missing from files."

Subscription Rates 1976: nonmembers U.S. 1 yr. $15, 3 yr. $32; Pan American Union $22.50, $54.50; Canada and other nations $23, $56. Air freight rates available on request. Single copies: Current $1.00. Rates for back issues and volumes are available from Special Issues Sales Dept., ACS, 1155—16th St., N.W., Washington, D.C. 20036. An annual index is available for $25. Standing orders are accepted. Back and current issues are available on microfilm. For further information, contact Special Issues Sales.
Published by ACS from 20th and Northampton Sts., Easton, Pa., weekly except for an extra issue in April and except the last week in December. Second class postage paid at Washington, D.C., and at additional mailing offices.
ACS assumes no responsibility for the statements and opinions advanced by the contributors to its publications. Views expressed in the editorials are those of the editors and do not necessarily represent the official position of ACS.

Advertising Management
CENTCOM, LTD.
(For list of offices see page 47)

Editorial

Editorials

Taxing our research and development effort

The scientific community, among other groups, has been a largely unresisting witness to the decline in research and development in the United States over the past decade. There have been sporadic protests, of course, but most of these were weakly structured and short-lived. This long-term decline in R&D, however, represents a potentially serious problem that needs more than just casual attention by both the scientific community and industry at large.

The U.S. research and development effort is a primary factor in this nation's ability to compete successfully in the world market place. It is our advances in electronics, materials, agriculture, chemicals and pharmaceuticals, and medicine, just to name a few, that have allowed the U.S. to achieve a position of economic and technological leadership in the world today—but we are throwing that lead away. While other countries are increasing their investment in research and development, we are letting ours decrease—and our ability to create economic growth and jobs is decreasing along with it.

With the increasing cost and levels of foreign oil imports, our need to export goods and services to maintain a balance of trade has increased drastically. And the exportable products come primarily from the high-technology arena served by research and development. It is this same high-technology arena, by the way, that offers the best opportunity of generating new jobs and reducing the unemployment that is presently such a major problem in the United States. The federal government can generate a lot of jobs, but these have a disturbing tendency to be nonproductive most of the time.

There is considerable hope that the incoming Carter Administration will help reverse some of the decline in federal impact on R&D, but in the meantime, we have evidence of another government move that goes in the opposite direction. The Internal Revenue Service has issued a new regulation, to implement the new tax reform(?)laws, that could particularly affect the U.S. chemical industry and chemical employment.

These proposed changes in section 861 of the Internal Revenue Code are direoted primarily at multinational corporations with substantial foreign sales. Under this regulation, a portion of domestic R&D related to foreign sales will no longer be a tax-deductible expense. This loss of a tax deduction for a part of research and development expenditures means that the overall cost of doing research will increase. And that means less R&D will be performed and a loss in present and potential employment in that same R&D sector—and in the industries that rely on that sector for new products. A couple of companies have indicated that this new regulation will add about 30% to the cost of research and development.

We can expect, naturally, that the tax lawyers will figure out some loopholes in the new regulation to reduce or eliminate its full impact on some companies, but that's not a very good solution to the overall problem. We need a regulatory tax structure that will foster technological innovation and R&D, not one that forces us to look for loopholes just to maintain it. It has been pointed out by some economists and manpower specialists, that we will have to create some 15 million to 20 million new jobs over the next decade to solve our unemployment problem and achieve satisfactory economic growth.

Technological innovation provides the products for domestic and international growth and it is that growth which will provide new jobs and economic stability in the future. If we reduce our technological competence by instituting counterproductive tax regulations, the future costs are going to be a darn sight bigger than the current tax revenues. And guess who will pay the difference!

Albert F. Plant

C&EN editorials represent only the views of the author and aim at initiating intelligent discussion.

The handicap of the legalistic approach

Philip J. Mause, Washington, D.C., counsel for the Environmental Defense Fund, had this to say at last month's meeting of the American Association for the Advancement of Science in Denver. It is excerpted verbatim from a paper in which he generally supported a proposal for an independent energy information authority within the federal government.

I think our society is unique in its domination by lawyers, and I think this domination has some relevance to the way we view the future. De Tocqueville noticed this domination more than a hundred years ago. For better or for worse, lawyers and people trained in the law permeate (unkind observers might say "infest") our political system and policy-making at every level of the government.

Indeed, we have a tendency in America to resolve any important issue that confronts our society by having a trial or quasi-trial. It is remarkable that the "science court" proposals seem to follow this pattern faithfully. It is only when one opens one's mind and questions the propriety of resolving disputes about the level and design of electric rates, the siting of nuclear reactors, the definition of peanut butter, and effluent standards for chemicals in trials and trial-like proceedings that the peculiar bias of our system toward litigation becomes clear.

I sometimes wonder how I would explain to an economist from the planet Mars why it is necessary to have a trial to determine whether electric rates should be based on marginal or average costs. Unfortunately, it would not be honest to dodge the question with humorous references to our Anglo-Saxon heritage—I have had more difficulty explaining our fixation with trials to English economists than I have in my worst nightmares about conversations with Martians.

Because facts—however developed—will be filtered through a system of decision-making which resembles our legal system, it is important to understand the special limitations on that system's ability for dealing with facts. The legal system has developed a peculiar and often useful methodology for dealing with questions of fact. It has evolved complex rules for making factual determinations about *past events,* but has never been particularly adept at dealing with *the future.*

Our society's approach to violent crime illustrates this dichotomy. While our legal system has evolved a complex set of procedures for determining the guilt or innocence of a suspect (a *past* fact), our process for determining which of a number of possible remedies are appropriate (probation, parole, confinement in a variety of institutions, execution, etc.) is laughable.

Once having determined what has happened in the past, we find ourselves incapable of dealing with its future significance. It is not hard to find analogies to this asymmetrical precision in dealing with the past and total failure to deal with the future in the areas of antitrust law, securities law, and family law.

The fact is that lawyers look at facts very differently from scientists—and our policy formation process tends to favor the approach adopted by lawyers. Although the future can only be intelligently discussed in terms of probabilities, lawyers continue to use burdens of proof—a concept which may not be very useful in dealing with an uncertain future. Thus, on top of all the inherent difficulties of dealing with the future—we have the application of analytical principles which make sense only in looking at the past. □

C&EN editorials represent only the views of the author and aim at initiating intelligent discussion.

Chemical & Engineering News
1155—16th St., N.W., Washington, D.C. 20036

Acting Editor: Michael Heylin
Assistant Managing Editors: William F. Fallwell, David M. Kiefer, James H. Krieger, Donald J. Soisson
Staff Editor: Ernest L. Carpenter
Senior Editor: Earl V. Anderson (New York)
Senior Associate Editors: Wilbert C. Lepkowski, Howard J. Sanders
Assistant Editors: Jeffrey L. Fox, David J. Hanson, Rebecca L. Rawls, Richard J. Seltzer, M. Mitchell Waldrop
Editorial Assistant: Theresa L. Rome
Editing Services: Joyce A. Richards (Head)
News Bureaus: New York: William F. Fallwell (Head), William J. Storck, Assistant Editor. Chicago: Ward Worthy (Head), Joseph Haggin (Staff Writer). Houston: Bruce F. Greek (Head). Washington: Janice R. Long (Head), P. Christopher Murray (Assistant Editor)
Foreign Bureau: London: Dermot A. O'Sullivan (Head)
Editorial Reference: Barbara A. Gallagher (Head)
Graphics and Production: Bacil Guiley (Head). Leroy Corcoran (Manager). John V. Sinnett (Art Director). Norman W. Favin (Designer). Staff Artists: Linda Mattingly, Diane J. Reich
Editorial Services: Arthur Poulos, Editorial Promotion; Marion Gurfein, Circulation Development

ADVISORY BOARD: Alfred E. Brown, Mary Carter, Theodore L. Cairns, Marcia Coleman, Arthur W. Galston, Derek P. Gregory, James D. Idol Jr., Gerald D. Laubach, Richard D. Mullineaux, Paul F. Oreffice, Rustum Roy, Edward R. Thornton, Herbert L. Toor, M. Kent Wilson

Published by
AMERICAN CHEMICAL SOCIETY
(202)-872-4600
Albert F. Plant, Publisher

EDITORIAL BOARD: Robert W. Parry (*Chairman*), Herman S. Bloch, Bryce Crawford Jr., Mary L. Good, Gordon L. Nelson, Gardner W. Stacy; *President-Elect:* Anna J. Harrison; *Representative Council Publications Committee:* Ernest L. Eliel; *Past-President,* Glenn T. Seaborg
© Copyright 1977, American Chemical Society

Subscription Service: Send all new and renewal subscriptions with payment to: Office of the Controller, ACS, 1155—16th St., N.W., Washington, D.C. 20036. All correspondence and telephone calls regarding changes of address, claims for missing issues, subscription service, status of records and accounts should be directed to: Manager, Membership & Subscription Services, ACS, P.O. Box 3337, Columbus, Ohio 43210; telephone 614-421-7230.
On changes of address, include both old and new addresses with ZIP code numbers, accompanied by mailing label from a recent issue. Allow four weeks for change to become effective.
Claims for missing numbers will not be allowed if loss was due to failure of notice of change of address to be received in the time specified; if claim is dated (a) North America: more than 90 days beyond issue date, (b) all other foreign: more than one year beyond issue date; or if the reason given is "missing from files."

Subscription Rates 1977: nonmembers U.S. 1 yr. $17.50, 3 yr. $37.50; Pan American Union $25.50, $61.50; Canada and other nations $27, $66. Air freight rates available on request. Single copies: Current $1.00. Rates for back issues and volumes are available from Special Issues Sales Dept., ACS, 1155—16th St., N.W., Washington, D.C. 20036. An annual index is available for $25. Standing orders are accepted. Back and current issues are available on microfilm. For further information, contact Special Issues Sales.
Published by ACS from 20th & Northampton Sts., Easton, Pa., weekly except for the last week in December. Second class postage paid at Washington, D.C., and at additional mailing offices.
ACS assumes no responsibility for the statements and opinions advanced by the contributors to its publications. Views expressed in the editorials are those of the authors and do not necessarily represent the official position of ACS.

Advertising Management
CENTCOM, LTD.
(For list of offices see page 67)

Letters

The legalistic approach

SIR: I for one do not agree that the "legalistic approach" is a "handicap" as Mr. Mause says in the Editor's Page of the March 7 issue. Our "adversary" system of settling disputes and making policy allows decision making to be made with as much information being brought forth as any method yet devised.

Mause uses as his main argument that this system works for determination of past events but is not "particularly adept" at dealing with the future. I ask: What approach is better? I think simply that with *any* policy-making approach it would be far more difficult to deal with the future than to determine the past.

Mause says, "The fact is that lawyers look at facts very differently from scientists." I disagree. I think good lawyers and good scientists will look at facts in pretty much the same way. The differences among them are more in their rationality and bias than in their scientific or legal training.

I think the real problem here is the notion among many "advocates" and "liberals" that "An ounce of prevention is worth a pound of cure." Or "It is better to do something about our problems now than to react to them later." Anyone familiar with feedback and feedforward control knows the fallacy here. You must know far more about the black box to use feedforward control (prevention) than to use feedback control (cure). I think that in most cases it is far better to let a potential social problem develop a bit so that it can be defined (using an adversary approach) and then make policy, than to try to anticipate and define the problem before it develops and institute policies before the problem even appears. Most social problems take a relatively "long" time to develop.

Lubbock, Tex. Paul R. Harris

SIR: Mr. Mause gives an excellent description of one limitation of the legalistic approach to problems. A related limitation is that a large number of similar trials (suits) resulting from a common problem do not provide the best (or even a good) answer to the problem. This limitation is easily apparent for the legalistic approach of awarding financial payment for suffering or permanent injury. The costs of the trials and awards are diffused to everyone as higher prices on higher insurance payments without any direct effect on eliminating the problem. Large awards for medical malpractice suits do not eliminate the causes of incompetent medical services. Large awards for automobile accident suits do not inhibit drunk drivers, repair defective cars, or stop near-blind or otherwise handicapped drivers.

We need to recognize that the legalistic approach is inefficient, expensive, and nonproductive for many situations to which we currently apply it. Many decisions involving the environment and economics require choices between undesirable possibilities—there are no choices available without major disadvantages. We need all the information available, public participation, and competent government officials and legislators to set policies, but we cannot afford to subject every decision to a legal review. In summary, a legalistic solution (a court trial) is undesirable and costly to society and is only justified when a highly undesirable situation cannot be corrected by simpler procedures.

Knoxville, Tenn. Paul A. Haas

SIR: The handicap of the legalistic approach in the March 7 issue of C&EN was a very appropriate comment for the Editor's Page. It is time that we face the fact that our laws are made by lawyers for lawyers with the consent of lawyers. It has gone so far that if a medical doctor pronounces a man dead, a judge can reverse his decision.

With our lives more and more regulated by laws, we need to examine the legal system to see if a new and better system needs to be devised. The present system is incapable of dealing with the future.

Wilmington, Del. Andrejs Baidins

Opportunity knocking?

SIR: There are 114 departments of chemical engineering in the U.S., and today virtually every one of them is seeking at least one new faculty member. Most of these opportunities are for junior-level faculty, but such people just are not being produced from our graduate schools in nearly sufficient numbers to meet this need.

Young Ph.D.-level professionals with a few years of experience in industry would be ideal candidates for these opportunities that now exist in such unprecedented numbers. Unfortunately, the mode of operation in industry is such that excellent individuals may have already built outstanding reputations for themselves and may already be undergoing grooming for greater things within their companies, and yet, these extraordinarily able individuals, though already famous within the walls of their corporations, may be virtually unknown in the broader professional community. One of the greatest difficulties of academic department heads is in identifying these scientifically very able men and women in industry so that they might be made aware of academic opportunities as they arise.

Have you ever wondered why professors receive such a large share of the national awards of professional societies? Are professors really responsible for such a large share of the most important work in pure and applied chemistry? Surely this relative dominance in professional recognition is just another artifact of this same barrier on the professional fame of an individual that exists at the walls of the corporation. True, some few professionals in industry have overcome this barrier, or perhaps it was quantum tunneling, but their numbers are a mere fraction of the exceptionally competent technical people in industry.

Will all of you outstanding chemical engineers, chemists, biochemists, and microbiolo-

Continued on page 54

Max Tishler: worried over research's future

This year's recipient of the Gold Medal of the American Institute of Chemists is Dr. Max Tishler, a man of immense energy (reputedly due to his passion for jelly-beans) and impressive accomplishments. Now emeritus professor of sciences at Wesleyan University, he was for 33 years a research chemist at Merck & Co., where he produced more than 100 patents in the fields of vitamins, steroids, antibiotics, and sulfonamides. He is a member of the National Academy of Sciences, a past president of the American Chemical Society, and in 1970 was the recipient of ACS's Priestley Medal.

The AIC Gold Medal has been awarded yearly since 1926 to "stimulate and recognize service to the science of chemistry or the profession of chemist or chemical engineer." Tishler's own goals have been more specific: He wants to help relieve the sufferings of the sick.

Often working late into the night—then being first to arrive at the lab in the morning—he has pursued his goal with an intensity that has been the despair of colleagues more used to a nine-to-five schedule. His dreams of easing pain and anguish are fired by the memory of 1918, when as a 12-year-old he delivered prescriptions for a Boston pharmacy during the great flu epidemic. The sufferings he saw then, he says, have had a lasting impact.

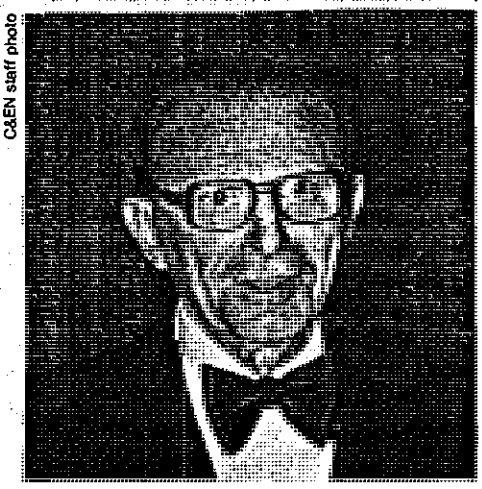
Working his way through school in another drugstore job, Tishler eventually became a registered pharmacist. Even today he proudly carries a copy of his license in his wallet.

After a brief flirtation with poetry, he graduated magna cum laude from Tufts University in 1928, with a degree in chemistry and plans for Harvard medical school. Chemistry proved too compelling, however, and in 1934 he obtained his Ph.D. under Dr. E. P. Kohler. Three years later, Tishler, by then an instructor at Harvard, was persuaded hy the late George W. Merck to join Merck Laboratories.

In those days the idea of industrial work was somewhat distasteful to chemists interested in basic research, Tishler recalls. A good university was the place to be. But Tishler was impressed by the fundamental work that Merck was doing at the time on vitamin B_1. And besides, he says, "It was the depths of the depression, and most of my colleagues at Harvard thought I was lucky to get the job."

In 1937 Tishler joined a research staff of 100; by 1969, when he was elected senior vice president for research and development, he was in charge of a staff of 2300. In his 33 years with Merck before his retirement in 1970, Tishler was instrumental in the discovery of dozens of new drugs and in the development of practical production processes for many others. He helped achieve a practical large-scale synthesis of vitamin K_1, for example, as well as vitamin A, vitamin C, and riboflavin. He also developed a synthesis for sulfaquinozaline, a long-acting drug effective against the poultry disease coccidiosis.

C&EN staff photo



"Serious possibility of becoming a hostage of government"

During World War II, Tishler led a team of microbiologists, chemists, and chemical engineers in developing mass-production processes for penicillin G and streptomycin. Largely as a result of these efforts, Merck was able to fulfill its commitments to produce penicillin in quantities sufficient for wartime.

Following the first synthesis of cortisone by a Merck chemist in 1948, Tishler directed development of a large-scale production process for the compound, a process involving chemistry of a sophistication then unknown to industry. Other developments under his direction have included new drugs for the treatment of heart disease, hypertension, rheumatoid arthritis, and other inflammatory diseases, mental depression, and infectious diseases.

In 1970, Tishler left Merck to become professor of chemistry at Wesleyan University in Middletown, Conn. In 1975, he became emeritus professor there. One attraction of Wesleyan may well have been the hothouse next to the chemistry lab—Tishler is an avid horticulturist. But the college life also gives him a chance to do research and to teach. "Chemistry is useful," he tells his students. "It can do things and serve society."

After such a busy, successful career, capped with many honors, Tishler might be expected to take a sanguine view of affairs. Yet he does not. Max Tishler is a worried man.

In his Gold Medal acceptance speech at the AIC annual meeting in New Orleans last month (C&EN, March 28, page 5) Tishler expressed his distress at the new and hostile pressures bearing down on basic research. "This is anti-intellectualism hostility," he said, "the ugly sentiment that frequently surfaced in the late '60's and that is still with us in many latent forms."

Tishler is no blind apologist for science. In 1969, as Priestley Medalist, he took the unpopular position that the federal funding slowdown—then just beginning—would be good discipline for a self-indulgent and inefficient scientific community. In 1963, he echoed Clemenceau, saying, "The future control over the power of science is too important to entrust to scientists .... Science demands a high price in energy and time for a scientist, and, because of the limitations of the human mind, imposes a narrowness on all but a few."

Yet he is concerned that modern science is facing an ancient challenge: "For the first time in this country, pure research faces the serious possibility of becoming, at least in part, a bostage of government and a servant of political power." A clear example, he said, is seen in the controversy over recombinant DNA research. "Society no longer accepts one of the basic precepts on which research ... is based, namely: The pursuit of knowledge is justified wherever it may take us, no matter how prepared or unprepared the world may be to cope with the truth scientists set before it."

Legislation to limit the kinds of recombinant DNA research that may be carried out already has been adopted in Cambridge and is pending in Congress, Tishler pointed out. "The cleavage of scientists themselves on these issues has bewildered and frightened the public," he said.

"We, as scientists, must act with wisdom and restraint," Tishler concluded. "As the decibels increase, the voices of reason are the first to be drowned out.... It is the right of society to know what the consequences of research can be, and to demand appropriate safeguards ... (yet) we must convince society, hy words and actions, that our interests and society's interest are the same."

Mitch Waldrop, C&EN Washington