NCI seeks a 'magic bullet' for cancer

Agency has screened 300,000 chemicals for biological activity in search for anticancer drugs, but less than one in 5,000 gets to the multimillion-dollar clinical test stage

Although some oxidation catalysts, antioxidants and vulcanization accelerators formulated by Goodyear Tire & Rubber Co.'s research division were found by the National Cancer Institute early this summer to retard tumors in mice, Goodyear's vice-president for research, Richard C. Waller, cautioned against "drawing any premature conclusions."

These chemicals have many years and millions of dollars worth of testing to go through if they are to reach the stage of clinical use in combatting cancer in humans. In fact, the chances of these rubber chemicals actually being used against cancer are slight—somewhere between 0.02 and 0.1%, according to NCI officials.

Nevertheless, NCI's drug synthesis and chemistry branch has been supplied with more than 300,000 chemicals since it began the widespread search for cancer fighters in 1956.

Many companies, including Dow, Du Pont and Union Carbide, have participated in the program.

Rewards can be large for developers of successful compounds, such as the nitrosoureas used to combat brain tumors and Hodgkins disease. But the odds have been so slim that NCI, rather than chemical and pharmaceutical companies, has supplied the leadership in anticancer drug research.

That could soon be changing, says Saul Schepartz, deputy director of NCI's division of cancer treatment and former director of the development program. He sees the return on investment improving and that could make research attractive to companies.

NCI's testing program has shown the way, and when industry is ready to take over, "we'll be prepared to pass it on to them," Schepartz says.

In the Beginning: NCI began by supplementing an anticancer development program that was already under way at the Sloan-Kettering Institute for Cancer Research (New York). The test program, which grew steadily, was given a resounding boost in 1972 by federal funding in the "war on cancer."

By 1974 NCI was screening up to 50,000 chemicals a year for anticancer activity. "That was probably a mistake to test so many chemicals," Schepartz concedes. But he says that at the time "we didn't know enough to predict the kinds of chemicals that would be effective, so we had to explore a variety of structures."

The number tested per year has been cut to about 15,000, according to Robert Ing, assistant to the chief of NCI's drug synthesis and chemistry branch.

NCI now restricts its search to new kinds of chemical structures. "We're now trying to preselect based on prior biological activity. If the chemical is a new structure we will test it, if it's a class of structure already tested then we reject it," says Schepartz.

Goodyear's Waller explains that his company's proprietary chemicals "interest NCI scientists because they might lead to some different mechanisms for fighting cancer than those used in the past."

NCI's Ing agrees: "We're looking for new classes of chemicals with unique features. Hopefully, we can use intellectual insight to determine possible activity."

Some Serendipity: Despite the "intellectual insights" less than one in 5,000 chemicals tested make it to clinical trials, according to Schepartz. Most of those that get there are based on rational chemical designs for specific biological activity. Although, he adds that there is "some serendipity" in the search for the right chemicals.

Methyl nitrosourea is an off-the-shelf chemical that has good biological activity, which NCI tried to capitalize on by having outside laboratories develop specific chemicals based on it. Result: two of the major anticancer drugs, BCNU—1,3-(2-bis chloro ethyl)1-nitrosourea, tradenamed carmustine—and CCNU—1(2,chloro ethyl)3-(4 methyl cyclohexyl)1-nitrosourea, tradenamed lomustine.



NCI's SCHEPARTZ see day when test program will be passed on to industry.

Similarly, DTIC—5(3,3 dimethyl. 1 triazeno) imidazold 4-carboxamide—is a major drug used to combat malignant melanoma that was designed by the Stanford Research Institute, based on the activity of imidazold carboxamide.

Maintaining Rights: Companies, such as Goodyear, that submit chemicals to NCI for testing, maintain proprietary rights to their compounds. Schepartz says they can have "all sorts of relationships set up, depending on how much they want to participate in the testing." And if the chemical goes to clinical trial, the company may want to license it. On the other hand, if an analog of the chemical is synthesized for testing, the company's proprietary rights may not be upheld, says Schepartz.

Long Pull: The kinds of tests the Goodyear compounds have passed (passed by about one in 1,000 of the chemicals submitted) is only the first step.

This step, which takes up to 60 days, involves implanting a tumor in a mouse sensitive to leukemia. The mouse will die within 15 days if untreated. If its life is extended a "meaningful" period of time through treatment, the chemical is considered to have good activity.

Successful passage of this preliminary test, which is repeated three times at a total cost of some $3,000, leads to a broader series of tests. These involve a variety of animals as well as a variety of tumors. Success at this stage is followed by production of the compound in kilogram quatities for pharmacological and toxicological testing and review by the NCI board to decide if it is a candidate for clinical testing. By this time up to $300,000 has been spent on the compound.

Clinical trials, which can take up to four years, can add several million dollars to the cost of the compound's development. Only six to 10 chemicals per year make it to clinical trial, says Schepartz.

Jack W. Germond & Jules Witcover: 1978's different drummer

File w/ Editorials 9-1/6

A month ago Gov. Michael Dukakis of Massachusetts received some political intelligence he should have taken more seriously. Although he was still 15 percentage points ahead of his competition in the Democratic primary campaign, he had lost nine points in about 10 days.

The apparent reason: The impact of the charge being leveled against him by Frank Hatch, one of the candidates in the Republican primary, that he had been derelict in trying to recover $100 million in tax delinquencies. But Dukakis was his usual ineffably assured self. When a visiting reporter suggested the tax delinquency issue might make Hatch a formidable opponent in the general election, he sniffed: "No, I've taken care of that."

As it has turned out, however, Michael Dukakis is the one who has been taken care of — defeated in the Democratic primary by Edward J. King, a hard-line conservative who used the high tax issue, capital punishment and abortion to score one of the year's many political upsets. King now will be facing that same Frank Hatch in the November election.

The simple answer everyone seems to be seeking is that the taxpayers' revolt is what brought Dukakis down. The explanation, however, is far more complicated than that — and far more threatening to other officeholders at all levels. It is neither a secret nor a surprise that the voters are hot about taxes; what is significant is what the results say about their attitude toward politicians in general and incumbents in particular. Color it hostile.

Patrick Caddell, an astute analyst of public opinion, sees the key element as what he calls "the level of frustration" in an electorate. Generally, he argues, that level is higher in the northern and northeastern states where taxes generally are higher than in those areas of the South and Far West that are economically most healthy. What the chance to vote for an anti-tax, anti-government candidate represents, in Caddell's formulation, is "a safety valve" that allows them to express those frustrations.

What is apparent from the results in the primaries so far this year, however, is that it is by no means only taxes — or only the north and northeast that are affected.

There are returns, for example, that suggest a combination of volatile issues is required. Edward King relied on abortion and capital punishment, as well as high taxes and Dukakis's reputation for being an abrasive personality. Similarly, in Minnesota a week earlier, Bob Short defeated Rep. Donald Fraser in a Democratic Senate primary on taxes, abortion and an apparently widespread distrust of the political establishment.

The latter, the search for new faces less identified with the power structure, has shown up in other states in which taxes have not been the only concern. That was an issue, for example, in South Carolina, where Richard Riley defeated Lt. Gov. Brantley Harvey for the Democratic gubernatorial nomination; in North Carolina, where John Ingram beat Luther Hodges Jr. for a Senate nomination; in Maryland, where Harry Hughes defeated acting Gov. Blair Lee; in Mississippi, where Maurice Dantin whipped Gov. Cliff Finch for a Senate nomination; in New Jersey, where political novice Jeffrey Bell upset Republican Sen. Clifford Case.

A Republican pollster has found the average job approval rating of 20 incumbent governors to be

Thursday, September 21, 1978 The Washington Star A-1

only 32 per cent. And Peter Hart, another insightful Democratic pollster, says the rule he is following is: "Don't count anything as free and safe this year." Says Caddell: "This (the Dukakis defeat) will scare the living daylights out of every incumbent up."

Some of those incumbents already are running scared. Gov. Hugh Carey of New York, for example, is no better than even money despite having won his primary. The same is true for Govs. Ella Grasso in Connecticut and James Rhodes in Ohio. Some of those who were looking forward to boat rides in November — Govs. Jerry Brown in California and James Thompson in Illinois, for example — no longer can be viewed as totally secure.

Indeed, if there was an incumbent who seemed safe this year, it had to be Dukakis. Although the other politicians derided his determinedly modest personal style — "The guy grows vegetables in his front yard," one of them growled in horror — they had considered him invulnerable to anyone like Ed King.

But what neither they nor Michael Dukakis heard was the sound of a different drummer in the politics of 1978.

WASH. POST 10/2/78

Carter Steering Democrats His Way

By Edward Walsh
Washington Post Staff Writer

Jimmy Carter has seen the future his political pollster mapped out almost two years ago and has served notice that he intends to take the Democratic Party in that direction.

Last Wednesday night, before a glittering black-tie audience of party officials and contributors, the president delivered the message that he will be preaching from now through the congressional elections this fall and quite possibly through the 1980 presidential campaign.

"I would like to caution all of you Democrats—those in my administration, those in the Congress—that we here in Washington must set an example," he said. "We cannot pass legislation that is identifiably wasteful . . . This is the future of our Democratic Party, a future in which we maintain our vision, even heighten our vision, while governing with prudence and responsibility that builds the confidence of our people in us."

The college-educated, white-collar, middle and upper-middle voting groups [are] growing so large that simply doing slightly better [among them] than in the past is not sufficient to guarantee election. If there is a "future" in politics, it is in this massive demographic change. We now have almost half the voting population with some college education, a growing percentage of white-collar workers and an essentially middle-class electorate.

—Patrick H. Caddell
Dec. 10, 1976, memo to President-elect Carter

Carter's speech to the Democratic National Committee fund-raising dinner was one of several the White House has prepared and tried out during the last several weeks in a search for the right tone for a new basic Carter "stump speech" the president can use this fall while campaigning for Democratic congressional candidates.

Its central message—that Carter and his party stand for "prudent" and "fiscally responsible" management with a heart—is being pushed heavily by presidential adviser Gerald Rafshoon to become the main theme of the Carter presidency through the fall elections and possibly beyond.

It is not a message traditionally associated with Democrats, but White House aides are convinced it is what got Carter elected in 1976 and will get him reelected in 1980.

Underlying that conviction is the belief that the middle-class constituency that Patrick H. Caddell pinpointed in his pre-inaugural memo must be won over and maintained, even at the risk of alienating such

See CARTER, A9, Col. 1

File w/ Ed. Boards

New Carter Theme: Fiscal

CARTER, From A1

traditional Democratic sources of support as organized labor and black groups.

"There are more people in the middle class now and more of a demand not for great social movements or a redistribution of wealth but to gain control of those things that threaten that way of life," one White House aide said.

Chief among the list of "those things" that now preoccupy the White House is inflation.

"Inflation hurts every one of us, not just the poor, not just the elderly," the president told the DNC dinner. It saps away our national strength and will and confidence. Very soon I will announce a new package of anti-inflation measures. They will be tough. They will require sacrifices from business, from labor, from government, from every family, every segment of our society."

Beyond inflation—the overriding domestic political issue at the moment—Carter will be stressing such themes as government efficiency, administration efforts to root out waste and corruption and to "reform" such aspects of the federal establishment as the Civil Service system and the tax code. They are all themes, White House officials believe, that will appeal primarily to the growing middle class, the people who, out of frustration with the performance of government, voted for Proposition 13 in California and have gotten behind similar across-the-board tax-cut efforts in dozens of other states.

According to White House press secretary Jody Powell, such an approach has always formed the foundation of the president's political philosophy and that, more than ever, he believes it is the direction in which the Democratic Party must move to accommodate itself to a changing electorate.

"One advantage the Republicans have had is that the country viewed them as more responsible, better able to handle money, while the Democrats were seen as sort of flighty," Powell said. "I've heard him say a number of times that if we could cut their legs out from under them on that issue, the Democratic Party would be in great shape for years to come."

Moreover, there is a conviction in the White House that many of Carter's problems—beginning with his astonishing slide in the polls during the 1976 election campaign and continuing during much of his presidency—resulted because he strayed from his basic appeal during the primaries as "a decent guy who could run things competently." As Carter sought to accommodate the demands of the various interest groups that make up the traditional Democratic coalition, one aide said, his image became "blurred" and he began to look like a "tinkerer" who was out of his element in the White House.

Responsibility With a Heart

Presidential aides insist that the president is not about to abandon Democratic commitments on unemployment, health care and a host of other social-welfare programs, but will demand that those commitments be fulfilled "responsibly." The White House, they say, will continue to try to accommodate itself to the traditional Democratic interest groups, but with limits.

Thus, it was at least symbolically significant that during the same week the president warned his party about "waste," he and Vice President Mondale—his ambassador to the liberal wing of the party—were engaged in intensive negotiations with the Congressional Black Caucus over the Humphrey-Hawkins "full-employment" bill.

Despite a minor spat, it all seemed to end well, with Carter renewing his all-out support for the bill, the top legislative priority of the caucus. What neither side bothered to mention was that the bill the president endorsed several months ago and reendorsed last week was a mere shell of the original Humphrey-Hawkins legislation, named for Rep. Augustus F. Hawkins (D-Calif.) and that towering symbol of traditional Democratic liberal politics, the late senator Hubert H. Humphrey (D-Minn.).

The White House rejected the original version as unaccountably inflationary and insisted on so many changes that the bill's stated goal—reducing the overall unemployment rate to 4 percent by 1983—may become meaningless.

In the White House, presidential aides say they recognize the risks in Carter's "true moderate" approach to social problems—alienating black leaders, organized labor and the liberal establishment even more. But they seem unconcerned.

"As for the blacks and labor, he will never satisfy them to the extent they want, and no Democrat or other president can do that responsibly," one official said.

"The lesson of the [1976] primary campaign was that those days are over," he added. "Labor didn't support him, no group supported him. He beat them all."

And so, Carter's aides believe, the president will win again in 1980 if he continues to aim his primary appeal to a tax-weary, inflation-conscious and growing middle class.

"If anyone thinks they are going to knock off Jimmy Carter by harkening back to LBJ and the Great Society and traditional Democratic coalition politics, I think they have misread the country," one official said.

Said another: "You could get a rebellion in the party that would produce a challenge for the nomination from the left. But when you get out there in the country on the campaign trail, that's exactly where I'd like to take a challenge."

Brenda Levenson

224-8941

2 8 G.
File
Editorials

Walter Lippman said: The best things of mankind are as useless as Amelia Earhart's adventure .....

...They are things that are undertaken, not for some definite measurable result, but because someone, not counting the costs or calculating the consequences, is moved by curiosity, the love of excellence, a point of honor, the compulsion to invent, or to make or to understand.....

....In such persons mankind overcomes the inertia which would keep it earthbound forever in its habitual ways. They have in them the free and useless energy with which alone men surpass themselves...

....Such energy cannot be planned and managed and made purposeful or weighed by the standards of utility or judged by its social consequences. It is wild and free.....

.....But all the heroes, the saints and the seers, the explorers and the creators, partake of it. They do not know what they discover. They can give no account in advance of where they are going, or explain completely where they have been....

...No preconceived theory fits them. No material purpose actuates them. They do the useless, brave, noble, the divinely foolish and the very wisest things that are done by men...

...And what they may prove to themselves and to others is that man is no mere creature of his habits, no mere automation in his routine, no mere cog in the collective machine, but that in the dust of which he is made there is also fire, lighted now and then by great winds from the sky..

Attached is a recently uncovered piece by Walter Lippman which I thought worth circulating in view of N.I.H. research.

PRODUCER: George Eckstein

PROD. #31360
(Formerly: #81832)
September 16, 1975 (Spec. Run
Brought to (S.R.)
December 26, 1975
Rev. 2/24/76 (F.R.)
Rev. 3/ 9/76 (F.R.)
Rev. 3/17/76 (F.R.)
Rev. 4/ 1/76 (F.R.)
Rev. 4/13/76 (F.R.)
Rev. 4/21/76 (F.R.)

A M E L I A

(Formerly: "AE")

by

Carol Sobieski

A.F. 10/25

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195 CONTINUED 195

RADIO OPERATOR
(hunched over mike)
KHAQQ. Come in three one zero five. Report position. Come in on three one zero five and I'll find you. I can hear you on three one zero five. I can find you. I can. Amelia. Amelia ---

The Commander lays a hand on the boy's shoulder, then leaves the room.

196 INT. RADIO ROOM - DAY 196

The Radio Operator is alone in the room, staring silently at the radio, its endless, infuriating static and the still-blinking homing signal -- dih, dah, dih, dah ---

OVERLAP: 12:00 Noon.

He starts turning off the radios, one by one, finally, last, the homing signal. And just sits, staring at the machines in disbelief. Then for no reason at all, he turns on the homing signal: dih, dah, dih, dah ---

NEWSMAN (V.O.)
Walter Lippman said: The best things of manking are as useless as Amelia Earhart's adventure ---

197 INT. RADIO STUDIO 197

A young man in a glass booth, reading into a mike, labeled Network.

NEWSMAN
-- They are things that are undertaken, not for some definite measurable result, but because someone, not counting the costs or calculating the consequences, is moved by curiosity, the love of excellence, a point of honor, the compulsion to invent, or to make or to understand ---

198 INT. RIDGE'S LIVING ROOM - NIGHT 198

Ridge is in an overstuffed chair next to a floor model radio. Her face is blotched with tears, she is picking at a handkerchief. Amy, five, her hair cropped like AE's, is asleep in her lap. Davy, 7, is asleep on the floor, his hand in the box with his pet snake.

NEWSMAN (v.o.)
-- In such persons mankind overcomes the inertia which would keep it earthbound forever in its habitual ways. They have in them the free and useless energy with which alone men surpass themselves ---

199 INT. OAKLAND FLIGHT ROOM - NIGHT 199

Rain at the windows. All lights are off except for one at the wall map on which AE's course is shown, to Lae. GP is there, by the map, smoking, staring at the island and the two pins marking the ships and the red line indicating the flight path ---

NEWSMAN (v.o.)
-- Such energy cannot be planned and managed and made purposeful or weighed by the standards of utility or judged by its social consequences. It is wild and free ---

200 EXT. OAKLAND AIRPORT - NIGHT - RAIN 200

Paul Mantz, hatless, coatless, soaked to the skin, is walking up and down the empty runway, hands clasped behind his back, walking and walking and walking.

NEWSMAN (v.o.)
-- But all the heroes, the saints and the seers, the explorers and the creators, partake of it. They do not know what they discover. They can give no account in advance of where they are going, or explain completely where they have been ---

201 EXT. PACIFIC OCEAN - DAWN 201

A new day, spectacular cloud formations on the horizon, a riot of color and hope, and endless expanse of ocean. Then a lone seagull appears, circling and diving for fish.

CONTINUED

201 ~~CONTINUED~~ 201

~~NEWSMAN~~ (v.o.)
-- No preconceived theory fits them. No material purpose actuates them. They do the useless, brave, noble, the divinely foolish and the very wisest things that are done by men ---

202 ~~VERY TIGHT ON AL'S FACE~~ 202

circled by the soft leather flying cap, goggles ~~docked on top~~, grinning the ~~all-out, exuberant grin.~~

~~NEWSMAN~~ (v.o.)
-- And what they may prove to themselves and to others is that man is no mere creature of his habits, no mere automaton in his routine, no mere cog in the collective machine, but that in the dust of which he is made there is also fire, lighted now and then by great winds from the sky.

~~FREEZE FRAME~~

FADE OUT

~~THE END~~

Cornell University
Ithaca, New York 14853

420 College Avenue, Sheldon Court
Department of Patents and Licensing
(607) 256-4945

~~EMA~~
~~ACK~~
~~NJL~~
Circulate
~~EJB~~
~~LBR~~
~~JGF~~
~~LCJ~~

PATENT BRANCH, OGC
DHEW

OCT 12 1978

October 6, 1978

Norman J. Latker
Patent Counsel
Department of Health, Education
and Welfare
Washington, DC 20201

Dear Mr. Latker:

Enclosed please find a copy of an article that recently appeared in the Cornell Chronicle.

Sincerely,

Joan Lockwood Parker

Joan Lockwood Parker
Technology Transfer Secretary

JLP
Encl.

Cornell Chronicle, 09/28/78

Patenting Is a Growing Idea at Cornell

FEATURE

For decades "patent" has been a dirty word among many university faculty in American higher education.

Things are beginning to change, however, at a number of the nation's leading research institutions.

Among the leaders of this relatively unnoticed revolution is Cornell, along with Stanford University, Massachusetts Institute of Technology, and the Universities of Wisconsin and Illinois.

Stanford, for example, announced last year that since 1970 its Office of Technology Licensing had distributed more than $750,000 to faculty inventors, their academic departments and the University general fund.

Cornell's own Department of Patents and Licensing has compiled figures going back nine years (when interest in patents picked up here) showing that the Cornell Research Foundation has received a total of $1 million from licensees of Cornell inventions. Most of the funds, $768,000, were paid to the inventors and to their departments for further research. The remainder was used for operating expenses of the University's expanding patent program.

Currently, CRF, a wholly owned subsidiary of the University, holds 92 U.S. patents and has applications pending in the United States on 24 others.

A question that arises is what is behind this gradual abandonment of the time-honored idea that the fruits of university research are part of the public domain?

An obvious answer, of course, is that given the financial plight facing higher education this kind of idealism goes out the window under the pressure of necessity.

The answer is not that simple, however, according to Theodore Wood, manager of the University's Department of Patents and Licensing, established in 1976. Before that time all University patent applications were turned over to Research Corporation in New York City, which performs this service for more than 300 institutions in the country. Establishment of the University's current program was based in part upon the recommendation of a study by the Cornell Class of 1922.

Speaking in his small office complex in 124 Day Hall, Wood said that in the 1960s certain departments in the federal government began to encourage universities to seek patents based on their research findings. While there never has been an official administration policy on encouraging use of the patent system, more and more federal departments are pursuing such a policy, Wood said.

Surprisingly, the greatest impetus has come from the Department of Health Education and Welfare. Norman J. Latker, patent counsel for HEW, has been a leading proponent of the patent system and the need for universities in particular to use it.

But why?

Latker and others, including Betsy Ancker-Johnson, former assistant secretary for science and technology, U.S. Department of Commerce, have argued publicly since the late 1960s that American business has fallen behind many European countries, not because it doesn't have new ideas for products but because too many of them never get developed and placed on the market. In their words American business is the victim of a growing "technology transfer gap" with most of the world's industrial nations.

They argue that by allowing new discoveries to enter the public domain immediately, private incentive to turn the ideas into marketable commodities is killed. It should be pointed out that a patented idea lasts 17 years in the U.S., then automatically enters the public domain.

As Wood says, "History shows that businessmen will seldom invest in an invention that is available to everyone."

Some argue that the "public domain idea" among faculty is a vestige of the pre-World War II university when the research effort on American campuses was relatively modest compared to today's standards. They also say it is related to "publish or perish" pressure. The patenting process can be drawn out and during that time the inventor feels constrained about publishing his or her research.



Sophie F. Capolongo, administrative aide in the Office of Patents and Licensing, displays a computer printout of Cornell patents to Theodore C. Wood, left, manager of patents and licensing in the University's Technology Transfer Program, and Thomas W. Mailey, who serves as manager of industrial liaison for the program.

With the influx of billions of federal dollars in the past three decades, American research universities have become a major source of ideas and information needed for the future growth of American industry. University contributions have been crucial in the success of the space program and America's world leadership in electronics and computers.

Shifts in government research support, the increased emphasis on patents and licensing and the inevitable growth in inter-relations with industry mark what appears to be a new era in the evolution of university research.

The question of whether patent and licensing will ever become a substantial source of revenue for universities is still open. The figures now don't indicate it will be, according to Wood.

There are other realities, however, according to Thomas W. Mailey, who works with Wood as manager of industrial liaison in what is called Cornell's Technology Transfer Program.

"We must be constantly aware," says Mailey, "that we exist to help inventors and move new ideas and concepts from research to industry. This does not mean that our total effort is towards making money—it means our orientation should be towards maximum exposure of good new technology resulting from research at Cornell."

Both Wood and Mailey feel their work is a new variation on the public service commitment of the university as the state's Land Grant institution.

Wood, who retired in 1970 after 17 years as a patent executive with International Business Machines, Inc. says his patent work at Cornell is the most challenging of his career, which began as an examiner in 1946 with the U.S. Patent Office.

The overall technology transfer program is under the direction of W. Donald Cooke, vice president for research, with the assistance of Thomas R. Rogers, director of the Office of Sponsored Programs.

But if you have any patentable ideas, Wood is the man to see.

Martin B. Stiles

Daniel S. Greenberg

WASH. POST
OCT. 17, 1978

'Disease-of-the-Month Club'

Among establishment health researchers, a mythical entity known as the "disease-of-the-month club" is on a par with escaped viruses, plagiarized research and canceled travel grants as an impediment to restful sleep.

In his 20 months as chief of health, education and welfare, cagey Joe Califano has perceived this publicly unrecognized bête noire of research. And, in a newly initiated campaign to remake federal health-research programs according to the Califano vision—with the stress on long-term planning, austerity and social utility—he has shrewdly offered the biomedical community a bargain: Cooperate with me, and, in return, research will, among other benefits, be insulated against the disease-of-the-month club.

For the biomedical savants to whom he recently presented this proposition, there's much appeal in this trade-off, since the "club" is to them as SALT is to Russophobes and double-digit inflation to pensioners, an abomination that pricks deep fears and unplugs combative hormones. What is the disease-of-the-month club?

It is the shorthand term for the often-successful tactic of whipping up public and congressional sentiment to compel the National Institutes of Health to pay some, or more, attention to a disease that does not much appeal to NIH's own scientific fancy. With a humanitarian flavor, then, it is a pork-barrel play for the government's health-research money. It is policymaking through the use of alarmist tactics, maudlin appeals and political muscle, rather than through cool appraisal of scientific value and "ripeness," which are the criteria that the biomedical high command prefers for deploying resources. As Califano understands, the club is anathema to the profession.

Referring to "the inevitable but not always desirable pressures that attend the distribution of substantial research dollars," he sympathetically reminded a recent assemblage of health scientists, "You're all familiar with the kind of disease-of-the-month pressures that attend the budget process within HEW and the Congress." None appeared mystified and none objected to the comradely alarm that he raised.

Nevertheless, some kind words are in order for the club, which, though almost always regarded with disdain, has actually served a useful role in the politics of medical research. For the process, which the establishment fears, and which Califano is nimbly exploiting, simply represents the application of democratic politics to the elitist business of biomedical research.

The club, such as it is, usually consists of people who, through personal misfortune, are concerned with a particular disease, and want their government to try to do something about it. Following the model of hog raisers, bomber builders and other successful agitators for government attention, they engage the services of public-relations specialists, pressure their elected representatives, and generally create a nuisance—until NIH, almost always reluctantly, finally yields and puts some scientists to work on the problem.

The track record of this process is written into many of the programs and even some of the titles of the institutes that together constitute the National Institutes of Health, and it's not a bad record. For example, it was only after parents of children with leukemia applied pressure through Congress that NIH turned attention to the difficult problem of suitable nutrition for patients undergoing treatment for that disease. In response to political pressure, the old National Heart Institute broadened its scope and became the National Heart and Lung Institute, and a couple of years ago it metamorphised into the National Heart, Lung and Blood Institute. What was formerly known as the National Institute of Arthritis and Metabolic Diseases is now the Institute of Arthritis, Metabolism and Digestive Diseases. In the same fashion, the former Institute of Neurological Diseases and Stroke is now the Institute of Neurological Diseases, Communicative Disorders and Stroke.

In some instances, the NIH leadership initially yielded to the changes as an inexpensive way to quell the din. But the inexorability of bureaucratic expansion can have virtues, too: For, once a disease gets on the letterhead, it's easier for research money to follow—and what's wrong with that?

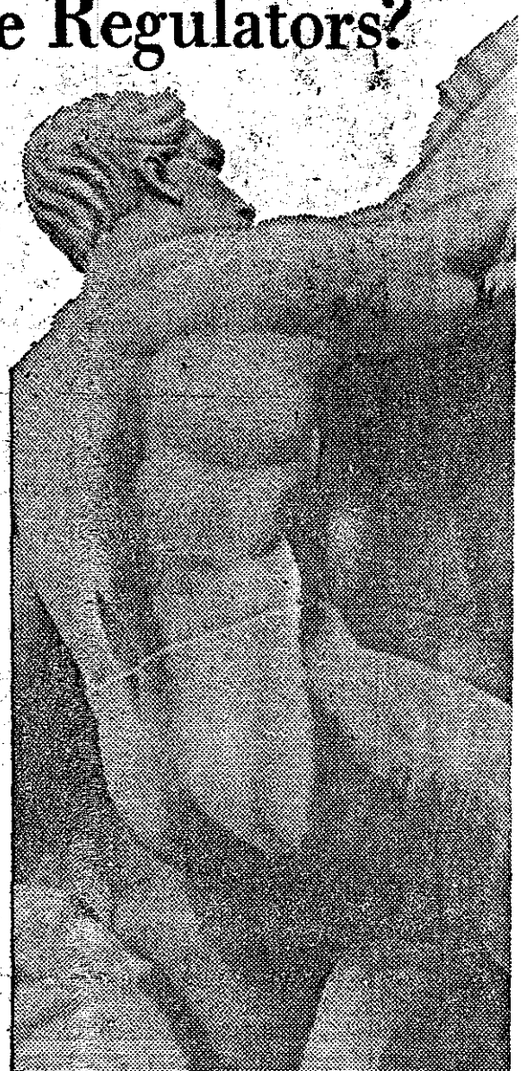
Cost-effectiveness worshippers—almost always unaffected by the ailments they deem unprofitable for research investment—are horrified by this emotional intrusion of politics into health-research affairs. But, as one special-interest health group, the American Narcolepsy Association—patient load a mere 250,000—recently pointed out to Califano: "We do not believe it is callous lack of regard for the needs of others which sometimes results in disease-of-the-month groups demanding special attention; rather, such efforts are the result of frustration with the existing system, which fails to give fair consideration to the needs of all and allocate research resources accordingly."

That's worth keeping in mind as HEW and the biomedical community plan the future of health research.

WASH. POST OCT 17 '78

Lloyd N. Cutler

Who Masters the Regulators?



Every school child learns about the separation of powers. The federal government has three branches—legislative, executive, judicial. Right? Wrong.

Oh yes, we forgot the regulatory branch. The ICC, the CAB, the FCC, the SEC, the FTC, the NLRB, the FEC, the CPSC and about a dozen other agencies operate under laws that make them independent of the legislative and executive branches. So there are really four branches. Right? Wrong, because each of these independent agencies is also independent of every other agency. So that makes about 23 branches? Careful, you may well be wrong again.

For there is a new theory abroad in the land that even regulatory agencies *within* the executive branch are also independent of the president and of one another. There are over 60 such agencies, many of them parts of a Cabinet department. According to this new theory, the president—the chief executive of the nation and the head of the executive branch—does not have the last word over what any of these agencies can do. Indeed, he cannot even have the first word. He is not supposed to intervene in their regulatory actions at all. Whatever you may have learned in civics class, the new theory denies that the president is in charge of the whole executive branch.

The new theory rejects any such unitary concept of the executive branch on both legal and policy grounds. The legal issue is now being tested in the case of OSHA's cotton-dust standards. It raises one of the most important constitutional questions of modern times.

OSHA is part of the Department of Labor. It was created by a 1975 statute to set standards for health and safety in the workplace. It proposed issuing a standard governing the permissible level of "cotton dust" in *textile mills*, where excessive levels have led to the widespread occupational disease called "brown lung." The proposed levels were challenged by the textile industry because they require expensive equipment and their technical feasibility is doubted. Charles Schultze, chairman of President Carter's Council of Economic Advisers, became concerned that the proposed levels and technical requirements would have an unduly inflationary impact, and he persuaded the president that certain modifications would provide a better balance between the nation's occupational health and anti-inflation goals. He wrote to Secretary of Labor Marshall, proposing these modifications with the president's approval. Secretary Marshall objected to the modifications, and in a meeting with both his Cabinet aides, the president worked out a compromise. That compromise was embodied in the final regulation, over the objection of the Textile Workers Union. The Union has now appealed OSHA's regulation to the courts on a variety of grounds. One ground is that the president's intervention was illegal, because the OSHA statute vests the power to issue the regulation in the secretary of labor, and the president could not lawfully instruct the secretary how to exercise his statutory discretion.

This case capsulizes a basic problem of our federal government today, a problem that has recently been examined by the American Bar Association's Commission on Law and the Economy, headed by one of the nation's most distinguished lawyer-statesmen, John J. McCloy. As the McCloy Commission noted, we have adopted a wide variety of economic and social goals—such as checking inflation, spurring economic growth, reducing unemployment, improving workplace health and safety, cleaning up the environment and closing the energy gap. We are only beginning to realize that many of these goals directly conflict with one another, and that even in a country as richly endowed as ours, all of them compete for the same limited resources. We cannot pursue them all in full measure at the same time. A critical task of modern democratic government is to make wise balancing choices among proposed courses of action that pursue one or more of these conflicting and competing objectives.

We have delegated each of our conflicting and competing goals to a different regulatory agency, sometimes even dividing a single goal (e.g., employment discrimination) among a number of overlapping and competing agencies. Each agency has limited responsibility for balancing a proposed action in pursuit of its primary goal against adverse impacts on the pursuit of other goals. Each agency asserts an independence from the political process, and from the other agencies, that weakens the national ability to make balancing choices, or to hold anyone accountable when choices are made badly or not at all.

Many of our regulatory agencies were created under laws that make them expressly independent of both the president and the Congress. While others like OSHA are merely part of an executive branch department, their governing laws vest the power to issue regulations in the secretary of the department rather than the president. To confuse matters further, some of these laws expressly require presidential review and approval of particular actions by the secretary, perhaps implying

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The writer is a Washington attorney and a member of the American Bar Association's Commission on Law and the Economy.



that he is not authorized to modify or disapprove other actions.

As a result, many of the interest groups who support the single missions of particular regulatory agencies, as well as many members of Congress and others who mistrust an "imperial" presidency, regard presidential intervention in the regulations issued by executive branch agencies as illegal, or at least undesirable. Where Harry Truman was fond of saying, "The buck stops here," they prefer a regulatory system in which the buck stops nowhere. And for a variety of political reasons, presidents have in fact been loath to step into regulatory issues. Indeed, a number of President Carter's aides regard his recent encounter with cotton dust as politically costly to him.

These are the constitutional and policy issues crystalized by the cotton-dust case. They are critically important because the clash between Charles Schultze and Ray Marshall over the cotton-dust standards is typical of many far more significant regulatory clashes within the executive branch. One with enormous consequences is the proposed smokestack emission standard for coal-fired power plants. The conversion of existing and projected generating plants from oil and gas to coal, with minimum damage to air quality, is of course a major component of our national program to close the energy gap. Congress has passed a law delegating this task to EPA and the Department of Energy—two agencies within the executive branch—and providing that if after consultation the two agencies do not agree on the air-quality aspects, the EPA shall decide. So far they have not agreed. Suppose the president concluded that the Department of Energy's position, or some compromise, was more in the national interest than EPA's position. Could he and should he intervene?

In this lawyer's opinion, the president does indeed possess the ultimate constitutional power over the content and the timing of regulations issued by executive branch agencies, so long as the action taken is within the agency's statutory authority. As a matter of political theory and policy, the president ought to assert such power whenever he deems it necessary to make an important balancing choice among conflicting and competing national goals.

Article II of the Constitution vests the executive power in "a president." It does not authorize the Congress to distribute some of that power to the president's subordinates free of presidential control. Its principal reference to executive departments is to the power of the president to "require the opinion, in writing, of the principal officer in each of the executive departments"—language that implies he is not bound to accept any such "opinion." It is the president, not any of his executive branch subordinates, who is constitutionally empowered to "take care that the laws be faithfully executed."

The Constitution adopts Montesquieu's brilliant theory of the separation of powers among the principal branches of government. The basic argument for the theory is the need for each of the three main branches to check and balance the other two. That argument does not justify the indefinite number of sub-separations of power *within* the executive branch that are implicit in the notion that the Congress may delegate specific compartments of power to separate officers of that branch, and at the same time deny the president the power to supervise their actions. That is the antithesis of check and balance within one of the principal branches. It is equivalent to conferring independent legislative power on each congressional committee without ultimate review by either House or the two houses in Congress, or to conferring independent judicial power on each federal district court, without ultimate review by the Supreme Court.

When major balancing decisions must be made, only elected officials and their immediate staffs can provide the requisite overview and coordination, and stand accountable at the polls for the results. The Congress cannot perform these tasks by legislating the details of one regulatory decision after another; that is why Congress delegated much of this power to executive branch agencies in the first place. The president is the elected official most capable of making the needed balancing decisions as critical regulatory issues arise within his own executive branch, while the most appropriate and effective role for Congress is to review and, where necessary, curb particular presidential interventions.

Should the president decide to take up the gauntlet, he should do so openly. He should observe appropriate procedural safeguards of public notice and opportunity for comment. He should comply with any applicable *ex parte* rules that would apply to the agency itself. He should confine his actions to the relatively few truly critical occasions when a balance needs to be struck between conflicting and competing national goals.

While I am no politician, it seems to me that would be good presidential politics. In so doing, he would be on firm constitutional ground, and he would be taking a truly presidential stance. Even though we all belong to at least one single-interest group, I think the general interest is what the majority of us care about most, and that we will support a president who shows he is determined to go as far as he constitutionally can to strike the needed balance.

Effect of regulations on innovation probed

I&EC symposium speakers cite cases where inconsistent, undue government regulation is depressing industrial productivity, efficacy of R&D

ACS Miami Beach

An ever more intrusive government may have encountered a minor Waterloo in pursuit of the risk-free society. There has been concern that regulations, amendments, laws, guidelines, and the like have had a major, measurable, and so far depressing effect on industrial productivity and on the efficacy of research and development. Those suspicions, invariably denied by the regulators, always have been abroad among the R&D community. They were voiced again last week in Miami Beach at a Division of Industrial & Engineering Chemistry symposium on effects of government regulations on innovation in the chemical industry.

Until now there has been no way to make the case for either side except by an annual, general, economic balance sheet. Now some objective, quantitative measures have been made that illustrate the negative effects of overregulation. Even if there were no such measures available, the case against overregulation has been aided by legislation that implicitly recognizes the problem. It may be ironic, as one observer put it, that the government is again trying to overcome the effects of too much law by passing more laws.

There are many who speak with telling effect against such proliferation. One is Dr. Bruce Merrifield, vice president, technology, for Continental Group Inc., who notes that the big regulatory push began about 1960. Prior to that time there were few performance regulations, although a number of other kinds of regulations existed, particularly product safety regulations. Since 1960, at least 15 major legislative acts have appeared and must be dealt with by industry. The chemical industry is particularly affected.

Merrifield cites rising income as among the forces that have contributed to this growth of regulation. Rising incomes often result in demands for new social legislation and are usually coupled with the increased sophistication of engineering and science. In the drug industry, the effect of regulation has been to discourage innovation. Merrifield notes that it now takes a U.S. drug firm about eight years and $54 million to bring a new drug to the market place.

A great threat to chemical innovation, Merrifield says, is the inconsistency of government regulations administered by different and often administratively competing agencies. This inconsistency causes companies to withdraw financial support from projects at critical times and leaves managements unable to predict acceptability of products or processes in many cases. This leads to another related concern—namely, regulation of the innovative processes themselves. Thus, the overall effect of regulation is altogether pernicious. R&D, Merrifield notes, is being squeezed out by a growing proportion of nondiscretionary work made necessary by regulation in a total environment of a fixed, or in some cases a decreasing, resource pool.

The remedies for the maladies of overregulation, says Merrifield, include pre-enactment impact studies for all regulatory acts as well as redress of grievances that already have resulted from regulations. Merrifield's prescription for regulatory relief also calls for consistency within government and recognition that a risk-free world is impossible. It also would be appropriate, he says, to institute zero-based regulating along with zero-based budgeting to reduce the complications in the regulations. There is no doubt that some regulations are necessary. But having said that, he notes, many R&D administrators find it hard to live with most of them.

If you can't beat 'em, join 'em, seems to be the approach of Michael Michaelis, of Arthur D. Little Inc. A recent study completed by ADL for the government concludes that federal funding of civilian R&D should be formulated in a larger context of industrial innovation, and that federally funded R&D, of itself, is insufficient to bring about significant technological changes in the private sector of the economy. Michaelis claims that it was probable that the study eventually contributed to the official approval for a Cabinet-level review of domestic industrial innovation. The study is due to be made public in the spring of 1979.

In the meantime, Michaelis points to the recently enacted Federal Grants & Cooperative Agreements Act of 1977 (C&EN, July 10, page 19) as an opportunity to come to grips with the innovation-depressing effects of government regulation.

Three types of relationships are specified in the act. One is straight procurement by the government. The second is an assistance relationship that doesn't actually involve the government in work performance. The third is an assistance relationship that does involve the government in work performance. Assistance means that the government pays all or part of the costs of a project, and this could mean that industry can enlist the government in financing work.

Michaelis regards the act as a "sleeper" in the fight to turn around the dismal innovative record of U.S. industry in recent years. Productivity, he notes, is down 25% and the decline in patents issued to U.S. citizens and companies has come at the same time that patents to foreign groups and individuals have doubled. The call is now for "institutional arrangements" to stimulate innovation, he says.

Despite the appearance of the act in February 1978, there has not been a stampede to get in on the benefits. In fact, some industrial observers suggest that "apathy is rampant." This has been manifested most notably in the lack of response to a call by the White House's Office of Management & Budget for comments and participation in implementation conferences following the act's signing.

Of all the chemical industries, the drug industry is the most highly regulated. Dr. Jean DiRaddo, projects manager at the Center for the Study of Drug Development at the University of Rochester, notes that even the discovery process itself is subject to regulation. That probably makes pharmaceutical innovation unique among the technology-based disciplines. Control over the innovation of drugs is exercised by the Food & Drug Administration under authority contained in basic legislation enacted in 1938 and 1962 and supplemented by many other amendments and authorizations that have progressively tightened FDA control. Key items in the legislation are the New Drug Application (NDA) procedure, which requires safety tests before marketing of a new drug, and a requirement for informed consent for an Investigational New Drug (IND).

DiRaddo noted that most drug legislation is aimed at avoiding risks. FDA is required to prevent harm from drugs but it has no mandate to promote health or to maximize benefits obtained from drugs. It is not surprising, therefore, to learn that innovation is being inhibited by regulation.

But what is innovation, DiRaddo asks. Pharmaceutical innovation can occur because of the synthesis of a new compound with a new structure [or new chemical entity (NCE)], by the discovery of a new pharmacologic action, by modifying the structure of an existing drug, by pragmatic modifications of the forms of drugs in use, by the discovery of new therapeutic effects not predictable from models, and by chance. The problem is how to measure the amount of innovation produced by one or all of these forms.

In a project under way at the University of Rochester, DiRaddo and her associates are using the number of NCE's taken into human testing stages of development as an absolute measure of innovation. They consider this a valid measure, since it represents a firm's decision that a compound is worth further testing, as well as being the first time that an NCE is placed outside the firm. An NCE that is selected for human testing still may have unknown therapeutic properties but its pharmacologic and toxicologic properties are known already.

DiRaddo believes that an important contribution of the Rochester project is that it allows detection of the effects of policy changes in drug regulation about six years earlier than was previously possible. Six years, on the average, are required for the total of IND and NDA stages in FDA regulatory procedures.

Other measures used in the project are the national origin of NCE's appearing on the U.S. market and a comparison of patterns of marketed drugs in the U.S. and the U.K. from 1972 to 1976.

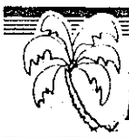
The Rochester project considered information on 1103 NCE's. A total of 859 were from 36 U.S. companies and 244 were from 10 foreign companies. The annual rate of NCE's tested in humans by U.S. companies rose from 70 in 1963 to 94 in 1965 and then declined sharply to a mean value of 62 for the period from 1966 to 1974. Constant changes in regulatory procedures make interpretation difficult, DiRaddo says, but there is little doubt that the declines in NCE's are attributable to FDA requirements.

In recent years there has been a strong shift of drug studies abroad. Between 1963 and 1969, only 8% of U.S. NCE's were first tested abroad. In 1973, this number rose to 34%, and to 47% in 1975 (incomplete data). The effect is particularly noticeable in larger companies.

The total time required for clinical investigation and approval of a successful NCE in the U.S. has risen from 31 months in 1966 to 82 months in 1975. A comparison with corresponding circumstances in the U.K. reveals that 2.5 times as many drugs are introduced in the U.K. as in the U.S.

More important than the numbers, DiRaddo says, are the clinical implications the data suggest. For one thing, delays in introducing certain cardiovascular drugs have resulted in a substantial increase in the mortality of patients in the U.S. A conservative estimate of this mortality is 10,000 lives per year. □

Monomer migration in polymers clarified



ACS Miami Beach

Migration rates of residual monomers may be linear functions of concentrations in amorphous polymers but not in glassy polymers below their glass transition temperatures. This summary of independent work described in a Macromolecular Secretariat symposium on chemical and physical lifetime limits of macromolecular materials may revise current thinking about whether certain concentrations of residual monomers in plastic packaging materials pose human health hazards.

Additional implications include effects of desorption of plasticizers or stabilizers on useful lifetimes of plastics, and partitioning of drugs between polymers and tissue fluids in drug delivery systems.

Dr. Isaac C. Sanchez of the National Bureau of Standards finds that partition coefficients of polyethylene oligomers between polyethylene and heptane solvent can be computed reliably from temperature, pressure, and density parameters of polyethylene, oligomers, and heptane, plus heats of mixing of oligomers in polyethylene and heptane. He uses straight-chain hydrocarbons from C_5 to C_{20} as model oligomers. Heptane simulates a fatty food.

Sanchez also has calculated partition coefficients between polyethylene and ethanol. Little information is published on this system for comparison, however. His further work will include esters and 3% acetic acid as solvents, polar additives, and other polymers.

When concentrations of residual monomers in such glassy polymers as polyvinyl chloride and polyacrylonitrile are very small, however, partition coefficients are not linear but rise exponentially with decreasing monomer concentrations, concludes Dr. Seymour G. Gilbert of Rutgers University. For many resin grades this finding may mean that at residual monomer levels of less than 0.1 ppm, there is zero effective migration from packaging into food contents.

Working with Dr. Joseph Miltz and Jack R. Giacin, Gilbert injected small, known amounts of vinyl chloride into vessels containing PVC and water or vegetable oil. He measured amounts of vinyl chloride in the water or vegetable oil at equilibrium and determined amounts absorbed by PVC by difference. PVC had been heated beforehand to reduce vinyl chloride to below 5 ppb.

Above 4-ppm initial vinyl chloride concentrations, partition coefficients rose as linear functions of concentration. Below 4 ppm, they rose exponentially. Gilbert explains his findings in terms of active site theory. In this theory, there are three types of vinyl chloride. One type is freely diffusible. A second type is bound to active sites but can diffuse. The third type is so tightly bound to active sites that it is nondiffusing. With relatively large initial vinyl chloride concentrations, a large proportion of vinyl chloride is diffusible. At smaller concentrations, proportions of vinyl chloride immobilized in active sites increase, and partition coefficients rise exponentially.

PVC containing 20% plasticizer gave similar results but had lower affinities for vinyl chloride. Gilbert says the presence of plasticizer reduces the number of active sites. He concludes that more vinyl chloride may be removed from plasticized PVC than from unplasticized PVC during processing. He also concludes that the amount of residual vinyl chloride that produces zero effective migration may be higher for unplasticized than for plasticized resin.

Gilbert, using inverse-phase gas chromatography, finds evidence for nonlinear adsorption of vinyl chloride as a function of concentration. In this technique, a gas chromatographic column is filled with resin granules, known amounts of monomer are injected into the chromatograph, and retention volumes are calculated from retention times.

Gilbert finds retention times and volumes increase as amounts of injected vinyl chloride decrease. By plotting reciprocal temperatures vs. logarithms of reciprocal retention volumes, he expects to find that activation energies of diffusion increase exponentially with decreasing amounts of vinyl chloride injected.

Similar exponential increases of activation energies of diffusion of acrylonitrile in polyacrylonitrile already have been found by Gilbert using inverse-phase gas chromatography. He concludes there exist residual acrylonitrile concentrations low enough that they are immobilized in active sites and thus nondiffusible.

Morris Salame of Monsanto also finds exponentially increasing activation energy of acrylonitrile with decreasing initial residual monomer concentrations. He measures diffusion rates from containers made from a glassy 30/70 styrene-acrylonitrile barrier polymer into 3% acetic acid or carbonated beverages. The polymer has a glass transition temperature of about 100° C.

When initial acrylonitrile concentrations are 10 to 15 ppm, the activation energy to move acrylonitrile molecules among resin interstices is 15 kcal per mole, Salame reports. At 3-ppm concentrations, activation energy is 20 kcal and rises to 30 to 40 kcal at concentrations below 0.1 ppm. The increase in activation energy results in a nonlinear relationship between migration rate and monomer content.

He measures acrylonitrile concentrations in 3% acetic acid or carbonated beverages at levels of less than 1 ppb by sparging solutions and analyzing sparged gas for the monomer by gas chromatography with a nitrogen detector.

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Letters

Gasohol as motor fuel

SIR: The remarks quoted by Dr. Lindquist (C&EN, Aug. 7, page 106) do not give a very balanced view of current gasohol possibilities. The economics and energy balance have been the subject of extensive study at the University of Nebraska (Dr. W. A. Scheller and others) and the situation is by no means static. Bear in mind:

1. Starting with corn grain, using traditional technology, there is indeed a net loss of energy in producing alcohol. However, the partial utilization of field wastes as fuel converts this into a modest positive balance.

2. The major energy requirement is in the alcohol plant, where it can be provided as coal or electricity.

3. There is ample scope for energy saving in the distillery, using vapor recompression and other heat economy techniques.

4. Alcohol can be produced from all kinds of low-value agricultural by-products.

There seems to be a possibility of producing at least a portion of our liquid fuel requirements from renewable resources (basically from sunlight) and it should be given a fair chance.

Concord, Calif. P. H. Blanchard

Tannin-containing substances

SIR: The item, "OSHA issues tentative carcinogen list" indicates that tannin is a Category I, confirmed carcinogenic substance, and that as a result exposure to it would be severely regulated (C&EN, July 31, page 20).

This should result in some interesting conflicts, especially if commercial products containing even trace amounts of tannin are to be regulated and handled as confirmed carcinogens. Tannins are widely distributed throughout the plant kingdom. The average individual probably ingests several grams of tannin each week. Coffee, and especially tea, is rich in tannin, as are also red wines, and to a more limited extent beer. Many, if not most, of the items offered in the produce section of the local supermarket contain tannins. Presumably canned goods derived from these items would also contain tannin. If the bureaucracy is right, we now have a choice: continue eating meat and run the risk of circulatory disease due to ingestion of cholesterol, or become vegetarian and run the risk of cancer due to tannin. If much of what we eat is not banned, imagine the Occupational Safety & Health Administration trying to regulate its production and distribution. Being a farmer may be dangerous to your health because of the crops being grown. In fact the soil itself may contain tannin from decaying vegetable matter.

Besides food, individuals come in contact with tannins quite often from other sources. Just consider the forest and products derived from it. The bark of many wood species contains appreciable tannin. Perhaps OSHA will prohibit the gathering of firewood and outlaw the use of Christmas trees. Those species normally used as Christmas trees are all rich in bark tannins. Deeply colored heartwood generally contains tannin, and these are the wood species also used in furniture. Can anyone imagine OSHA regulating all of the industries involved with wood, such as the construction industry, because the wood contains tannin?

Bureaucracies, such as OSHA, should either exhibit some competency or be made liable for their action. The overwhelming use of tannin-containing substances by mankind through millennia was evidently not even considered by OSHA when classifying tannin as a Category I carcinogen.

Herbert A. Schroeder
Associate Professor of Wood Chemistry, Colorado State University, Fort Collins

Letter to the Editor

C&EN encourages readers to contribute to this letters section. However, please keep letters reasonably short, 400 words or fewer. As we receive a heavy volume of letters, persons writing letters are limited, as a general rule, to one letter within any given six-month period.

Safety training

SIR: Safety training in our academic institutions has lagged well behind today's increased awareness of chemical hazard and the continuing promulgation of federal regulations.

I would like to suggest consideration of the idea that the American Chemical Society either recommend or require that all chemistry graduates (at all degree levels) receive at least two credits' worth of safety, hygiene, and toxicology as part of their curriculum.

Academic institutions, if left to their own devices, will be 10 to 15 years late in providing this basic and sorely needed training. They need to be encouraged gently, or perhaps more firmly, by tying the course into our accreditation requirements.

James A. Kaufman
Member, ACS Division of Chemical Health & Safety (Probationary), Wellesley, Mass.

More on innovation

SIR: Regarding the editorial "Innovation and national security" (C&EN, July 17) and a recent letter "General lack of concern" (C&EN, Aug. 14), I believe a more fundamental principle underlies this discussion: the ability to weather change. The key to survival in a varying environment is adaptation. Thus the capacity to adjust connotes security. A major threat, therefore, is capital-enhanced stagnation: accumulating available natural and social resources in standing machinery to the extent that innovation is curtailed.

In business, the rate at which a new industrial process can supplant an earlier one is inversely proportional to the magnitude of existing installed capacity. In addition to the capital expenditure for procuring and operating new facilities, the cost of conversion must include those segments of the old network (labor and equipment) to be retired. Hence, acquired capital represents inertia against change. Similarly, the sprawling bureaucracy of our government and other social institutions did not develop overnight. But the price of alternatives (though I am sure more efficient ones could be organized) increases with the complexity and manpower of the agency to be dismantled.

Another ramification involves various attitudes apparently fostered by capital-enhanced stagnation. "Protecting one's investment" has survival value in the short run. But relying on inefficient organizations and facilities merely because they exist, and change is more difficult, can be catastrophic. Eventually, institutions devote more effort to self-perpetuation (maintaining the status quo) than toward their assigned purposes. (Certain agencies of our government and military, I fear, have already reached this stage). An example of the above principles appeared in the recent news. The state of Ohio shelved plans to switch to environmentally cleaner low-sulfur coal because the high-sulfur coal is currently mined locally and thousands of jobs were at stake. (I do not advocate unemployment; however, the cost of change must include relocating these workers).

Unless one can predict future events with absolute certainty, over accumulated capital cannot be avoided. It can definitely be minimized, however, "Sunset laws" and "closed-cycle accounting" (cost seldom reflects the expense of disposal except in the case of deposit bottles) seem reasonable. On the other hand, a known set of social priorities would be useful to establish a system of values for ranking alternatives based on those aspects of a changing society which are to be preserved. After all, as the world changes, so must society—rationally or cataclysmically.

D. Wayne Berman

Pasadena, Calif.

SIR: I wish to congratulate you on the initiation of discussions on "Innovation and national security," (C&EN, July 17, page 25). I hope this is only the first of a series on this subject.

The views of Dr. John J. Ford deserve serious consideration by the technical community. Reductionism and bureaucracy have grown to massive proportions in large corporate research organizations with the resulting tendency toward suppression of innovative thought and action.

I have to wonder if you did not include the remarks of John C. Connor to illustrate one of the problems so precisely described by Ford. Connor repeats the old refrain of big business that they are taxed too much and this is hurting small business! If he is really interested in the independent inventor why does he not support a special subsidy for them, to be paid for by increased taxes on those large corporations whose research expenditures are low in relation to investment? By what logic does he arrive at the conclusion that the budget for the Department of Energy should be less than oil company profits? Perhaps DOE's expenditures should be even higher now to save us from economic ruin later.

I suggest that ACS sponsor a series of local seminars on innovation in the U.S., with special effort being made to obtain participation by nontechnical corporate executives and managers. Participation by independent innovators and by other technical societies should be encouraged, both in planning and in presentations. One year of hard work along these lines could produce invaluable data for the use of those already working to reverse the decline of innovation in U.S. science and industry.

Eugene F. Hill

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The drug arecoline

SIR: Science/Technology Concentrates (C&EN, July 24, page 19) referred to two recent papers in *Science* and in the process perpetuated an error. The drug arecoline was incorrectly referred to as "arecholine" in one of the original papers and in the concentrate, thereby implying a relationship to choline that does not exist.

Arecoline is not a choline derivative but is the chief alkaloid in seeds of the areca palm. Arecoline does not "act by increasing concentrations of acetylcholine in the brain," but is thought to stimulate directly certain types of acetylcholine receptors.

Indianapolis Ray W. Fuller

Dilemma of toxic risks

SIR: Frank J. Weigert, in his letter, "Determining toxic risks" (C&EN, July 24, page 4), is one of the first to speak out for more logical mathematical modeling of the risk from low concentrations of carcinogens. For a variety of compelling reasons, economic and environmental, our thinking should begin to move along the lines he outlines instead of in the opposite manner advocated by regulatory agencies.

The dilemma is particularly apparent in the energy area, where carcinogens are involved in both nuclear and fossil fuel plants. The BEIR report on radiation, a massive compilation of human epidemiology and animal experimentation, arrives at the conclusion that the response to incremental dosages is exponential; that an algebraic increase in radiation above background produces a percentage increase in the probability of cancer. In mathematical terms, $P = Ae^{kD}$, where A is the background response, and D the exposure above background.

This is also the approach of the Rasmussen report (WASH-1400), which has been severely criticized by antinuclear people, who prefer the more "conservative" linear model. This, despite its scientific meaninglessness, is the one used by most working biometrists. On the other hand, research on chemical carcinogens, sponsored by the Energy Research & Development Administration, Environmental Protection Agency, and Occupational Safety & Health Administration, is being fitted into models which fit their political needs for closer regulation of the workplace and environment, and of energy sources which compete with nuclear energy. One such model [Crump, Guess, and Deal, National Institute of Environmental Health Sciences (preprint); Hartley and Sielken, *Biometrics*, **33**, 1 (1977)] is $P = 1 - e^{(c\prod_{i=1}^{k}(a+bD))}$, where c is a function of duration of exposure, and D the dose rate from k sources. Such models will have a slope greater than the linear model and may be convex upward. To paraphrase W. C. Fields and the old temperance "mellerdramas," they overemphasize the importance of the fatal first exposure, not to Demon Rum, but to some chemical which has served society well.

A table (see table below) showing the relationships of hypothetical dosage response curves which are congruent at $P = 0.10$, $D = 20$, and $P = 0.50$, $D = 100$, for the four models discussed may be instructive. It will now be seen that Weigert's proposal, with probably the best logic, is by far the least conservative at very low dosages. But what disturbs me far more is that ERDA is allowed to play by one set of rules, while the rest of us poor mortals have to go along with EPA-OSHA thinking. This means that for carcinogens of equal potency, we have to clean up over four times as much!

Winslow H. Hartford

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Approximate hypothetical probability of cancer by models

Dosage above background	Weigert	BEIR (exponential)	Linear	Crump, Hartley et al.
100	0.50	0.50	0.50	0.50
10	0.022	0.018	0.050	0.067
1	0.0001	0.0016	0.0050	0.0069
0.1	$<10^{-6}$	0.00016	0.00050	0.00069
0.01	$<10^{-9}$	0.000016	0.000050	0.000069