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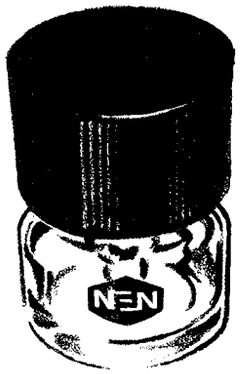

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COVER

The dairy cow (upper right) is the genetic mother of the ten calves. She was superovulated, and the embryos were recovered from her uterus 1 week after conception. After 3 to 10 hours of culture *in vitro*, the embryos were transferred to the uteri of the ten recipient cows (left) for gestation to term. The cattle are owned by Colorado State University. See page 351. [J. Messineo, Fort Collins, Colo.]

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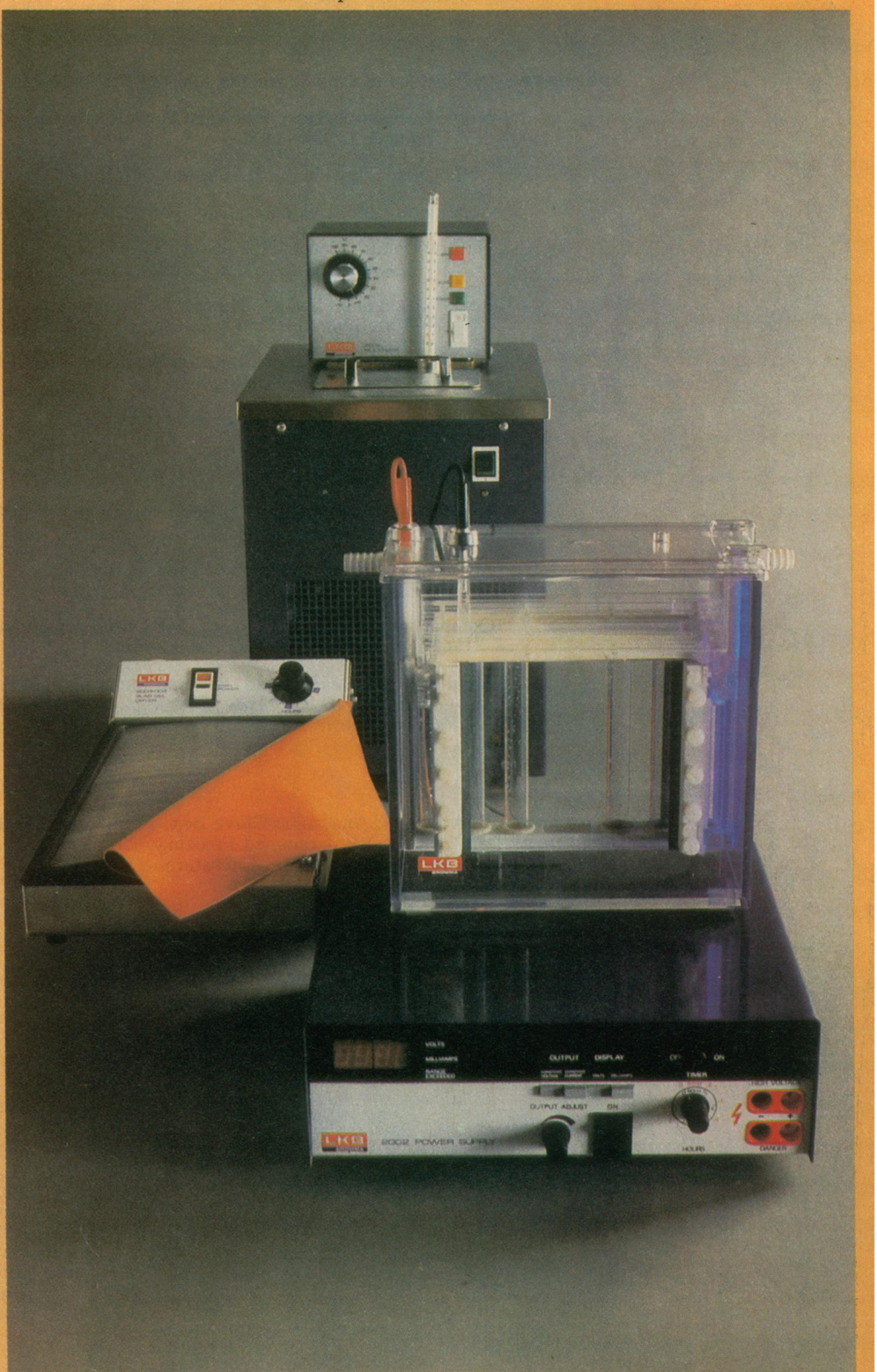

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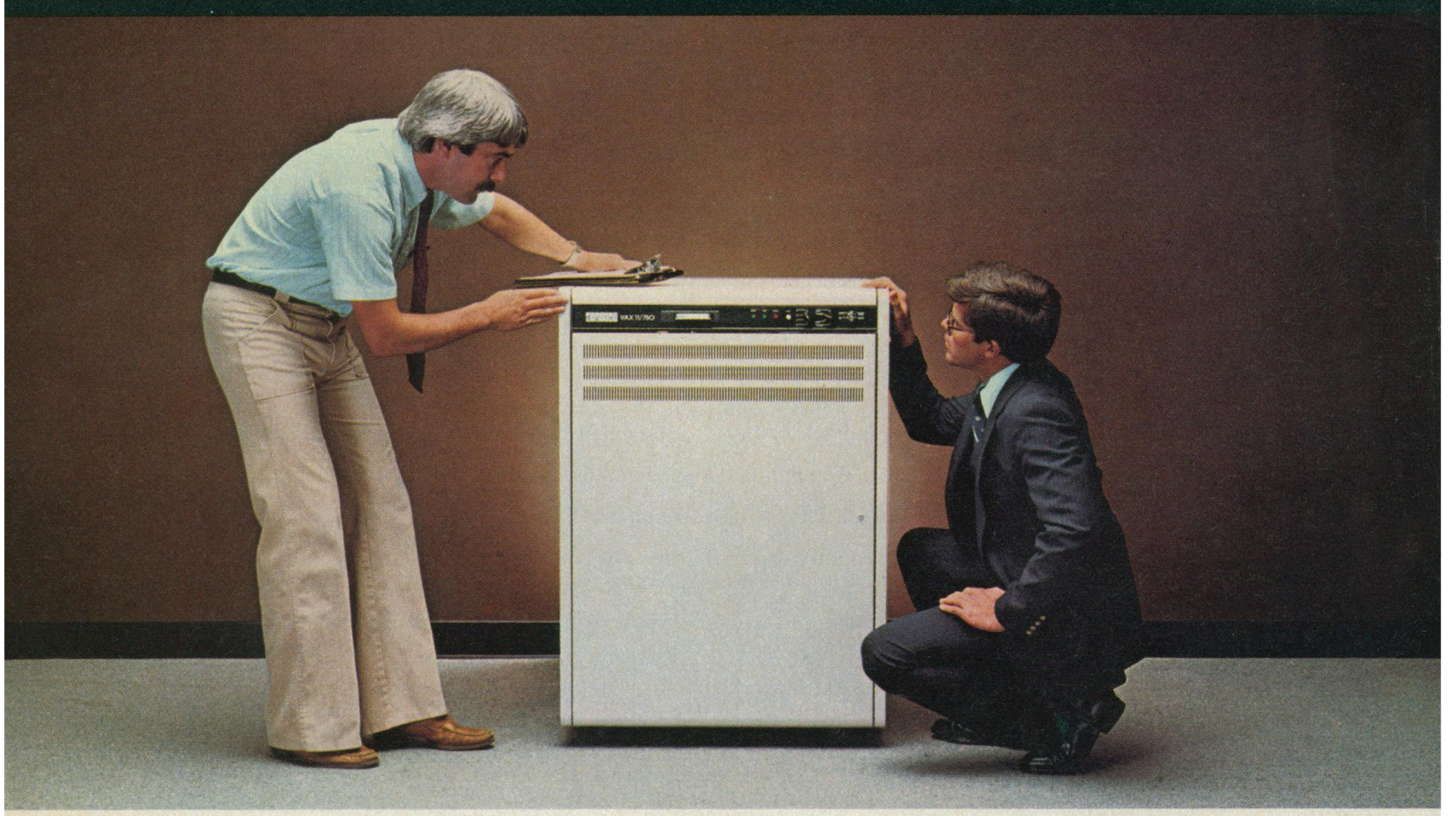

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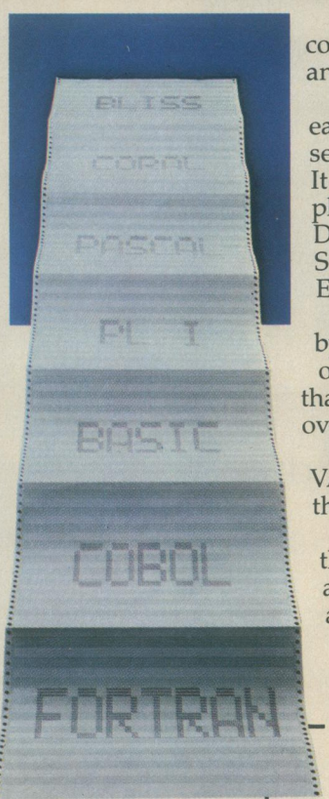

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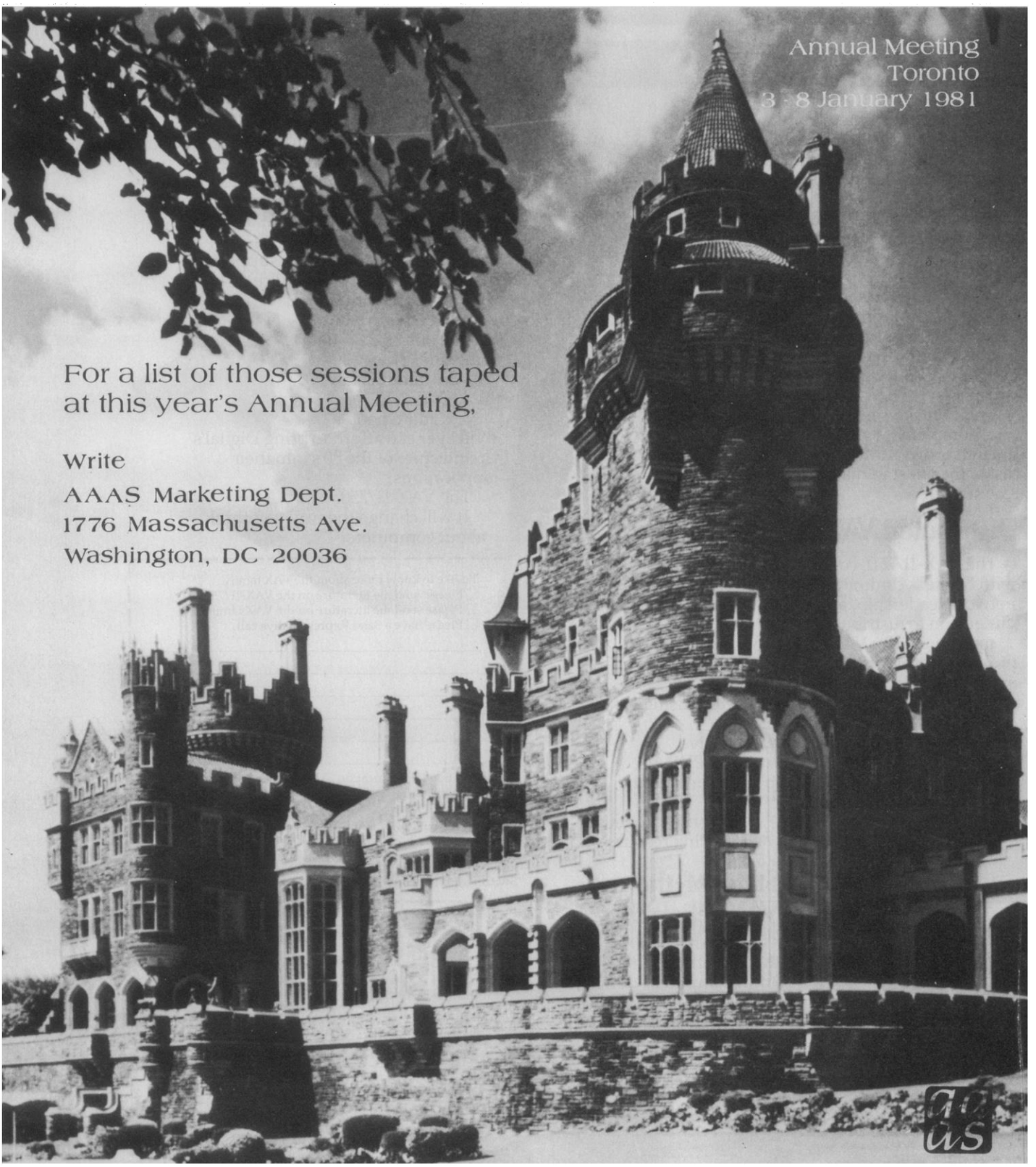

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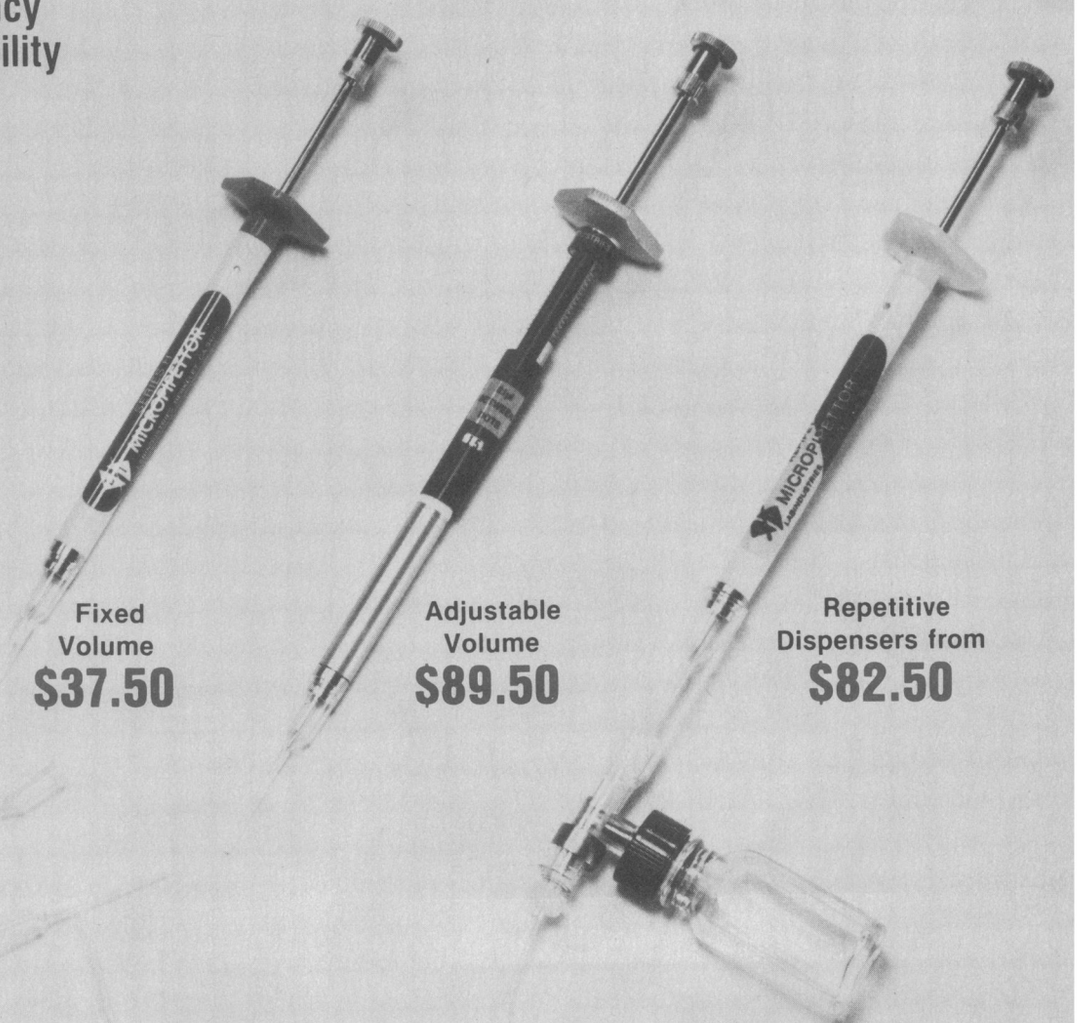

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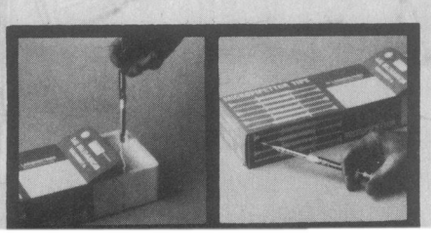

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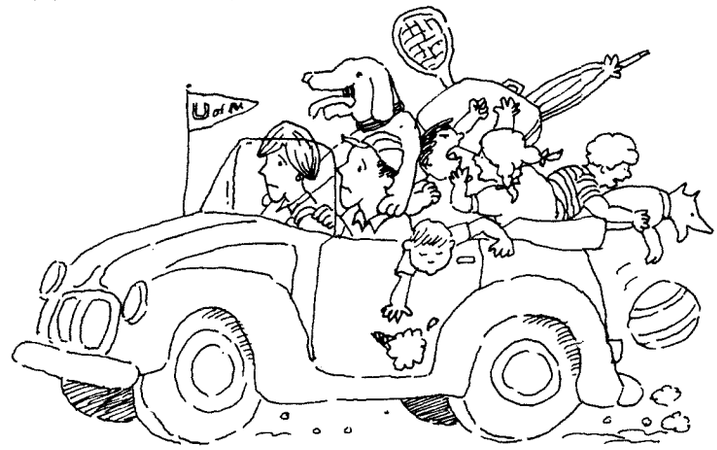

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LETTERS

Carcinogens and Regulation

As staff members of a governmental unit that provides information about the toxic potential of substances used in California workplaces, we found Gio Gori's "The regulation of carcinogenic hazards" (18 April 1980, p. 256) provocative. No one disputes that animal experiments only approximate the complexity of human exposures and genetic heterogeneity. Nevertheless, they have identified as carcinogenic chemicals which have later been shown to cause cancer in humans. They are thus valuable indicators of potential human carcinogens, and help us formulate rational policies to reduce the carcinogen burden borne by the public. We are particularly concerned with two of the issues Gori addresses: the validity of giving test animals the maximum tolerated dose of a suspected carcinogen daily over their life-spans, and the legitimacy of extrapolating from animal studies to humans.

Though high doses undoubtedly overcome some defense systems in animals, they increase the sensitivity of a cancer bioassay. High doses are given to increase the likelihood that even a weak carcinogen will produce a measurable effect and to compensate for the relatively small numbers of animals used in even the best of animal cancer tests. To detect a weak carcinogen at low doses with statistical certainty would require extraordinary numbers of animals, a requirement that would reduce the number of compounds that could be tested each year to far below our already limited capacity. Most scientists agree that it is better to have small-scale tests of a large number of substances than large-scale tests of only a few.

Bioassays that subject a small number of animals to low doses may fail to detect weak carcinogens to which great numbers of people may be exposed. For example, it has been estimated that 3.5 million workers a year are exposed to the solvent trichloroethylene (TCE) (*1*). In tests in male mice TCE causes cancer in about half the animals at a daily lifetime dose of approximately 1150 mg/kg (*2*). We have concluded that the legal standards for permissible workplace exposures are too close to that level; we have proposed a policy with a greater margin of safety (*3*).

We agree with Gori that such an extrapolation from rodents to humans is difficult. But conclusive evidence for carcinogenicity in animals exists for about 200 chemicals (*4*, *5*), while the number of identified human carcino-

gens—less than 30—is limited to agents that have produced a relatively large excess of cancers or extremely rare ones. For seven of these compounds (aflatoxin, 4-aminobiphenyl, bis(chloromethyl)-ether, diethylstilbestrol, melphalan, mustard gas, and vinyl chloride), the demonstration of carcinogenic effects in animals preceded evidence of carcinogenicity in humans. For these and eight additional human carcinogens, animal studies would have predicted the target tissues in humans (*4*). In addition, for three of six compounds examined the cumulative lifetime dose required to produce a carcinogenic effect is roughly comparable in animals and humans (*6*). Given these predictive results, our approach is to respond to the animal data rather than to discount it.

The consequences of failing to respond may be grave. California workers were exposed to the nematocide 1,2-dibromo-3-chloropropane (DBCP) and became infertile (*7*); 17 years earlier DBCP had been shown to cause testicular effects in rodents (*8*). Another pesticide, nitrofen, which is a carcinogen (*9*) and teratogen (*10*) in animals, has been used in California in amounts upward of 500,000 pounds a year (*11*). In August 1980 the manufacturer recalled the product from California distributors, and the state's Department of Food and Agriculture issued an emergency order suspending all permits for nitrofen use. Should we utilize the animal results on other substances as a basis for regulatory policy, or should we wait to see whether there are effects in humans?

The alternatives Gori offers are unsatisfactory. Cost-benefit analysis as a means of developing regulatory policy leaves unanswered the crucial question of distributive justice: who reaps the benefits and who takes the risks in cases of uncertain chemical hazards? In our view, the onus of a less than stringent cancer policy falls disproportionately on workers by virtue of their occupational exposure to known and suspected carcinogens.

In advocating a "regulatory court" for the determination of a substance's toxic potency, Gori fails to acknowledge the biases in such a procedure. In his assurances that it would result in a pluralistic representation of risk and cost he disregards the economic pressures that shape the breadth, intensity, and effectiveness of political argument.

Continuous evaluation of the methods of assessing carcinogenicity is important, and Gori's discussion is useful in that process. We think, however, that his premises provide a foundation for policies which would go too far toward

increasing exposure to possibly hazardous chemicals. Given the lessons of DBCP and other carcinogenic chemicals cited here, we prefer the more conservative approach: one that supports the full use of animal data in devising policies to create a healthful workplace.

MARC LAPPÉ, KIM HOOPER
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Gori attacks an important problem. Each year some 30,000 chemicals are synthesized in the United States alone. Perhaps 3000 of these are new compounds produced in significant quantities (*1*). At present, assessing carcinogenic risk by means of lifetime studies in rodents may take up to 3 years and cost $250,000 per chemical (*2*). Therefore, lifetime studies simply do not meet the need. However, Gori's assertion that we should substitute relative toxicity measurement for quantitative carcinogenesis studies because our dependence on the latter is "largely motivated by the ideal of absolute safety at all costs" is not a proper argument. The facts are that (i) current regulatory practices for chemical carcinogens are neither rational nor effective, and (ii) chemical carcinogenesis testing is capable of detecting and approximately quantitating cancer risk at a reasonable cost, whereas toxicity testing per se is not.

With regard to absolute safety standards, such as those embodied in the Delaney clause, Gori makes a valid point: it is unreasonable and nonproductive to require that a chemical found to be carcinogenic in a rodent at any level and over any period of time should be banned forthwith. However, Gori's assertion that the current tests are not predictive of risk in humans because "mice could be from 3×10^4 to 10^9 times more cancer-prone than humans" is fallacious. Extrapolative predictions of the rates of cancer incidence from animals to humans can yield quite reasonable comparisons (*3*). For example, extrapolated data on aflatoxin B_1 carcinogenicity yield values on the order of tenfold less sensitivity in man (*4*). It seems to me that this is sufficiently accurate for the purpose of defining approximate threshold values. It is not reasonable to suppose that this information is invalid simply because rodents are more sensitive than man or because a few chemicals do not have detectable effects in all biological systems.

As for the problem of the cost of the lifetime tests, there are alternatives. Although no single carcinogenesis testing system is 100 percent effective, many short-term bioassays are quite good. With a combination of short-term in vivo tests, most chemicals (certain steroid hormones being notable exceptions) can be tested for carcinogenicity or tumor-promoting ability in 6 months or less at a cost of approximately $5000 each. I estimate that it would require about $15 million to quantitatively test the 3000 most common chemicals. Furthermore, since a great deal is known about the structures and reactivity of chemical carcinogens, many of these compounds (for example, aliphatic hydrocarbons) would not have to be tested. This level of expenditure of money and effort seems to me quite reasonable for the assurance that most of the chemicals to which we are exposed are unlikely to be carcinogens.

RICHARD H. TULLIS
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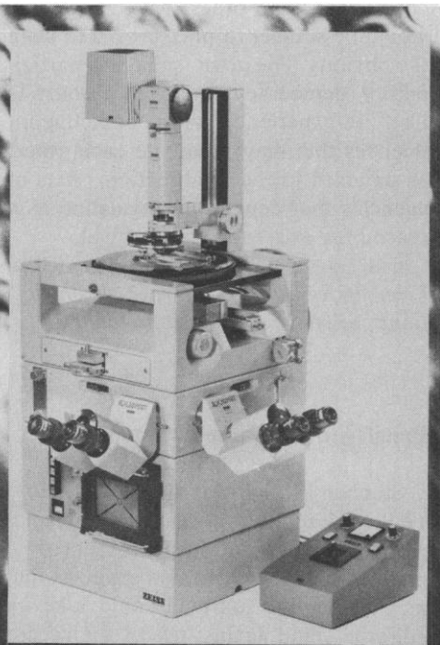

Endosperm of Haemanthus Katherinae.
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10 μm

I agree with Tullis that current regulatory practices for chemical carcinogens are neither rational nor effective, but I cannot agree with him, or with Lappé *et al.*, that our experience justifies qualitative or quantitative reliance on animal testing for regulatory decisions in this area.

That one or a few tests give apparently accurate approximations of risk to human beings is no justification for concluding that all tests are equally valid; many thousands of such tests do not provide even the appearance of approximation and are unpredictably discordant and ambiguous.

In restating that maximum tolerated doses are necessary to show an effect with weak carcinogens, Lappé *et al.* fail to recognize that this is only a statistical imposition, oblivious of real biologic difficulties ranging from overloading of metabolic and physiologic conditions to assumptions about dose response functions that are not scientifically verified or even verifiable.

If Lappé *et al.*, as regulators, wish to use animal tests for determining carcinogen threshold limit values as in their TCE example, they have the legal power to do so, but their decisions ought to be considered as being determined by a judgment of prudence and not as defensible by scientific data. Technical grade TCE has been shown to increase liver tumor incidence in mice but not in rats. If the tests were predictors of human target tissues, as these authors assert, hepatomas should be frequent in exposed workers. Any increase of these rare tumors would be readily noticed, but I am unaware of such findings.

The point they seem to have missed in my article is that, because animal tests are unreliable predictors of human risk and cannot consistently predict either safety or hazard, only two alternatives are left; one is irrational fear and the operational paralysis it ultimately implies, the other is a measure of prudence. Despite what anyone says about reliance on animal data, at the roots of regulatory decisions one invariably finds a balance of prudence and perceived need. Regulators adjust their pronouncements according to how extreme a regulation can be before it incurs a public revolt or a court challenge or causes an unsupportable economic burden. Saccharin is a signal case, where the public decided that the risks are hypothetical and the benefits tangible. As a consequence, a flood of protest has forced Congress to suspend the Delaney amendment for this substance.

It is often professed that scientific data support regulatory decisions, but usually they are not the real basis for regulation. This is demonstrably true even when precise measures of human risk are available through epidemiologic data.

Many have advanced the astonishing apology that no better information is available than animal data. In a similar vein, Lappé *et al.* argue that failure to respond to animal data may have grave consequences. Because animal data cannot tell whether it is harmful to regulate or not, or how harmful it might be, surely this is not a scientific statement but rather a political one, and one that can be properly resolved only by a comprehensive cost-benefit analysis of the options available, these being not to regulate at all or to do so at various levels of intensity. Animal data may contribute only tangentially to such a decision. To say that this process, and the regulatory courts that I and others have suggested, would be subject to pressures is to state the obvious. The point is that in a participatory democracy a citizen's court is likely to experience many conflicting influences that may moderate each other, as opposed to the unidirectional bias of agencies that depend on regulation as a reason for existence and survival.

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Privileged Communication

Stephen M. Schwartz (Letters, 7 Nov. 1980, p. 590) refers to the risk of plagiarism or pirating of ideas presented in grant applications. He also suggests that major scientific journals could take an editorial stand against use of the access privilege by scientists.

Such a stand has already been taken by the Committee of Editors of Biochemical Journals of the International Union of Biochemistry, of which *Science* is a corresponding member. Point 1 of its Code of Ethics, adopted in 1969, reads as follows: "All manuscripts received in the editorial office should be considered privileged communications, and be so identified." A privileged communication may be defined as a confidential document not to be shown or described to anyone except to solicit assistance in reaching an editorial conclusion provided that this privileged status is made clear to the referee.

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23 January 1981, Volume 211, Number 4480 SCIENCE

Science Education: Rhetoric and Reality

In 1980 the federal government seemed, at last, to have discovered the low estate into which science education in this country has fallen. The Secretary of Education and the acting director of the National Science Foundation (NSF) delivered to the President, at his request, an assessment in a report which did not whitewash the facts. Headlining their recommendations was a call for "A new national commitment to excellence in science and technology education for all Americans."

That was in October. By Christmas, hopes for federal leadership in the "new commitment" were jolted by the Administration's markup of the 1981 budget of the NSF, with a cutback in support for science education. Never mind that the report to the President had warned that "there has been, over the past fifteen years or so, a shrinking in our national commitment to excellence and international primacy in science, mathematics, and technology." When budget imperatives confront the needs for science education, the budget prevails. Science education continues its decade-long record as NSF's habitual loser.

In the past 12 years, the total budget of NSF has more than doubled in current dollars, while in constant dollars the funding of science education has suffered a two-thirds erosion. In 1970, funds for science education amounted to 27 percent of NSF's total budget, but for 1981 the science education share is down to 7.5 percent. If all were well with the state of science and engineering education, there might be nothing to complain about. But if the Secretary of Education and the acting director of NSF are right in what they report, there is a great deal to complain about. The meaning of the budget action is that the government has chosen to disregard its own findings on the predicament of science and engineering education.

Budget policies are seldom models of economic or political logic, as we have come to realize. But there is this much to be said of them: they are symbolic proxies for the nation's values, expressed in consensus terms. They serve to signal, however imperfectly, the government's view as to how national priorities should be ordered. What we must ask, then, is what inputs go to construct this process of ordering. When a President is sufficiently aroused to call for a fitness report on science and engineering education in the United States, and is given bad news, it would be reasonable to suppose that even painful budget choices would take the findings into account. Instead, the latest budget actions have brought science education in NSF to its smallest share of resources in the last 30 fiscal years. If state and municipal governments, trapped between rising costs and taxpayer revolts, take their cues from the federal government and economize at the expense of science education in the schools, the road back to "excellence" will indeed be a long one.

President Carter will soon send his budget for 1982 to the Congress, whereupon President-elect Reagan will promptly recall it and substitute his own. If the passion for squeezing government's "controllable" outlays should take advantage of the vulnerability of the science education budget, lumping it in with other discretionary programs that make up the celebrated "coast-to-coast soup line," matters would become desperate very quickly. The Reagan Administration has the opportunity, without compromising prudent economic policies, to reorder priorities and set a positive course toward rebuilding America's excellence in science and engineering education.—WILLIAM D. CAREY

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