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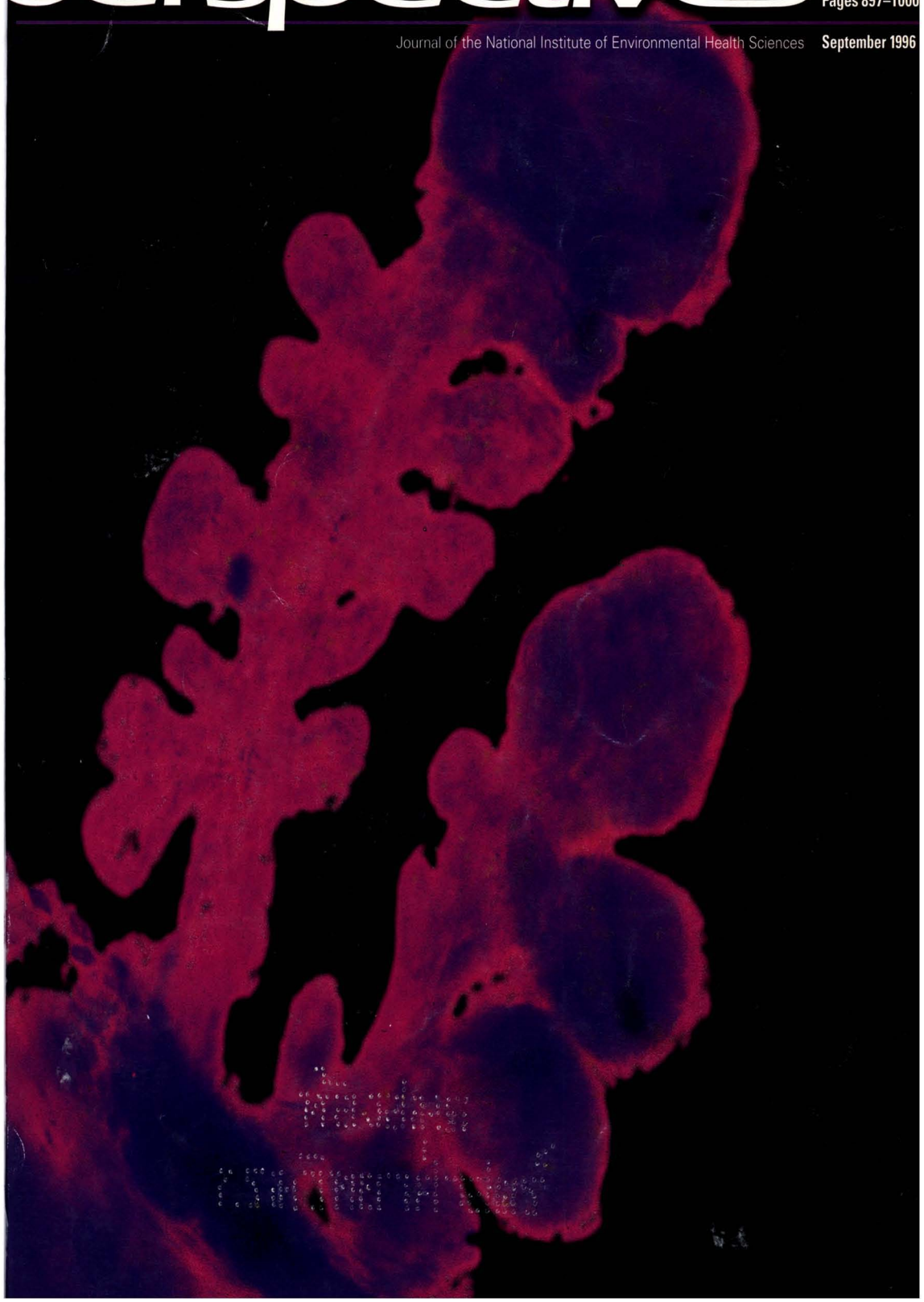

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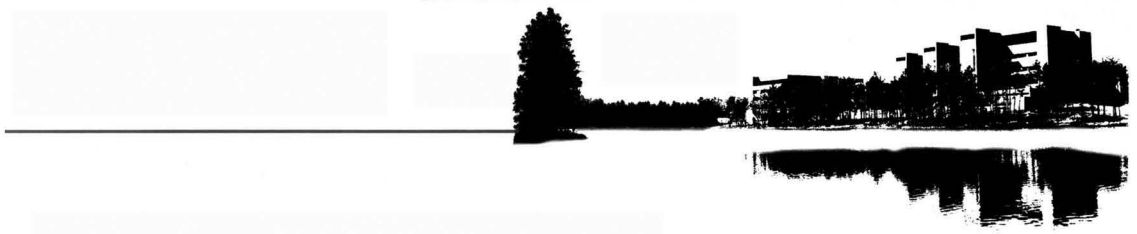

On The Cover: Intraductal proliferations that form when terminal end buds of the rat mammary gland become enlarged after DMBA administration (Russo and Russo, p. 938).

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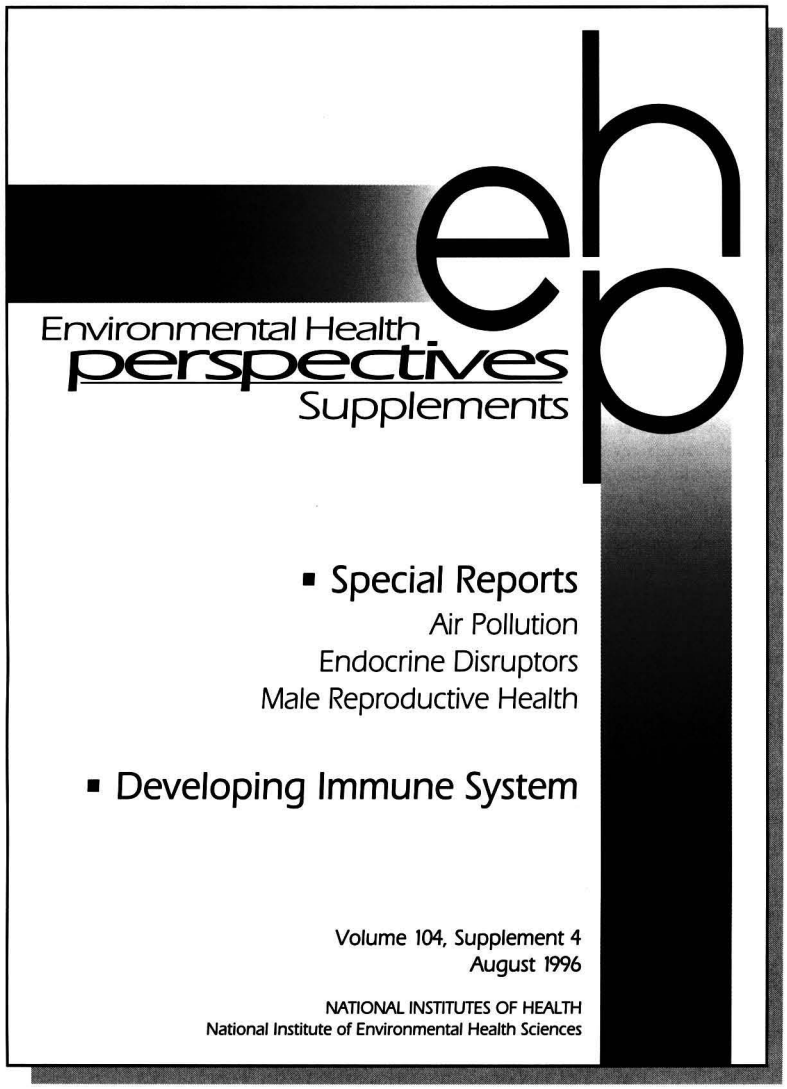


A Tradition of Progress

EHP Supplements continues its 24-year tradition of publishing monographs based on current environmental issues and conference proceedings, as well as an annual review of environmental health. In Supplement 4, several major environmental issues are highlighted including air pollution, endocrine disruptors, xenoestrogens, and environmental pollutant effects on the immune system.

For subscription information, see p. 994.
For a listing of published volumes of *EHP Supplements*, see p. 999.

In This Issue

Risk Policy for EMF Exposure

Sahl and Dolan suggested in a **Commentary** (p. 908) that a precaution-based approach should be taken for avoidance of potential EMF health risks. This was clarified as a common sense approach and recommended as an effective component of a comprehensive set of EMF policy options because the electric power industry believes there is scientific uncertainty about the potential health impacts from exposure to electromagentic fields and that adoption of costly avoidance measures would defer resources from more important public health priorities.

Risk Assessment for Mammary Tumors

A **Commentary** by Neumann et al. (p. 912) suggested that Russo's review of rodent models for breast cancer should help to channel research efforts and resources into the proper areas for support of appropriate research on risk assessment for human mammary carcinogenesis. Additional recommendations for an effective research program addressing this topic were reported by a working group of the ILSI Risk Science Institute and the U.S. EPA Office of Pesticide Programs.

Just What the Herbalist Ordered?

As herbal medicines gain in popularity in Western countries, government agencies, the herbal industry, and consumer advocacy groups are calling for research and public awareness about the effects of such substances. The **Focus** (p. 924) discusses international efforts to examine existing research on herbal medicines, as well as questions about their safety and how they should be regulated.

Still Safe to Drink

The Safe Drinking Water Act (SDWA) may be the only major piece of environmental legislation to be signed into law this year. Both the Senate and the House have unanimously passed similar bills to reauthorize the SDWA. The **Spheres of Influence** (p. 930) discusses the history and current status of the SDWA, and looks at the changes proposed by these bills.

Fish out of Water

Researchers at the NIEHS have developed transgenic fish that may serve as tools for detecting chemicals in water and the risks they pose to humans and wildlife. The **Innovations** (p. 934) discusses the method by which the transgenic species were created and their potential use as a marker for genetic damage caused by toxic chemicals.

Rodent Models for Breast Cancer

Mechanism-based toxicology, molecular and cellular approaches, and comparative *in vitro* systems are used to rapidly screen chemicals, to investigate low dose chemical dose responses, and to validate biomarkers for toxicity. Russo and Russo (p. 938) review these topics and describe studies of mammary tumors in rodents; they conclude that traditional whole animal studies must be continued until adequate information on the predictive value of mechanism-based toxicology for risk assessment is obtained.

Lead Poisoning in Children

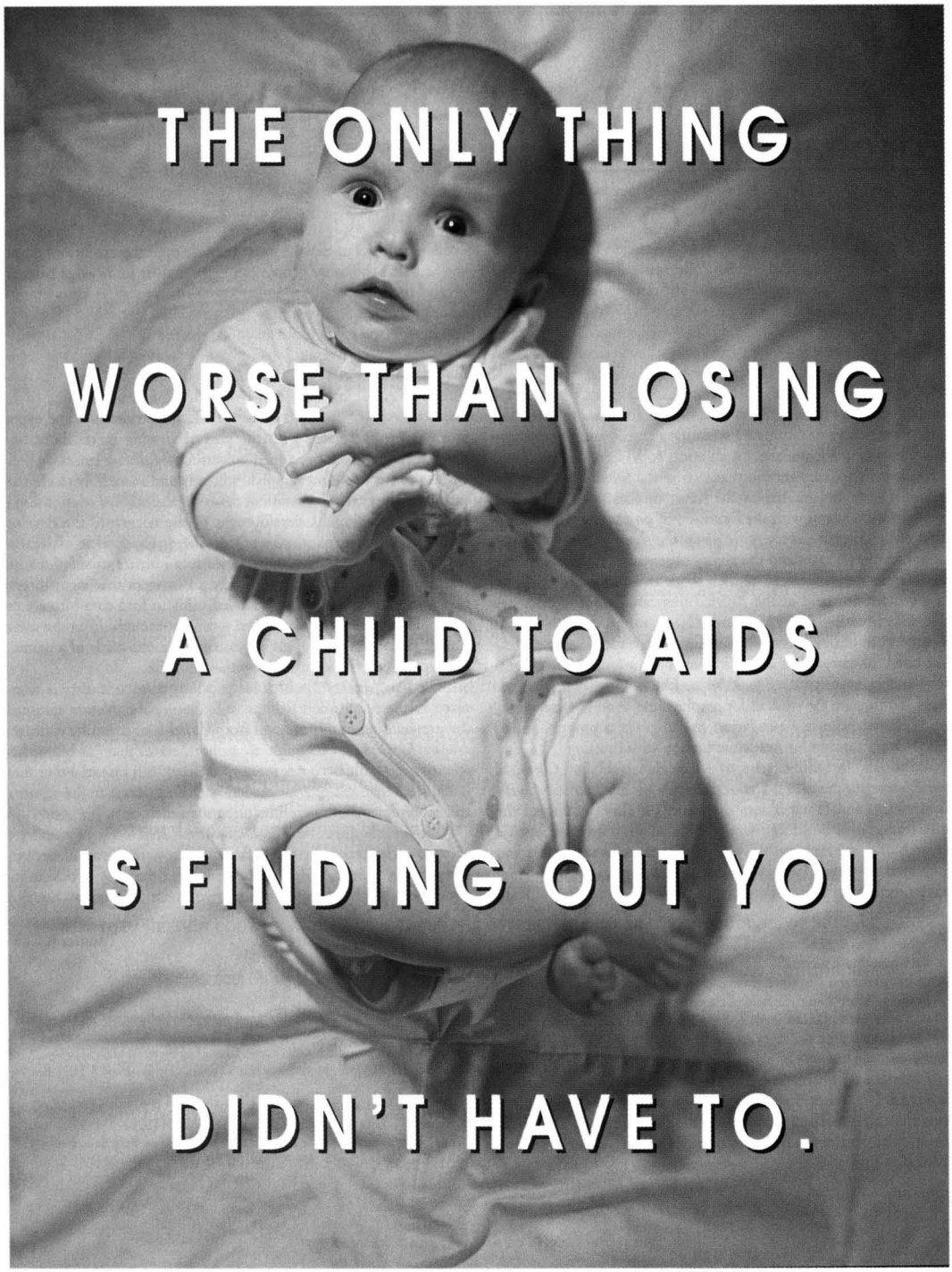
Children in New York identified with moderately elevated blood lead levels (25–55 µg/dl) were not given lead mobilization therapy because they showed only limited response to chelation tests (p. 968). Instead, their parents were notified of lead hazards and provided educational instruction about lead toxicity, sources, and treatment during 10 clinical and 3 home visits; if necessary, children were given iron therapy. Lead paint hazards were quantified by visual and analytical measurements, and a home environmental score (HES) was assigned. Markowitz et al. (p. 968) found that the HES was predictive for moderate lead poisoning and that, without any additional treatment, repetitively measured blood lead levels in children declined during the 24 weeks they were enrolled in a comprehensive intervention program.

Ventilation Rates in Adults and Children

Beals et al. (p. 974) measured the exchange of air in the lungs of children and adults during exercises representing a variety of normal activities. Accurate measurements for the variances in ventilation rates are needed when quantitating exposure to environmental contaminants to make estimates of risk assessment. Distributions of ventilation rates representative of the range of every day activities of adult males, females, and children for varying lengths of time are mathematically evaluated and presented for 6–13, 13–19, 19–60, and over 60 years of age.

Cooking Fires and Respiratory Symptoms in Mexico

Respiratory toxicity from cooking over wood fires is common in Mozambique (p. 980). Ellegård monitored air pollution during cooking time using wood, charcoal, and modern fuels and reported 2–6 times greater air contamination from wood. Coughing indices were directly associated with wood fire cooking but were not related to use of charcoal or modern fuels. Use of charcoal as cooking fuel was recommended as an economical and healthy replacement for wood; modern fuels like LPG and electricity are beyond the means of most households.



Thousands of women will lose a child to AIDS simply because they didn't get an HIV test during their pregnancy.
They didn't know they were infected, so they couldn't take advantage of new treatments that can
help stop the spread of HIV from mother to baby.
If you're pregnant, please get an HIV test. For confidential HIV/AIDS information 24 hours a day, call 1 800 342-2437.

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Editorial

A Broader View

Last year the National Academy of Sciences' Committee on Science, Engineering, and Public Policy published a report titled "Reshaping the Graduate Education of Scientists and Engineers" (*1*). Since then, there has been general approval of the recommended changes, such as broadening the knowledge base of the student, expanding student support through educational or training grants, and improving the availability of career information.

A desire to broaden the perspectives of scientists is not a new theme; recently, however, the idea has received more attention with the objective of improving scientific research and the employability of our new graduates. In an effort to address this perceived need, interdisciplinary meetings known as the Scientist to Scientist colloquia were inaugurated by the Keystone Center in 1991. The meetings were begun with the intention of promoting the appreciation of the diversity of scientific fields, the sheer pleasure of learning for learning's sake, and the ability of scientists to communicate the interest and excitement of their work in an accessible fashion. In a symposium held at the 210th American Chemical Society's National Meeting in 1995, Janet Osteryoung of the National Science Foundation's Division of Chemistry listed several areas that cried for integration of disciplines such as molecular recognition, molecular electronics, and the health and environmental sciences. To prepare the student for employment outside of academe, the National Science Foundation has in place a program titled Grant Opportunities for Academic Liaison with Industry.

Editorials, including those by Madeleine Jacobs of *Chemical and Engineering News* (*2*), Deborah Barnes of *The Journal of NIH Research* (*3*), and Floyd Bloom of *Science* (*4*), have examined the importance of a wide knowledge base in improving scientific research and the employability of scientists. A lively debate was generated by the National Academy of Sciences report in the Letters sections of several journals. In one of these letters, William J. Schulz (*5*) wrote

> When I look around me and consider why some of my colleagues have been more successful than others, even if all have comparable technical capabilities, the answer is obvious. People who can relate to things other than their field of expertise—for example, the business environment, customers, economics—are the people who can leverage their expertise more successfully.

Christian de Duve, in his book *Vital Dust: Life as a Cosmic Imperative* (*6*), states that "active science narrows the mind more often than it broadens it, the reason being the increased specialization of facts, concepts, and techniques. As we dig deeper our scope shrinks."

A narrow focus may be more the rule than the exception, despite the fact that the more people can expand their knowledge base, the greater their potential for contributing to science. A clear example of this potential for innovation was noted in a fascinating article that appeared in *Scientific American* (*7*). Author James Burke weaves a story about the complex, serendipitous interconnectivity of events that can lead to great discoveries. His example starts with an observation by Antonie Thonisoon (who later changed his name to van Leeuwenhoek) of drawings of shot silk (a fine, iridescent, and expensive weave). Fascinated with the idea of viewing materials in finer detail, Leeuwenhoek developed powerful magnifying lenses. In a circuitous route, one discovery led indirectly and incredibly to another, including the first observation of microorganisms, the relationship of electricity to light, the development of the telegraph, the development of Nobel's underwater mines, the establishment of weather forecasting, the use of vacuum valves to automate calculations, the first electronic calculator, and finally a discovery that went directly back to shot silk, the use of punched cards to feed data into a computer. The punch card idea came, strangely enough, from the use of similar cards to automate the production of cloth made of a material too expensive to make mistakes with—shot silk.

The importance of a broader perspective for scientists is recognized in the publication field as well. *Science* and *Nature* epitomize the presentation of information from all fields of scientific endeavor. *Nature Medicine*, in its guide to authors, states that "as biomedical science necessarily becomes more specialized, it is essential that there is a journal that will provide readers with clear access to the advances and achievements of disciplines other than their own."

In the same spirit, we at *Environmental Health Perspectives* try to provide information that will facilitate cross-fertilization between scientific disciplines. We do this in the belief that it is critical to our understanding of the impact of the environment on human health.

Thomas J. Goehl

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SOCIETY OF TOXICOLOGY

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We announce our intention to make awards of recognition for the best platform and/or poster presentation by graduate students or postdoctoral fellows in the areas of reproductive and developmental toxicology at the 36th Annual Meeting of the Society of Toxicology to be held March 9–13, 1997 in Cincinnati, Ohio. General areas of research may include male or female reproductive toxicology, reproductive endocrine toxicology, teratology/developmental toxicology, and/or postnatal development. By November 8, 1996, candidates for these awards should send to the address below a copy of the abstract that is being submitted to the Society for this meeting. An outline of the talk or a copy of the poster material should also be included, if possible, to assist the judges in their evaluation. The abstracts and posters should describe the original research which may include applied studies, investigations of mechanisms of toxic response, or studies of basic mechanisms of action. Interested individuals may request Society information and abstract forms from the Society of Toxicology in Reston, Virginia (703) 438-3115 or sothq@toxicology.org. All submitted material will be treated as confidential. The winning presentations will be announced at the Annual Meeting of the Specialty Subsection in Cincinnati. For further information, contact:

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Commentary

An Evaluation of Precaution-based Approaches As EMF Policy Tools in Community Environments

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This paper explores the use of precaution-based approaches as policy tools when responding to concerns about power-frequency electric and magnetic fields (EMF) in community environments. The combination of public concern and scientific uncertainty about potential health impacts from exposure to EMF challenges society to adopt EMF policies that balance the benefits of electric power against the possibility that some aspect of the use of electricity may be harmful. Inappropriate policy responses can undermine the economics of society's use of electricity and have other adverse consequences on public health. These adverse consequences result from the inappropriate diversion of scarce public and private resources. Precaution-based approaches are rooted in individual concepts of common sense and can be an effective component of a comprehensive set of EMF policy options. Precaution-based approaches do not replace science-based policy options and should only be used when the available science-based guidelines are not applicable. The application of these approaches should balance the real and expected costs and benefits of taking or not taking action. Given our current scientific knowledge, actions taken to reduce EMF exposure should necessarily be low cost because the expected benefits are uncertain. Society also needs to avoid adopting EMF policies that could incur high costs from distorting resources from other, more important, personal and public health priorities. *Key words*: common sense, prudent avoidance. *Environ Health Perspect* 104:908–911 (1996)

There is public and scientific concern that power frequency (50/60-Hertz) electric and magnetic fields (EMF) in residential settings influence cancer or other diseases. While the issue of a relationship between EMF and cancer has been the focus of research (*1–2*), results have not established a connection between EMF exposures and cancer or other diseases (*3–5*). The scientific community has been unable to resolve public concern and is uncertain what conclusions will result from future research. The scientific questions will be resolved in due course by the normal scientific process of research, peer review, and debate. Scientists cannot predict how long it will take to answer the remaining key questions, but it is likely to be several years. In the meantime, the combination of public concern and scientific uncertainty challenges society to adopt policies that balance our needs for and value of electrical power against the possibility that some aspect of the use of electric power may be harmful. This balancing is not unique to the EMF issue and is a fundamental goal of individual or societal decision making for a wide range of issues.

Science-based evaluations of the potential hazards from EMF exposure are an essential part of an appropriate public policy response. The traditional method of setting science-based policy, exposure standards, or health guidelines for potentially harmful agents has been to first obtain firm data concerning hazard and dose response and then set threshold exposure levels with appropriate margins of safety. This method has been used by quasi-governmental scientific panels in evaluating the need for and setting EMF exposure guidelines (*6*). Because of insufficient evidence for a health hazard, inconsistent results from research programs, and relying on well-accepted biophysical principles, these expert panels have consistently concluded that there is insufficient evidence of a hazard for EMF exposures (*6*).

This response from the scientific community has limited regulatory policy options and has not resolved public concern. Precaution-based policy approaches incorporate information about the scientific uncertainty, address the possibility of a health risk being identified in the future, and provide a means to respond to public requests for meaningful actions today. These policy responses can fill the gap between the time when the public becomes aware of an issue and when the scientific community provides a firm determination of the potential risk. These precaution-based policy approaches should be seen in addition to, not as substitutes for, the science-based evaluations. This paper explores the use of precaution-based approaches as a means of assisting regulatory decision makers, electric utilities, and the public in responding to the evolving EMF controversy. Our goals are to elaborate on the rationale of precaution-based policy approaches and provide criteria that help define when they should be used with regard to the EMF issue.

The EMF Science

EMF naturally results from the generation, distribution, and use of electricity. Community exposure results from electric utility transmission and distribution facilities, internal wiring of buildings, the use of electric appliances and equipment, and ground return currents (*7,8*). A brief overview of the EMF science will help provide a context for the subsequent policy discussion. An electric field is a natural force field created by voltage. The strength of these fields is measured in units of volts per meter (*7,8*). A magnetic field is also a natural force field produced by the flow, or current, of electricity. The strength of the magnetic field is measured in units of microtesla (*7,8*). In spite of the substantial amount of research performed over the past 25 years, scientists still struggle to answer four fundamental questions. Can electric or magnetic fields found in community environments influence health? If they can, what are the biologically important characteristics of exposure? If there is a health risk, who is at risk, and how large is the risk? What steps can be taken to reduce the risk (if one exists at all)? There are well-established biophysical models for the interaction of EMF with biological systems (*9*); however, these biophysical models do not support the possibility of significant health impacts from magnetic fields in the range found in community environments (i.e., up to 1,000 mG) (*10*). New biophysical models have been proposed to explain how magnetic fields under 1,000 mG could interact with cells, but these do not enjoy wide acceptance within the relevant scientific community or from experimental evidence (*9*).

Neither the parameters of the risk from EMF exposure, if it exists, nor the size of the population at risk, if any, are known. If there is a risk to health from EMF exposure, those at risk could be a relatively few sensitive people with a consequent low public health impact or a larger part of the pop-

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ulation with a lower but more widespread risk. Since the scientific community has no operational or theoretical model of dose, our ability to define exposure or to identify populations who may be more exposed is limited. Not being able to answer the fundamental scientific questions about the presence of a risk or the relevant characteristics of exposure hampers our ability to direct scientific resources to specific research questions, to establish new science-based exposure mitigation policies, and to engage in a public policy debate about their costs and benefits. It is hoped that new results from the international research efforts now underway will adequately answer these scientific and public health questions, establish clear policy directions, and resolve the public concerns.

Why Are EMF Policies Important?

Even though there is no scientific consensus that EMF exposures influence health, it is important that we develop and implement effective policies that respond to the scientific uncertainty and public concern. The use of electricity is ubiquitous throughout society. In both developed and developing countries, the reliable and economic availability of electricity is essential to economic progress and maintaining public health. Because the use of electricity is so widespread, questions relating to its safety are important. The proven value of electricity to the economic and public health of our society demands that care be taken in determining what policy measures to adopt. Without such care, and particularly if there are no health impacts from EMF, unanswered public concerns about health questions may result in wasting individual and society resources. This has the potential to impact on the reliability and cost of society's use of electricity, and have other adverse consequences on public health by diverting limited public and private resources from known public health risks. Reasons for implementing effective EMF policies at this time include maintaining the fundamental public health value of electricity to our society, responding to the uncertainty about the nature of the possible risk, and the need to build new electric utility facilities and maintain the reliability of existing facilities.

The Policy Construct for Precaution-based Approaches

Our challenge is to identify and implement effective policy options that incorporate the current scientific knowledge and enjoy the wide acceptance of society. People within our society consistently use concepts of precaution in everyday life, both personally and in their organizations. Generally, these are not well defined and can include a variety of actions. Precaution-based approaches provide opportunity to implement interim policies that are meaningful. In the context of the EMF issue, precaution-based approaches describe a particular set of possible actions that are consistent with individual and societal concepts of acting sensibly. This includes funding research to resolve the scientific questions, informing members of our society about the scientific issues, and implementing interim steps to reduce the possible risk from EMF by eliminating or limiting exposure, when this can be done at modest cost and with minimum inconvenience. These approaches are based on 1) the recognition that a hazard may or may not actually exist; 2) their applicability mainly to new facilities; 3) their low costs; 4) the fact that they do not distort public priorities; and 5) their use for a transitional period. Specific precaution-based EMF policy responses maintain their value when these five elements are balanced.

The explicit recognition that a true risk may not exist is a key element of precaution-based approaches because this helps keep the issue in perspective. If the scientific community concludes that there is no risk from EMF exposure or that the possibility of a risk is too speculative, then we should respond to public concern with an effective education program. If, on the other hand, a risk for EMF were to be established, it would then be appropriate to rely on the scientific community to recommend specific protective measures using established public health risk assessment/risk management criteria (*11*). Within the context of electric utility facilities, actions taken under this kind of policy approach should generally be reserved for the design, siting, and construction of new facilities because of the flexibility and economy that is available when new facilities are constructed. Actions taken are limited to no- or low-cost because higher cost actions are inappropriate due to the uncertainty of achieving any health benefits. Avoiding the distortion of public health priorities is a critical element because it would be a mistake to divert scarce resources from something with known benefits to the uncertain benefits of reducing exposures to EMF. It is important that information about potential health risks be presented to individuals and society so that they allocate attention to the full range of personal and public health issues to achieve greatest benefit. Because the risk is uncertain, actions taken should be transitional. As new information becomes available to either clarify the presence or absence of a risk, to better define the relevant characteristics of exposure, or to identify ways to efficiently reduce EMF exposure, actions should be appropriately modified. As a more fundamental concept, if a risk is established to actually exist, the public health-based risk assessment and risk management model would provide the more appropriate and necessary guidance upon which to base individual and societal allocation of resources (*11*). If a risk is not identified, then the scientific community and public health agencies should implement effective education programs to resolve public concerns.

Existing Precaution-based Approaches

With respect to the EMF issue, the concept of precaution-based policies had its genesis in the United States around 1989 when prudent avoidance was proposed as a policy option in a report to the Office of Technology Assessment of the U.S. Congress (*12*). Nair et al. (*12*) described prudent avoidance as

> looking systematically for strategies which can keep people out of 60 Hz fields arising from all sources but only adopt those which look to be "prudent" investments given their cost and our current level of scientific understanding about possible risks.

In several jurisdictions of the United States, steps to site and construct new facilities include consideration of options to reduce EMF. For example, as part of the siting of a new 220kV transmission line, the California Public Utilities Commission ruled that the evidence for risk was insufficient to mitigate fields under the California Environmental Quality Act, but it would be appropriate to take other precautionary steps (*13*). These steps included education about EMF to the affected public and taking EMF into consideration in the design and siting of the new line, when these are low cost (*13*). California (*14*) has since adopted a set of generic policies that include reducing EMF from new transmission and distribution facilities by balancing reliability, safety, and cost effectiveness. California's electric utilities have developed formal design guidelines to reduce EMF from new electric utility facilities. The California Public Utilities Commission has defined no-cost and low-cost steps as those which total less than 4% of the total project costs (*14*).

The Colorado Public Commission has decribed the state's concept of prudent avoidance:

> The utility shall include the concept of prudent avoidance with respect to planning, siting, construction, and operation of transmission facilities. Prudent avoidance shall

> mean the striking of a reasonable balance between the potential health effects of exposure to magnetic fields and the cost of impacts of mitigation of such exposure, by taking steps to reduce the exposure at reasonable or modest cost. Such steps might include, but are not limited to 1) design alternatives considering the spatial arrangement of phasing of conductors; 2) routing lines to limit exposures to areas of concentrated population and group facilities such as schools and hospitals; 3) installing higher structures; 4) widening right of way corridors; and 5) burial of lines.

Some health departments have also adopted policies or published informational literature that recommend prudent avoidance as a policy tool. The Hawaii Department of Health recommends a prudent avoidance policy that includes taking "...reasonable, practical, simple, and relatively inexpensive actions... to reduce exposure" (*16*). The Connecticut Department of Health Services requested the Connecticut Academy of Science and Engineering to address the EMF policy question. Their report concluded that it would be inappropriate for health authorities to recommend prudent avoidance to the general public (*17*). However, the Connecticut Siting Council did order the electric utilities to follow electric and magnetic field best management practices (*17*). These are implemented on a project-specific basis and include public notice and participation and the use of low-EMF designs for new facilities.

In Australia, the electric utility industry, through its trade association, the Electricity Supply Association of Australia Limited (ESAA), has adopted a policy of acting prudently in relation to the EMF issue. ESAA has stated that acting prudently includes practicing prudent avoidance when building new transmission and distribution facilities. In New Zealand, a similar approach has been taken by the electric transmission authority, which won its judicial approval in a 1994 siting case.

Several Nordic health agencies have advocated the use of caution in their policy approach to the EMF issue (e.g., Sweden, Denmark, Norway). All of these agencies assessed the EMF scientific literature and concluded that adverse health effects from exposure to EMF have not been established. The Nordic health agencies agreed that there is some evidence that EMF exposure may pose a risk to health and they suggest a cautious approach when building new electrical facilities, homes, and schools (including kindergartens and child care structures) near existing electrical facilities such as powerlines and substations. However, all have rejected imposing arbitrary low numeric EMF exposure levels since these are not supported by the scientific literature. The policy of the Swedish Radiation Protection Institute suggests that low cost mitigation action be considered when EMF exposure levels reach 10 times what would be considered normal for that particular environment.

Interest has also been expressed in relation to prudent avoidance for new schools and residential/office building development. Particular interest in the concept for schools has been shown in California (*18*), New York, New Jersey, Canada, and Sweden. This has resulted in restrictions for siting these new schools close to electric utility facilities and in informing parents and teachers about the sources and field strengths in classroom and play areas. Remodeling plans have also been reviewed to take advantage of opportunities to reduce fields. The basis for these approaches is to address concerns about proximity to transmission lines, not to limit exposures to EMF per se.

Why Precaution-based EMF Policies Make Sense

Precaution-based policy approaches make sense because they provide an opportunity to take incremental steps to improve the desirability of the future with respect to emerging issues. Prudence or caution can be implemented by individuals, businesses, or government, but is not a justification for costly actions (*19*). To await the outcome of the scientific process before adopting semi-formal prudent policy responses could mean missed opportunities to include a wider range of interests and take simple steps to reduce or modify the EMF environment at low cost. The use of this policy tool does not replace science-based policy options but it should incorporate current scientific knowledge into the decision process.

These precaution-based policies include the provision of information that assists individuals to better understand the sources of EMF and thus identifies options that people can take to limit their exposure. To exercise such a choice, individuals need to be provided with information about sources of EMF exposure. This information can help empower individuals to take advantage of decision-making processes. Public education material on EMF provides this kind of information and gives people and organizations the opportunity to make such informed choices.

Wolves Dressed as Sheep: Nonscience-based Numeric Standards

Science-based numeric standards for EMF enjoy wide acceptance (*8*). Some jurisdictions have adopted or considered adopting nonscience-based numeric standards under the guise of being cautious or prudent or as part of an ALARA (as low as reasonably achievable) type response. In reality, they are neither cautious nor prudent. They represent an attempt to give the illusion of certainty to what is inherently uncertain. Such a policy response was argued for in Australia, but was rejected (*20*):

> Any standards fixed for the purpose of avoiding the possible risk to health created by the fields would be based only on guesswork. They might either give a sense of false security or create unnecessary alarm, but in any case they would serve no useful purpose, having no rational basis.

Emphasis was placed on the fundamental problems associated with the lack of knowledge regarding exposure and dose (*20*):

> It is not known at what threshold of exposure (if any) a risk arises or what conditions are necessary to create a risk. If the suggestion that a risk exists at a level of exposure as low as 2–3 mG is correct, the difficulties of avoiding the risk will be great, for levels of ambient exposure as low as that are likely to be common. However, it has not been established under what conditions the risk, if any, arises. It is by no means clear whether the risk (if any) is created by intensity of exposure, duration of exposure, occasional bursts of exposure at higher than usual frequency or intensity, or intermittent exposure. It is not established whether or not a dose–response relationship exists, or whether the risk (if any) arises at a threshold, or in windows, of intensity.

Approaches incorporating a numeric standard are not an appropriate EMF policy option because a hazard has not been established to exist, dose has not been defined, it is impossible to define exposure in the context of human health impacts, and the emergence of new technologies is not expected to provide additional policy options. ALARA type responses are also inappropriate to the EMF issues because they do not provide guidance as to what is reasonable in the context of the EMF issue. While it may be difficult to implement a well-defined set of actions that are part of precaution-based approaches, the very lack of definition is the source of its strength. Problems are created when decisions are based on precaution-based approaches but are implemented through overly constructive or numeric approaches (*21*). If the policy approach relies on a numeric standard, it will fail because it pretends to fall within the shadow of scientifically accepted actions but cannot be defended by science.

Discussion

The need for and the value of using precaution-based policy approaches such as

the cautionary approach or prudent avoidance has been controversial. The basis for the controversy is that these approaches are viewed as overly subjective and biased against using the best available scientific or technological information, and they lack natural boundaries to their costs (*22*). We would argue that these approaches are valuable because they are accessible to individuals and organizations prior to formal societal actions. Coupled with an inclusive process, these policy approaches are seen to be addressing peoples' concerns rather than simply waiting for more formal science-based regulation. This will ultimately increase the support for and use of formal science-based standards and guidelines.

There is an enormous value to society in using the scientific method when formulating decisions. Its use helps to define the need for, use, and value of precaution-based policy approaches. The scientific method provides the tools for implementing precaution-based policies. Without this basis, we run the risk that policy will be developed solely in the domain of perception. Using individual perception of risk as a basis for taking action inherently undermines rational decision making and makes individual and institutional actions unduly influenced by advertising strategies. Reliance on perception of risk rather than informed decision making when taking action would lead to inefficient individual and society policy decisions. Taking actions based on mere possibilities, or unfounded perception, should be avoided and should not be part of a precaution policy approach. With regards to EMF policy, we as a society must try and create a decision-making process that does not require the ad hoc molding of objective truth based on the manipulation of public perception. Providing structure and guidelines for precaution-based policy approaches helps us to achieve this aim.

Within the constraints outlined in this paper, precaution-based approaches are a sensible response both to scientific uncertainty and the concerns of the public. Two traps to avoid are the exclusion of affected parties from the decision-making process and the attempt to shroud our uncertainty about the existence of a risk and the relevant exposure characteristics in potentially obscure science-based arguments. Interim policies that respond to scientific uncertainty should be indifferent to the ultimate outcome of the health question (that is, they should not presuppose the connection between exposure and disease), they should be flexible, and they should be derived from the input of the full range of affected groups. It is valuable to expand our understanding, application, and evaluation of these policy tools so that they can be used more effectively by decision makers continuing to struggle with responding to uncertainty. Carefully used, precaution-based policy approaches provide an excellent supplement to existing science-based exposure guidelines without compromising the legal or public policy positions of those who use them.

Precaution-based approaches should result in policies that help create desirable futures for society. Our fundamental goals are to increase cultural and societal trust in our scientific and regulatory authorities (*23*), improve the use and understanding of the scientific methods when responding to complex issues (*24*), and avoid ineffective risk regulation and inappropriate litigation (*25*).

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Mammary Gland Neoplasia

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Determining how findings of chemically induced carcinogenic effects in rodents can properly be interpreted for human health poses a continuing challenge to the risk assessment community. One approach begins by comparing and contrasting carcinogenic processes in rodents and humans, identifying biologically significant similarities and differences and gaps in scientific knowledge and understanding. Russo and Russo (in this issue) use just such an approach to evaluate the current state of scientific understanding of the comparative mechanisms of mammary tumorigenesis in humans and rodents, particularly the role of reproductive hormones. This commentary describes the basis for this review and suggests some of the implications the report may have for human health risk assessment and for future research. ***Key words:*** **breast cancer, chemical carcinogens, estrogen, hormones, interspecies extrapolation, mammary tumors, risk assessment, rodent bioassay.** ***Environ Health Perspect*** **104:912–914 (1996)**

During 1992, the International Life Sciences Institute's Risk Science Institute, in partnership with the U.S. Environmental Protection Agency (EPA), Office of Pesticide Programs (OPP), formed a working group to examine the relationship(s) between chemically induced mammary tumors in laboratory rodents and human breast cancer. Specifically, the working group composed of scientists from government, industry, and academia was asked to consider five questions: Is a dose-related increase in mammary tumor incidence in rodents a credible indicator for potential human risk? Is the mechanism of tumor development partially or completely mediated by hormones? Does the mechanism of carcinogenic response function with or without a threshold? How do various routes of exposure (e.g., oral, inhalation, subcutaneous) affect rodent mammary carcinogenesis and how should such information be used to select an appropriate animal model for human risk assessment? What information and methodology should be used to estimate potential human risk?

Through subsequent meetings and discussions, it became clear that a fundamental barrier to addressing these questions was the absence of data on the initiation and progression of chemically induced mammary tumors in women. It also became apparent that a thoughtful comparative analysis of the role that reproductive hormones play in rodent mammary tumorigenesis and human breast carcinogenesis would be critical to addressing such questions. If modes of action, modulatory activities, and temporal influences of hormones on tumorigenic processes could be established, hormonal effects could potentially be separated from chemical effects, which would facilitate broader understanding of mammary tumorigenesis. Indeed, the late Eugene Paynter of the OPP initiated just such a review during the late 1980s. Using Paynter's work as a starting point, Irma Russo accepted the working group's invitation to undertake this critical review of the state of the science and to discuss those factors that might be relevant to resolving these issues.

Mammary Gland Neoplasia

The accompanying report, "Mammary Gland Neoplasia in Long-term Rodent Studies," by Russo and Russo (*1*) is the result of this effort. It carefully examines the developmental biology of the mammary gland in rodents and in humans in the absence of known exposure to xenobiotic chemicals, noting that there are distinct anatomical and developmental differences between the mammary glands of rats, mice, and humans. These differences become more apparent when the influences of parity, lactation, gland involution, and other physiologic processes on the tissue are considered.

When the influence of reproductive and other hormones is examined, the differences between the mammary glands of rodents and humans are even more evident. Rodent studies employing ovariectomy and hormonal replacement therapy underscore the importance of the endocrine milieu in mammary gland development and involution.

Hormone-dependent neoplasia varies significantly between species and among strains within a species. The incidence of mammary tumors among untreated female rats is variable, 20%–60% after 2 years (*2*). In contrast, the overall lifetime incidence of breast cancer among women in the United States is about 12% (*3*). Female rats and humans develop mammary tumors of unknown etiology that are hormonally regulated to various degrees. Although these types of mammary tumors in mice also are susceptible to endocrine-mediated regulation, most are associated with infection by mouse mammary tumor virus. Rodent mammary gland tumors seldom metastasize, reflecting another fundamental difference between most human breast cancer and rodent mammary tumors.

From an experimental perspective, the long latency and variable incidence of mammary tumors among untreated female rats limits the practical utility of studying such tumors as models of human disease. Genotoxic agents such as dimethylbenz(*a*)-anthracene (DMBA), *N*–methyl–*N*–nitrosourea (MNU), and 3–methylcholanthrene (MCA) are among the most commonly used compounds to elicit mammary gland tumors in rodents. These agents are thought to act as initiators within the context of the multistage model of carcinogenesis. Tumor promotion in mammary tissue may be hormonally mediated because the expression of tumorigenicity following initiation with such genotoxic agents is determined, at least in part, by age-related endocrine kinetics.

In mice, tumors induced by such compounds have a long latency and require multiple exposures. In contrast, such tumors can be elicited in rats after a single exposure during a critical period in postnatal development and have a much reduced latency period. The incidence and number of chemically induced tumors vary with dose and route of exposure and between different strains of rats administered identical doses by identical routes. Although there are certain anatomic, histologic, and developmental similarities between the mammary glands of rats and humans, there is little

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or no direct evidence that these or other genotoxic agents do or do not induce breast cancer in women. However, such compounds can induce mutations and/or neoplastic transformation of human breast epithelial cells *in vitro*.

Epidemiological studies have generally failed to identify specific chemical exposures or other factors that contribute substantively to the likelihood of developing breast cancer. Because breast cancer risk is associated with nulliparity, late first full-term pregnancy, early menarche, late menopause, and exposure to ionizing radiation at a young age (*4*), some have suggested that breast cancer may be initiated by exposure to carcinogenic compounds during a narrow window of opportunity extending from menarche until the time of the first full-term pregnancy (*5*). Studies of chemical exposures of susceptible subpopulations of women, e.g., those expressing the BRCA1 (*6*) or BRCA2 (*7*) gene products, may provide the opportunity to better understand the relationship between human breast cancer and chemical exposure.

Underlying all such generalizations is an extensive and complex literature characterizing the modulatory effects of reproductive and other hormones on all aspects of mammary gland growth, development, and disease. A plethora of endocrine interactions can permanently affect mammary gland structure, organization, and function as well as altering, at least in rodents, the response to exposure to mammary tumor-inducing chemicals. Ovarian and placental hormones, pituitary and thyroid hormones, androgens, and insulin have all been demonstrated to affect the tumorigenic responses of rats exposed to genotoxic mammary carcinogens. Similarly, various growth factors, e.g., inhibin, fibroblast growth factors, and other cytokines, can modulate the development and growth of chemically induced mammary tumors in rats. Although the complex hormonal environments associated with the rat estrous cycle and the human menstrual cycle differ in detail, the modulatory effects of rat hormones on mammary tumor development and growth raise the possibility of similar hormonal modulation of human breast cancer. Indeed, studies of women undergoing ovariectomy, estrogen replacement therapy, and tamoxifen therapy as a treatment for breast cancer provide evidence of endocrine involvement in human disease.

Relevance for Risk Assessment

The impetus for the review by Russo and Russo (*1*) was to evaluate the relevance of findings of chemically induced mammary tumors in rodents for human health risk assessment. To address this issue, it is appropriate to consider their findings in light of the questions and issues raised with the working group.

Is a dose-related increase in mammary tumor incidence in rodents a credible indicator for potential human risk? In the absence of evidence to the contrary, the EPA considers findings of mammary tumors in chemical-exposed rodents indicative of the potential of the chemical to cause cancer in humans (e.g., breast cancer in women). Although the report by Russo and Russo (*1*) identifies certain differences as well as similarities between the mammary glands of rodents and humans, these findings do not substantively challenge the EPA's current assumption. The paucity of human data with respect to chemical exposure precludes determination of whether such findings are truly predictive of human risk. The issue is further confounded by the observation that most of the chemicals that elicit mammary gland tumorigenesis in rodents are genotoxic agents and represent only a small fraction of the compounds to which women are likely to be exposed. From a risk assessment perspective, consideration of factors including dose response, route of administration, and mode/mechanism of action will influence assessment of the relevance of the results of the animal studies for predicting the response of women. Relevance also will be influenced by the type, incidence, number, and size of the chemically induced tumors and the occurrence of tumors in other tissues and organs.

Is the mechanism of mammary tumor development partially or completely mediated by hormones? Russo and Russo (*1*) indicate that mammary tumorigenesis can be modulated by hormones. Although there is evidence that ovariectomy and the subsequently ablated hormonal microenvironment can inhibit tumor development and growth, the synergistic, agonistic, and antagonistic relationships among the various hormones that are known to influence rodent mammary tumors suggest that they are modulatory in effect. There is clearly a need to better understand the basis for such modulatory effects and the implications that hormonally modulated rodent mammary tumors have for breast cancer in women.

Does carcinogenic response operate with or without a threshold? The report by Russo and Russo (*1*) does not address this issue. This concern reflects the observation that estrogen and other hormones which modulate mammary tumorigenesis operate through receptors. In at least some ligand/receptor systems, a threshold number of receptors must be occupied to elicit a full biologic response. Whether or how this applies in the consideration of chemically induced mammary tumors remains to be determined. Although mammary carcinogens may act through the estrogen or other hormone receptors, endocrine disruption may occur during hormone synthesis, secretion, or transport, or at the level of second messenger activation or function (*8*). The uncertainty in our understanding of the relationships between the estrogen receptor and its various agonistic and antagonistic ligands is illustrative of the complexity of this issue. For example, the responses of cells bearing mutated estrogen receptors may be stimulated by tamoxifen but inhibited by estradiol (*9*).

How do various routes of exposure affect rodent mammary tumorigenesis and how should such information be used to select an appropriate animal model for human risk assessment? Various routes of administration have been used in the study of rodent mammary tumorigenesis. In the case of DMBA, tumors are typically induced by intragastric administration, while MNU-induced tumors can be induced by intravenous or subcutaneous administration. However, carefully selected doses of DMBA and MNU administered by different routes to animals of a single strain elicit similar incidences of tumors with similar latency periods. Such observations suggest that various routes of exposure may be acceptable for hazard characterization studies, but the evidence is limited with respect to the number and types of compounds considered. Ideally, the route(s) of exposure used during rodent studies to assess the carcinogenic potential of chemicals should reflect the most likely or significant route of potential human exposure. Given the dearth of information about chemically induced human breast cancer, it seems premature to select a single animal model or route for use in hazard identification studies. Even suggesting combinations of models and routes would be more speculative than informed.

What information and methodology should be used to estimate potential human risk? Clearly there is a need to make better use of human data by designing better studies or asking better questions of existing databases (*10*). Occupational exposure studies may help us to identify and understand some aspects of chemically induced breast cancer. Perhaps more information can be extracted from rodent carcinogenicity studies that would facilitate interpretation of the results. Better characterization of test compound pharmacokinetics and pharmacodynamics would enhance under-

standing. Outside of the current 2-year carcinogenicity bioassay, further animal studies of the etiologic factors associated with carcinogenicity in various test species may lead to improved assessment of breast cancer risk in women (*11*). For example, normal human breast tissue might be transplanted into immunologically incompetent rodents to determine whether exposure to certain chemicals elicits the tumorigenic response observed in normal mice exposed to the same chemicals. Performing biologically based dose–response studies in rodents following full-term pregnancy, lactation, and mammary gland involution might illuminate the apparent protective effects of pregnancy and lactation in humans. Testing chemicals in multiple strains of rodents, including those with low and high incidences of spontaneous mammary gland neoplasms, may elicit greater appreciation for, and understanding of, variability in the tumorigenic response. Pharmacokinetic studies performed using human breast tissue *in vitro* and with rodents both *in vivo* and *in vitro* may allow the use of the parallelogram approach to risk assessment (*12*). *In vitro* studies of the molecular biology and biochemistry of hormone receptors with respect to measurable physiologic endpoints, e.g., cell proliferation or cell activation, are valuable in understanding and validating the use of *in vivo* and *in vitro* estrogen screening assays (*13*). Such studies could provide more satisfying answers to the simply stated but complex questions raised earlier.

Russo and Russo (*1*) bring together a wide array of observations and information about mammary gland tumors in rodents and humans. The resulting synthesis may help to channel research efforts and resources along lines that will ultimately provide insight into the difficult issues that confront the risk assessment community relative to the interpretation of the findings of mammary tumors in rodents.

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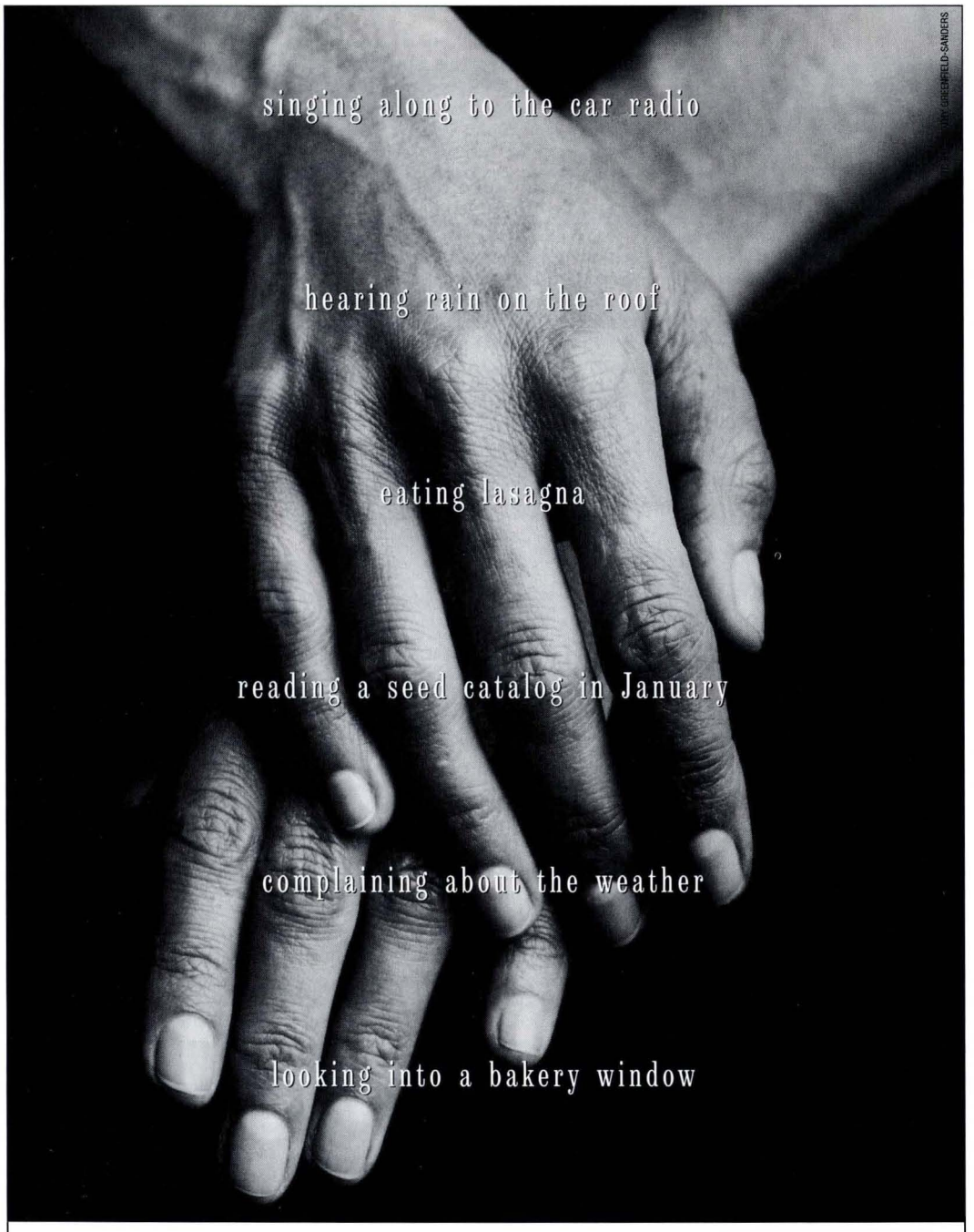

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Forum

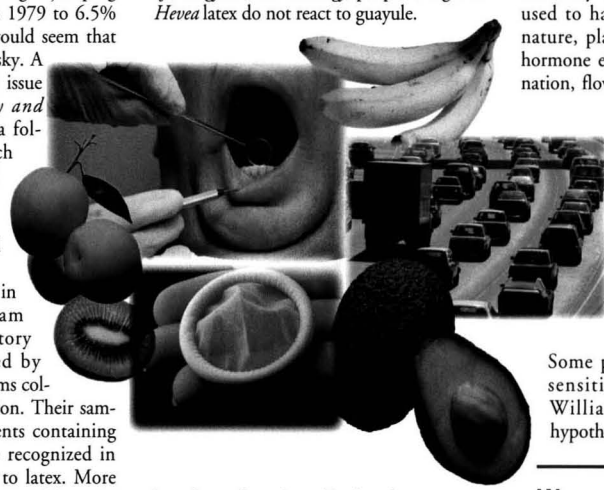
Latex Allergies Stretch Beyond Rubber Gloves

With the number of latex allergies jumping from a single case report in 1979 to 6.5% of Americans in 1994, it would seem that latex is dropping from the sky. A report in the January 1995 issue of the *Journal of Allergy and Clinical Immunology* and a followup article in the March 1996 issue of *Chest* find that urban air does contain latex particles, shed into the environment by normal tire wear.

Along a four-lane road in Denver, Colorado, a team from the Allergy Respiratory Institute of Colorado led by immunologist Brock Williams collected particulate air pollution. Their samples included black fragments containing latex proteins, which were recognized in tests by human antibodies to latex. More than half (58%) of the airborne debris was small enough to be inhaled into the lungs. Airborne latex could partially explain the rise in latex sensitization. "Until we know more about it," says Williams, "it's difficult to weigh the importance of airborne latex to the overall problem. But it's probably in every city in the world with cars."

Proteins in the sap of the Brazilian rubber tree (*Hevea brasiliensis*)—used to produce latex—trigger latex allergies ranging from annoying skin rashes to anaphylactic shock. The surge in latex allergies coincided with increased global demand for latex gloves in the late 1980s to prevent the spread of HIV and hepatitis. Manufacturing shortcuts, such as skipping washing steps that remove latex proteins, contributed to the epidemic that first struck medical personnel exposed to latex-containing supplies. Recent studies find that latex allergies affect up to 14% of healthcare workers.

Because 57 latex proteins are known allergens, removing them is impractical. So is avoiding rubber, which is found in 40,000 items, including 300 medical products. To circumvent latex allergies, USDA researchers at the Western Regional Research Center in Albany, California, have developed hypoallergenic rubber from guayule (*Parthenium argentatum*), a shrub native to the southwestern United States. In clinical trials to be published in the *Journal of Allergy and Immunology*, people allergic to *Hevea* latex do not react to guayule.



Latex in our lives. A combination of exposures to proteins found in latex products and certain foods may be the cause of a rise in latex allergies.

The USDA team, headed by plant physiologist Katrina Cornish, created processing methods to extract guayule and manufacture rubber products with superior resilience, strength, and elasticity. The USDA granted an exclusive license for the patented technology to American Medical Products in Burlingame, California. The first guayule products will be medical supplies for latex-sensitive patients and medical workers. Cornish is continuing genetic studies to improve latex yields and adapt guayule for growth in diverse climates.

Up to half of latex-sensitive patients also show allergic reactions to certain fruits including avocados, bananas, kiwifruits, papayas, and peaches, according to a study published in the October 1994 issue of the *Annals of Allergy*. "These plants contain the same proteins that are allergens in latex," says Dennis Ownby, director of pediatric allergy research at Henry Ford Hospital in Detroit, Michigan. People with fruit allergies should warn physicians before undergoing procedures, he says, because anaphylactic reactions from contact with physicians' latex gloves have occurred in those with mild fruit allergies.

Williams, now director of research at IBT Reference Laboratory in Lenexa, Kansas, theorizes that this fruit/latex cross-reactivity is worsened by ethylene, a gas used to hasten commercial ripening. In nature, plants produce low levels of the hormone ethylene, which regulates germination, flowering, and ripening. But when forced to ripen quickly under high ethylene concentrations, plants produce allergenic wound-repair proteins, which are similar to wound-repair proteins made during the tapping of rubber trees. Sensitive individuals who ingest the fruit "get a higher dose and worse reaction," suggests Williams. Some people may even first become sensitized to latex through fruit, Williams suggests, although this hypothesis remains to be proven.

Women's Health Initiative

Attempting to make up for the historic exclusion of women from clinical research, Bernadine Healy, then head of the National Institutes of Health, launched the Women's Health Initiative (WHI) in 1991. The WHI is an ambitious effort to evaluate several strategies aimed at preventing heart disease, breast and colorectal cancer, and osteoporosis in postmenopausal women.

The initiative is divided into three parts. The first part encompasses three clinical trials evaluating the benefits of a low-fat diet, hormone replacement therapy, and calcium and vitamin D supplementation, respectively.

The second part of the initiative, an observational study, runs simultaneously with the clinical trials. Participants are followed for 8 to 12 years while investigators track a wide range of factors to determine the relationship of these variables to disease outcome. Participants regularly fill out questionnaires on items such as diet, environmental exposures, exercise, and smoking. In addition, clinics store participants' blood samples for later evaluation. Both the clinical and observational studies began recruiting volunteers in 1993.

The third part of the study, a collaborative venture with the Centers for Disease Control and Prevention (CDC), funds a variety of disease prevention programs at several university-based centers nationwide. With the particular goal of including women of diverse races and lower socioeconomic status, these projects focus on such issues as improving delivery of diabetes care, reducing cardiovascular risk among black women, and measuring physical activity in women. This arm of the initiative began in 1995 and will run on a five-year funding period.

To date, approximately 65,000 women have enrolled in the observational and clinical trials at 40 centers around the country. The director of the initiative, Loretta Finnegan, says the investigators aim to have 164,500 participants by 1998. The study will be completed in 2005, at which point researchers will analyze data. They expect to provide results by 2007.

This is the largest study of women ever undertaken and the numbers involved can become overwhelming. To manage the project on all levels, the NIH established one central coordinating center in Seattle, Washington. Staff at the center manage all data from that location, aided by a computer network. "All of our sites are connected all the time by a network," explains Garnet Anderson, a project director for data coordination at the center. Thus, Anderson can freely access data from all 40 clinical centers.

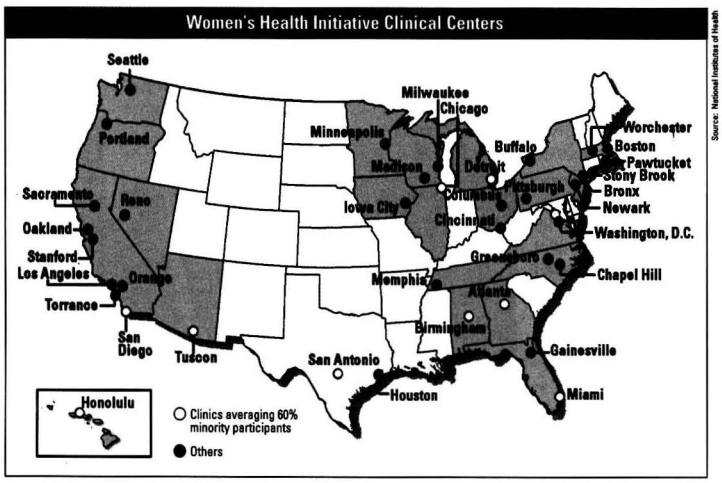
Because the initiative extends over such a long period, the scientists must continually reevaluate the research protocol and integrate new data as they become available. Judith Ashley, a study investigator and assistant professor in the Department of Medicine at University of California at Los Angeles, is impressed with the adaptability built into the study. As an example, when recent research results indicated that women who have not had a hysterectomy should not take estrogen without progesterone because of increased incidence of cervical dysplasia, the investigators responded quickly and changed the study design.

The WHI is approximately one-third of the way through its projected life span. So far, outside organizations are optimistic about the project. "We are pleased that NIH is taking on a comprehensive study of women's health," said Lisa Cox, program director for the National Women's Health Network, a public interest group devoted to giving women a stronger voice in the nation's healthcare system. "We hope the study will finally provide answers to questions that have been posed for a very long time—questions such as the relationship between hormone replacement therapy and breast cancer."

According to Luella Klein, director of women's health issues for the American College of Obstetrics and Gynecology, the initiative has already provided benefits by calling attention to gender in research. "Partly because of the uproar that was generated [before the creation of the WHI, when the NIH realized that only about 13% of research funding was going to female-specific research], there are data now coming out that never would have come out before, because nobody ever bothered to divide data by men and women."

While Klein is enthusiastic about the initiative, she voices concern about its size. In this time of budget cuts, such a mammoth endeavor makes an easy target. Klein says she has seen other large studies discontinued prematurely and worries that the WHI could be another victim. "I hope they make it to the end and that modifications are made as needed," she said.

Since 1993, women ranging in age from 50 to 79 have been signing up to participate in this landmark study. Many may not live to see the final results. But as Ashley comments, "They're concerned about their children and their grandchildren. They [participate in] the examinations and the trial because they care about themselves and other women."



National Strategy on Endocrine Disruptors

Mounting scientific evidence and recent media attention have heightened public awareness about endocrine disruptors, chemicals that mimick or interfere with the actions of hormones. Exposures to high doses of these chemicals, such as organochlorine compounds including DDT, PCBs, and dioxins, can be strongly associated with declines in offspring, increases in cancers, and reductions in reproductive functions in wildlife and humans. Because the various research projects on endocrine disruptors conducted by federal agencies lack cohesion, the government is working to coordinate and integrate research needs and goals.

The White House Office of Science and Technology Policy's Committee on Environment and Natural Resources (CENR) has created an interagency task force to develop a national strategy for research on endocrine disruptors. The goals of the working group include identifying key scientific questions about endocrine disruptors; developing an inventory of current federal research programs on endocrine disruptors; identifying research gaps in ongoing programs and assessing research needs to facilitate coordination across the federal government; initiating outreach efforts to public interest, private sector, and international groups; and promoting educational activities to disseminate information to the scientific community. The working group is chaired by Lawrence Reiter, director of the EPA's National Health and Environmental Effects Research Laboratory. George Lucier, director of the Environmental Toxicology Program of the NIEHS, serves as vice chair for human health and Michael Mac, program manager for status and trends for the National Biological Survey of the Department of the Interior, serves as vice chair for ecology.

Research Needs Identified for Endocrine Disruptors

Research Area	Research Need
Basic Research	Dissection of direct immune–endocrine interactions Understanding of cellular and molecular mechanisms Sensitive, inexpensive, and widely available analytical tools Understanding the biological significance of subtle low-dose effects Identify and characterize critical windows of susceptibility across species Characterize source of population heterogeneity in dose responsiveness (age, gender, nutrition, etc.)
Exposure Determination	Rapid and inexpensive exposure monitoring methods for use in wildlife populations Increased monitoring efforts to identify status and trends of EDs Environmental causes of liver, brain, and lung cancers
Mixtures	Research to address the additivity principle for mixtures *In vitro* and *in vivo* studies of complex mixtures to evaluate validity of TEQs Identification and testing of environmentally relevant mixtures Systematic evaluation of species, cellular, and age dependent response to mixtures of EDs
Multidisciplinary Studies	Systematic field and laboratory studies focused on critical uncertainties Examination of correlation of effects between wildlife and mammalian models Multidisciplinary studies on effects of endocrine disruption Examination of multiple endpoints and multiple tests of ED action
Risk Models	Statistical models to predict risk from exposure and effects Improvements in study design Evaluation of toxicity and mechanistic endpoints across species Toxicokinetics and toxicodynamic studies of environmentally relevant chemicals Quantitative dose response models based upon receptor theory/biochemical interactions Establishment of training programs in biomathetics for BBDR model construction

Source: Adapted from Kavlock RJ et al., Research needs for the risk assessment of health and environmental effects of endocrine disruptors: a report of the U.S. EPA-sponsored workshop. *Environ Health Perspect,* 104(Suppl 4):715–740 (1996).

"Although trends in hormonally related diseases have not been clearly linked to environmental chemicals, it is probable that endocrine disruptors are contributing to human diseases and dysfunction. The question then becomes how much they are contributing," Lucier said. "What is needed is high-quality basic and applied research to examine a number of critical areas."

Many individual federal agencies have been working to develop research needs and priorities. In April 1995, the EPA sponsored an interdisciplinary workshop on the human health and ecological effects of endocrine disruptors to identify research gaps and determine future research priorities. According to the workshop summary, attendees concluded that research should focus primarily on effects on development of reproductive capability, on improved exposure assessment, and on the effects of mixtures. (See conference summary report, *Environmental Health Perspectives,* August 1996.)

The goal of the CENR working group is to evaluate and harmonize the needs and priorities of the various agencies. Lucier says that an interagency approach is important to the development of a national strategy. "The most effective way to utilize basic research to make sound policy decisions is to develop interagency approaches that maximize its application to multiple agencies," he said. "We will develop cross-cutting approaches useful to all agencies." An interagency approach also maximizes communication, Lucier added.

The CENR group has worked to put together a document prioritizing federal research needs. According to a preliminary draft of the strategy, the highest priority is determining the effects of endocrine disruptors on developing organisms, particularly on the reproductive system. Other priorities include assessing the potential carcinogenic effects and the toxicology of mixtures and assessing the nature and extent of contamination in the area of exposure. The group is also working to develop a comprehensive evaluation of all federally funded research projects on endocrine disruptors. According to Lucier, the group will also focus on how to link scientific activities to public policy decisions. The strategy is due out in September.

Rewarding Cancer Research

Alfred G. Knudson, Jr., and Joseph F. Fraumeni are this year's recipients of the Irving J. Selikoff Award for Cancer Research. Knudson and Fraumeni earned the award specifically for "research on the molecular origins of cancer and its application to the management of populations at high risk," said Sheldon Samuels, vice president for policy studies at the Ramazzini Institute, which was founded by Selikoff to promote occupational and environmental health research. The Ramazzini Institute sponsors the annual award.

Selikoff, who died in 1992, is remembered for his work at New York's Mt. Sinai School of Medicine in linking cancer and other diseases with environmental pollutants such as asbestos. The award consists of a plaque and a monetary prize given from a fund developed by Selikoff at the Ramazzini Institute. "We decided to keep the fund alive," Samuels said, adding that the fund is entirely privately endowed. The award is given to scientists who demonstrate excellence in expanding genetic research on how to repair cancer-causing damage—to prevent cancer from later appearing even though people have been exposed in the past. The award recipients are selected by a panel of officers at the Ramazzini Institute.

P.E. Rogol

Selikoff standouts. Alfred G. Knudson, Jr. and Joseph F. Fraumeni (left to right holding boxes) are the 1996 winners of the Irving J. Selikoff Award for Cancer Research. They are flanked by Philip Landrigan (left) and Arthur C. Upton (right) of the Mt. Sinai School of Medicine.

Knudson, a researcher at the Fox Chase Cancer Center in Philadelphia, Pennsylvania, was chosen for his research on developing models of carcinogenesis. "He is not only a great laboratory scientist, but he happens to be a conceptualizer, a theoretical biologist whose models of carcinogenesis are the basis of much of the research on the interface between the environment and our genetic inheritance," Samuels said. "Knudson was one of the conceptual pioneers who discovered the family of genes associated with retinal glaucoma, which is important in understanding cancer in general, because this same family is important in other cancers."

Fraumeni, who is director of the Division of Cancer Epidemiology and Genetics at the National Cancer Institute (NCI) in Bethesda, Maryland, was given the award for his research in environmental and genetic factors in cancer, and in clarifying the role of genetic susceptibility.

According to Samuels, one of Fraumeni's most significant accomplishments has been the development of a program at the NCI in genetics and epidemiology. The program, links molecular biology, epidemiology, and prevention. "We are just now beginning to see the fruits of [Fraumeni's] work," Samuels said. "He deserves to be recognized for his achievement in pulling that program through." The awards were presented 21 May 1996 at the Mt. Sinai School of Medicine. "It's a great honor," said Fraumeni. "Both Dr. Knudson and I were delighted to receive the award given in memory of Dr. Selikoff, who contributed so much to the area of environmental cancer research.

New Evidence on Sperm Counts

In 1992, a Danish research team led by Niels Skakkebaek at the National University Hospital in Copenhagen published in the *British Medical Journal* the results of a meta-analysis of sperm count studies covering 50 years. The team concluded that human sperm counts had declined by as much as 50% during that time. Since then, many environmentalists, journalists, and reputable scientists have relied on this study to assert that environmental toxins are having an adverse effect on male fertility. Of special concern are both natural and manmade compounds called endocrine disruptors.

Three reports in the May 1996 issue of *Fertility and Sterility* challenge the assertion that sperm counts are declining worldwide. Sperm quality is measured by

EHPnet

Food, Drugs, and More

One-fourth of the money spent each year by Americans is spent on products regulated by the U.S. Food and Drug Administration; this amounts to over $1 trillion worth of goods—from eyeshadow to AZT—that must meet FDA guidelines for product safety and quality. Currently, all foods and drugs (for both animals and people), cosmetics, and radiation-emitting equipment are FDA regulated, and the agency seems poised to add the $2.8 billion tobacco industry to this list. From proposing tobacco regulation to researching the effects of the "morning after" pill, this obligation requires that the FDA study and debate some of the most divisive issues facing the nation. Part of the continuing dialogue between the FDA and the public consists of the agency's home page, located at **http://www.fda.gov/fdahomepage.html**, the entranceway to a well-designed resource on FDA programs and regulations.

From the home page, a user can choose one of eight icons to link to the home pages of specific FDA programs, read the FDA news, or change to another directory. Despite the aesthetic appeal of the site, however, the complex structure of the FDA can make it difficult to find the particular information being sought. The FDA search engine, which can be accessed from the bottom of the home page, offers another way to find FDA documents on specific subjects. Also located on the home page is a Comments link that allows users to correspond with the FDA via electronic mail.

Through the FDA News link, users can find information such as the text of proposed tobacco regulations and guidelines for protecting children from lead poisoning. The results of recent research studies are also presented here along with current press releases and product recalls (under the Latest FDA Enforcement Report link). This site also offers a calendar of upcoming meetings and symposia and a searchable archive of past press releases, papers, testimonies, reports, articles, and major speeches. Another link brings up the latest issue of *FDA Consumer* magazine, with full text of articles and back issues.

The Foods icon links users to information from the Center for Food Safety and Applied Nutrition, along with external biology-related resources that can be accessed from the CFSAN page via the Info link. Other links connect users to consumer advice on food handling, information on food additives like olestra and MSG, and facts about foodborne illnesses. The Bad Bug Book, which can be found under the Foodborne Illness link, provides descriptions of common pathogens as well as information about disease outbreaks and symptoms.

The Center for Drug Evaluation and Research site, linked through the Human Drugs icon, is evolving into a comprehensive resource on drug composition and regulation. Information on how the FDA screens new drugs, approves them for market, and ensures accuracy in testing, formulation, and labeling can be reached from the CDER home page by selecting the About CDER icon and following the Office of Compliance link to the Annual Report FY 95. Also within the annual report are pages on FDA drug recalls and a directory that lists FDA personnel by their area of expertise. The Division of Over-the-Counter Drug Products maintains lists of drug name changes and will soon host a complete database of active drug ingredients. The Drug Info icon on the CDER home page brings users to a list of approved drug products with therapeutic equivalence evaluations along with descriptions of drugs that have been approved in the last three years. Guidance documents for the drug manufacturing industry can be reached from the CDER home page via the Regulatory Guidance link.

The links to other FDA programs—Biologics, Devices and Radiological Health, Animal Drugs, Cosmetics, Field Operations and Imports, and Toxicology—all provide data pertinent to those particular fields. For instance, the Center for Biologics Evaluation and Research (Biologics link), which oversees the manufacture and sale of vaccines and blood products, provides a link to the Vaccine Adverse Response Reporting System. The Center for Devices and Radiological Health provides a useful list of safety alerts and advisories under the Program Areas link, and the National Center for Toxicological Research can be reached through the Toxicology icon.

four factors: motility, morphology, semen volume, and sperm numbers. One of the studies, by C. Alvin Paulsen and colleagues at the University of Washington School of Medicine, looked at data from 500 Seattle-area men between 1972 and 1993 who met criteria for normal general and reproductive health. Results showed no decrease in sperm quality by any of the four standard measures.

Another study, by Harry Fisch and colleagues in the Department of Urology at the Columbia-Presbyterian Medical Center in New York, was based on data derived from the general U.S. male population. Using the records of the three oldest sperm banks in the United States, the Fisch team found that instead of a decline, results showed a statistically significant increase in sperm counts in the last 25 years (from 77×10^6/ml in 1970 to 89×10^6/ml in 1994). Fisch attributes the Danish study's conclusions to problems with nonuniformity of data and other methodological considerations.

The Fisch study did note marked geographical differences among the three data sources, with New York having the highest sperm counts and Los Angeles having the lowest. No explanation for this disparity was offered, and Fisch is currently investigating the issue.

Zoologist John Peterson Myers believes that Fisch's conclusions are "statistically challengeable" but agrees that "the emerging geography of sperm count change" deserves more research attention. In the genetic melting pot of the United States, he says, geographic variations point toward environmental rather than ethnic factors.

In certain geographic areas including Denmark, there has been a marked increase in male reproductive disorders such as testicular cancer, undescended testes, and hypospadia. Studies in France, London, and Scotland also suggest that sperm quality has declined in these areas in the last two decades. Skakkebaek believes these problems are connected to increased exposure of the male fetus to estrogens. There is also strong evidence from animal studies that suggests that environmental toxins, especially synthetic estrogens, can cause reproductive abnormalities. A new book, *Our Stolen Future,* written by World Wildlife Fund researcher Theo Colborn with journalist Diane Dumanoski and Peterson Myers, collects evidence from many sources to bolster the claim that environmental toxins are threatening reproductive health in many species including humans. The authors note that some 51 families of synthetic chemicals have been identified as hormone disrupters, including PCBs, dioxins, and furans.

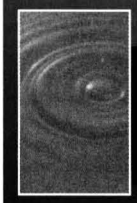
Of the information in *Our Stolen Future,* Fisch warns that "you cannot extrapolate from animals to humans," and that while "there are definite environmental risks, . . . it's anecdotal evidence." Toxicologist Stephen Safe of Texas A & M University notes that the places where sperm counts have declined are "all Western world places where there's no apparent or obvious chemical gradient [known presence of unusual concentrations of chemicals] that I can see. These [new studies] would suggest that there are regional problems. We don't understand them, and we may want to come up with new hypotheses."

Despite their criticism of what they deem environmentalist alarmism and of the methodologies in earlier studies, even skeptics do not deny the general idea that human reproductive health may be threatened by environmental chemicals. Don Wolf of the Oregon Health Sciences University Andrology Laboratory believes the more extreme environmentalist claims are "trying to skew the data to support the hypothesis. The available data are simply insufficient to allow any hard and fast decisions." But he adds that it is "important that we don't completely ignore these concerns."

Errata

In the Forum article *Fueling the Gas Debate,* on page 689 of the July 1996 issue, Dr. Myron Mehlman was incorrectly identified as a staff scientist at the Environmental and Occupational Health Sciences Institute at Rutgers University. Dr. Mehlman is an adjunct professor of environmental and community medicine at the Robert Wood Johnson Medical School at the University of Medicine and Dentistry of New Jersey.

The NIEHS News article *BRC Criteria Revised,* on page 824 of the August 1996 issue, incorrectly stated that Donna Shalala, secretary of the Department of Health and Human Services, has approved a revision of the criteria for listing a substance in the Biennial Report on Carcinogens. The statement should have read that the Secretary "is expected to approve" such a revision.



International Symposium on Waterborne *Cryptosporidium*

March 2–5, 1997
Newport Beach, California

Cryptosporidium is a significant concern to the water industry. Industry professionals, along with public health experts, have been focusing their research efforts in many areas including source water protection, water treatment processes, detection methods, risk assessment, health effects and treatment, and communications. This symposium will provide a forum for the exchange of information on the most recent *Cryptosporidium* research occurring worldwide. In addition, the symposium will provide direction for identifying future research needs.

Technical Program
The symposium will consist of 3 days of papers on a variety of subject areas related to waterborne *Cryptosporidium*, including, but not limited to:

- Sources/Occurrence
- Disinfection effectiveness
- Surveillance/epidemiology
- Source protection
- Detection methods
- Regulatory framework
- Risk assessment
- Communications
- Treatment approaches
- Lessons learned
- Research needs

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Environmental Interactions at Harvard

HARVARD UNIVERSITY
KRESGE CENTER FOR ENVIRONMENTAL HEALTH

Since 1854, when John Snow removed the handle from the Broad Street water pump and thereby halted a London cholera wave, public health researchers have concentrated on the problems of crowded urban conditions. The Kresge Center for Environmental Health has followed that tradition by working to understand the problems of cities and proposing standards and measures to protect public health.

Established in 1958 as the Division of Environmental Health Sciences and Engineering at the Harvard School of Public Health (HSPH), the interdepartmental consortium of researchers and teachers was renamed the Kresge Center in 1966. James Whittenberger was the center's first principal investigator and the architect of environmental science at the HSPH. The center began receiving NIEHS funding soon after that institute's establishment in 1962. In fact, the Kresge Center grant was the second grant awarded by the NIEHS, and is the longest continually awarded grant in the institute's history.

Whittenberger, "one of the giants in environmental science" according to Joseph Brain, director of the center's respiratory biology and inhalation toxicology core, had a strong interest in respiratory physiology but felt that the center should expand its focus beyond his own physiological emphasis. He attracted colleagues such as Benjamin Ferris, a pioneer in occupational respiratory health, and Mary Amdur, who developed early animal models for studying respiratory health. In this fashion, the Kresge Center branched out into areas including toxicology, environmental medicine, radiation biology, and occupational health.

As a result of this expansion, the Kresge Center has initiated and participated in groundbreaking environmental research throughout its history and has continually contributed to public health policy formation, not only in the United States, but also abroad. In addition, researchers at the Kresge Center have devised and implemented a variety of new tools for conducting public health research. Now under the direction of John B. Little, a Simmons Professor of Radiobiology at the HSPH since 1982, the center has five core research programs: radiobiology and experimental carcinogenesis, biochemical and environmental toxicology, respiratory biology and inhalation toxicology, environmental epidemiology, and occupational health.

"The goal of the center is interaction," says David Christiani, a professor of occupational medicine. "It's a conceptual enterprise that involves bringing together departments that wouldn't normally have natural affinity. The center provides an infrastructure to support and nurture those interactions."

The Six Cities Study

The Kresge Center has made some of its strongest contributions to understanding urban environmental health problems through its studies in air pollution. A series of important revelations in urban air composition began in 1974 with the Six Cities Study, which looked at the effects of sulfur oxides and particulate matter in six major U.S. cities with significant fossil fuel air pollution.

Using data from questionnaires and periodic measures of lung function, the Six Cities Study showed that particulate matter had important health effects never before considered. Subsequent studies at the Kresge Center and a number of other centers demonstrated that there was a strong positive correlation between particulate matter and mortality. The relationship has been shown to exist not just in the United States, but in cities in South America, China, and Eastern Europe.

Following the release of the study's results in 1993, recalls David Dockery, an associate professor of environmental science and epidemiology, the American Lung Association brought suit against the EPA to tighten its standards on particulate matter pollution. The resulting Clean Air Act Amendments passed by Congress in 1993 and the EPA staff paper on particulate matter, which will be used to develop new exposure standards, are replete with data from the Six Cities Study.

"The quality and quantity of the data were both very impressive," says Mort Lippmann, a New York University Medical Center professor of environmental science who served on the EPA's Clean Air Scientific Advisory Committee. "This was the largest epidemiologic study of the effect of pollution on individuals that was available. It was done very carefully over a long period of time, and it had to be taken very seriously."

Harvard School of Public Health

A home at Harvard. Located at the Harvard School of Public Health, the Kresge Center is the longest continually awarded grant in NIEHS history.

Six Cities Study data were also cited in the EPA's standards for nitrous oxide and ozone. Numerous foreign countries have consulted the study when reviewing their limits for particulate matter pollution.

The Kresge Center followed the Six Cities Study with more large epidemiological investigations of air pollution and public health. The Twenty-four Cities Study, completed in 1992, looked at the effects of acid aerosols on chronic respiratory symptoms in 4th- and 5th-graders, while the Five Cities Study, underway since 1992, is studying the effects of acid aerosols and ozone on schoolchildren in urban areas.

In addition, Brain points out, center researchers have also devised animal models that mimic various respiratory diseases, such as an animal treated with sulfur dioxide that suffers from chronic bronchitis. Using a particulate matter concentrator that suspends particulates from the air around the center for use in the laboratory, researchers can continue to study the effects of these pollutants.

"The hallmark of the center has been the interdisciplinary approach to health assessment," says Dockery. "We have strong exposure assessment and analytic capabilities with biostatistics and epidemiology. The center makes all this possible."

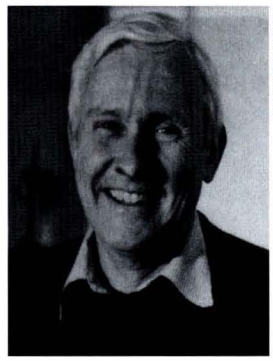
Upstream Epidemiology

Increased awareness of the dangers of particulate matter led to interest in exactly how these pollutants create disease. One line of inquiry has been through the use of biomarkers that signal the early onset of inflammation in response to toxic substances before any clinical changes take place.

"The most common criticism of epidemiology," Christiani says, "is that we arrive on the scene to count the bodies. This so-called 'upstream approach' allows us to look at small physiologic changes and see whether cytokines are being expressed that indicate the beginnings of inflammation and disease."

Samples are being experimentally collected via nasal lavage and assessed for the presence of biomarkers. As Christiani points out, there is very little difference between the nasal and bronchial epithelia, so changes in one should reflect changes in the other. Currently, a respiratory and occupational collaborative group in the center is simultaneously performing nasal lavage and lung washes on workers exposed to fuel ash in a local power plant in order to correlate results of the two assessments. Urine is also collected in order to determine the internal dose.

Using an inductive coupled plasma mass spectrometer, Joe Paulauskis, an assistant professor of molecular biology, can determine whether the cytokine interleukin-8 has been switched on—an early sign of inflammation—in samples taken from workers. Investigations such as these may lead to less expensive, more sensitive measures of worker dose and sensitivity to pollutants.



Harvard School of Public Health

John B. Little

"As fuel burning becomes more and more efficient," Christiani says, "we're seeing a steady increase in the amount and fineness of particulate matter in the atmosphere and in its metallic content. While the health effects of these materials are not fully understood, it's pretty clear that they are dangerous."

An interdisciplinary program headed by Richard Monson, a professor of epidemiology and director of the center's occupational health core, recently received major support from the NIEHS Superfund Program to identify biomarkers of exposure to lead, vanadium, PCBs, and arsenic—all Superfund target chemicals. A common genetic polymorphism in the delta-aminolevulinate dehydratase (ALAD) gene has been associated with elevated lead levels in children. The ALAD gene may provide a useful biomarker for the effectiveness of treatments for lead poisoning. Christiani is also leading a four-year effort, supported by the National Cancer Institute and the NIEHS, to identify genes that can be used as biomarkers for susceptibility to lung cancer. "The center provides infrastructure that allows us to give a thorough look at some very important questions," he says. "As a result, we have a record of turning small pilot investigations into some broad-reaching projects."

Induced Genomic Instability

One of the first steps in preventing cancer is determining the processes that lead to carcinogenesis. Since he was charged with developing the radiobiology and experimental carcinogenesis core in 1965, Little has been working to determine how and why radiation causes cancer.

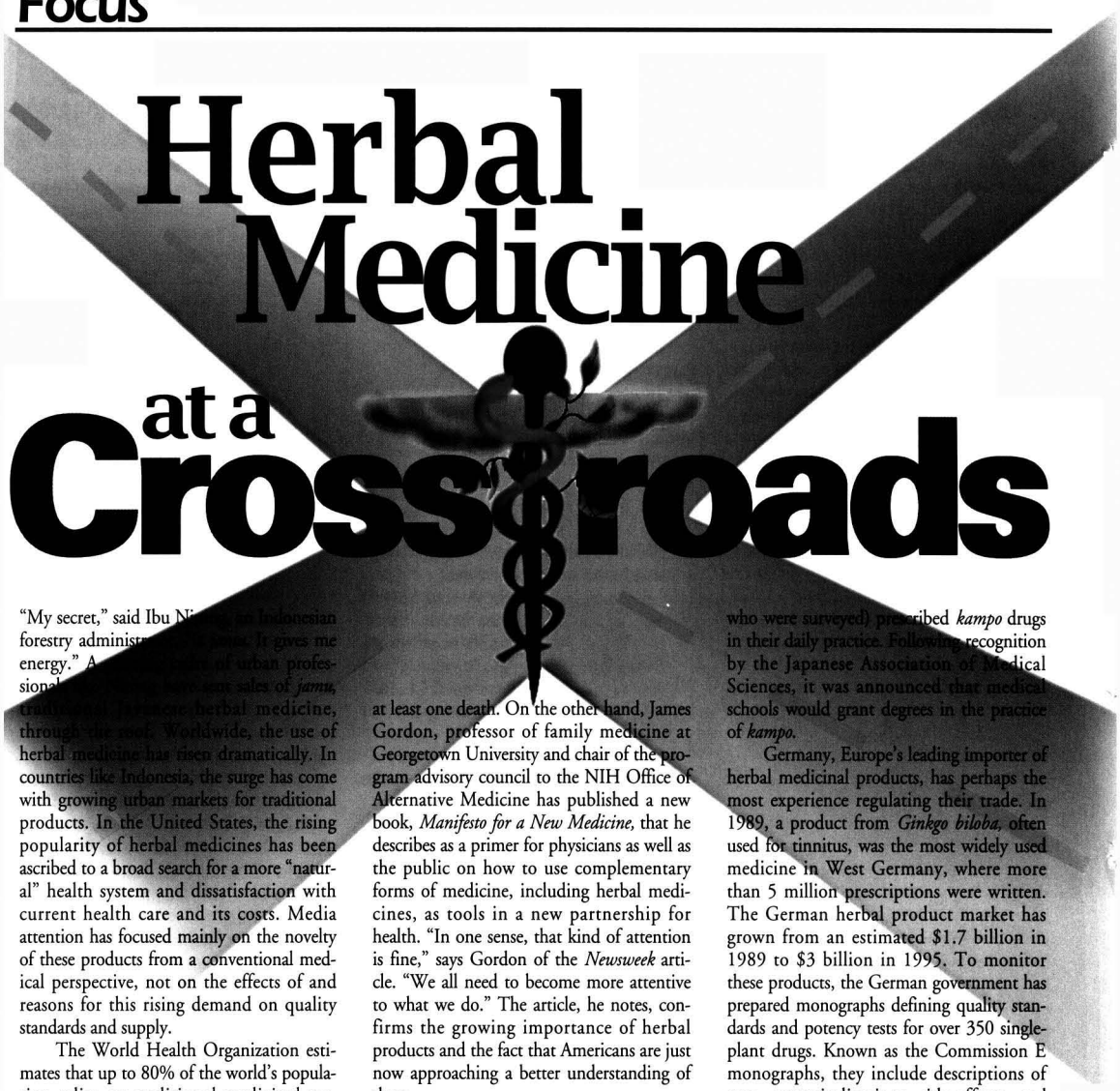
One line of inquiry that has recently borne fruit is the study of induced genetic instability. Little and his colleagues have discovered that some cells, when exposed to radiation, do not immediately experience cancerous mutations. However, the progeny of these seemingly unaffected cells appear to be at increased risk for mutagenesis—in some cases even 40 and 50 cell divisions later. "These findings may have implications for understanding why there is often such a long period between exposure to a carcinogen and cancer induction," Little observes. "We still don't know why, 40 years later, cancers still arise in people who were exposed to radiation from the atom bomb. Induced genomic instability, if we can figure out what it is, may provide the explanation."

Important studies on basic cancer processes are also ongoing in the toxicology core. Leona Samson, a professor of toxicology, has been looking at alkylation damage to DNA and how that damage is enzymatically repaired. Samson recently cloned the gene for ADA, a protein that appears to perform an important DNA repair function in bone marrow. Damage to marrow is frequently the limiting factor in cancer radiation treatment and chemotherapy. Further research on this protein may allow clinicians to protect bone marrow and thus use stronger anticancer measures.

"There is a bidirectional flow of information that occurs under the center that wouldn't occur if it wasn't there," says Armen Tashjian, Jr., a professor of toxicology and director of the center's biochemical and environmental toxicology core. "It brings together different kinds of people doing different kinds of things, and that's a distinct advantage of the center philosophy."

John F. Lauerman

Herbal Medicine at a Crossroads



"My secret," said Ibu Ni[illegible] Indonesian forestry administr[illegible]. It gives me energy." A[illegible] of urban professional[illegible] have seen sales of *jamu*, traditional Indonesian herbal medicine, through the roof. Worldwide, the use of herbal medicine has risen dramatically. In countries like Indonesia, the surge has come with growing urban markets for traditional products. In the United States, the rising popularity of herbal medicines has been ascribed to a broad search for a more "natural" health system and dissatisfaction with current health care and its costs. Media attention has focused mainly on the novelty of these products from a conventional medical perspective, not on the effects of and reasons for this rising demand on quality standards and supply.

The World Health Organization estimates that up to 80% of the world's population relies on traditional medicinal systems—not Western medicine—and in many of these systems herbal medicine plays a key role. In the United States, according to a survey published in the *New England Journal of Medicine* in 1993, nearly one in three Americans surveyed use some kind of alternative medical treatment.

In the past year and a half, U.S. debate over herbal medicines has arisen again, fueled by legislation that moves closer to acknowledging the role of herbal medicines as a complement to Western medicine. On the one hand, a 6 May 1996 *Newsweek* cover story announced the dangers of an unregulated herbal drug industry. The article followed an FDA warning against all products containing ephedra—a stimulant derived from *Ephedra sinica* used to control weight and boost energy— and the report of at least one death. On the other hand, James Gordon, professor of family medicine at Georgetown University and chair of the program advisory council to the NIH Office of Alternative Medicine has published a new book, *Manifesto for a New Medicine,* that he describes as a primer for physicians as well as the public on how to use complementary forms of medicine, including herbal medicines, as tools in a new partnership for health. "In one sense, that kind of attention is fine," says Gordon of the *Newsweek* article. "We all need to become more attentive to what we do." The article, he notes, confirms the growing importance of herbal products and the fact that Americans are just now approaching a better understanding of them.

Regulation

As herbal medicine use has increased, countries have wrestled with the need to regulate these products for public safety. In Japan, where only physicians practicing Western medicine are licensed, the growing popularity of *kampo* (Japanese herbal medicine in the Chinese tradition) has challenged the medical system. *Kampo*, the primary form of medicine in Japan up to the mid-1800s, is less targeted against disease than Western medicine, and in fact, does not assign names to diseases; nonetheless, scientific studies have confirmed the effectiveness of some *kampo* remedies. In the 21 August 1993 issue of *The Lancet*, Catrien Ross reported that 70% of Japan's more than 200,000 doctors (including all doctors aged 30–40 who were surveyed) prescribed *kampo* drugs in their daily practice. Following recognition by the Japanese Association of Medical Sciences, it was announced that medical schools would grant degrees in the practice of *kampo*.

Germany, Europe's leading importer of herbal medicinal products, has perhaps the most experience regulating their trade. In 1989, a product from *Ginkgo biloba,* often used for tinnitus, was the most widely used medicine in West Germany, where more than 5 million prescriptions were written. The German herbal product market has grown from an estimated $1.7 billion in 1989 to $3 billion in 1995. To monitor these products, the German government has prepared monographs defining quality standards and potency tests for over 350 single-plant drugs. Known as the Commission E monographs, they include descriptions of uses, contraindications, side effects, and dosages.

France has also officially recognized more than 200 medicinal plants and provided specifications governing their sale. To advance the state of herbal medicine, European trade associations formed the European Scientific Cooperative for Phytotherapy (ESCOP) under the auspices of the European Economic Community (EC). ESCOP is publishing a series of plant species monographs for EC marketing authorization.

The British appear to be moving in the same direction. The 22 April 1995 issue of the *British Medical Journal* included an article suggesting that special licensing of herbal medicines for treatment of minor illnesses may be the best way to safeguard public health. Peter A. G. M. De Smet, a Dutch