UNRESOLVED ISSUES IN THE CONFLICT BETWEEN INDIVIDUAL FREEDOM AND GOVERNMENT CONTROL OF FOOD SAFETY

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Unresolved Issues in the Conflict Between Individual Freedom and Government Control of Food Safety

By PETER BARTON HUTT

This paper was presented by Mr. Hutt at the Conference on Public Control of Environmental Health Hazards, New York Academy of Sciences, New York City, June 29, 1978.

FOR OVER 70 YEARS, Congress and the Food and Drug Administration (FDA) have pursued a straightforward and simple policy that no risk can be tolerated in the nation's food supply. The Federal Food, Drug, and Cosmetic Act prohibits any "poisonous or deleterious substance,"[1] and the Food Additives Amendment of 1958 requires that all food additives be proved "safe" before marketing and explicitly prohibits any food additive found to induce cancer in test animals.[2] The FDA, in turn, has pursued this congressional mandate with unflagging determination, and has eliminated from the food supply any ingredient that failed to meet the rigorous statutory standards.[3] Objections to such action, on the ground that it was inhibiting freedom of individual choice, were either ignored or summarily overruled.

In light of this history, one can barely suppress astonishment at the events of the past few months. Congress specifically enacted legislation to permit the continued marketing of saccharin,[4] a food ingredient which the FDA has concluded was in violation of three separate

[1] 21 U.S.C. 342(a)(1).
[2] 21 U.S.C. 348.
[3] See, e.g., 21 CFR part 189, proposed in 38 *F. R.* 20040 (July 26, 1973) and promulgated in 39 *F. R.* 34172 (Sept. 23, 1974).
[4] P.L. 95-203, 91 Stat. 1451 (1977).

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[4] P.L. 95-203, 91 Stat. 1451 (1977).

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safety standards under the Federal Food, Drug, and Cosmetic Act.[5] FDA Commissioner Kennedy, who had staunchly defended the ban on saccharin and opposed the legislation to permit continued use of that ingredient, then defended with equal vigor the right of consumers to exercise an informed and free choice in the marketplace:

"...far from assuming that all the answers lie in Washington and all the directions must be marked 'made in Washington,' we are instead operating on the basis of the principle that the best way to regulate is through imparting knowledge in the understandable way, thus permitting informed individuals to make choices based on wants and desires. This approach is made difficult, and extrinsic regulation made more necessary, first, when knowledge is not imparted; second, where there is a mistrust of the individual citizen's capacity for choice; and third, when the subject of choice is so complex that it is, as a practical matter, impossible for informed choice to operate. It is the task of regulators, no less than educators, to overcome the first difficulty, to refuse accepting the second, and to shrink to the absolute minimum the legitimate area for the third."[6]

Not to be outdone, Federal Trade Commission Chairman Pertschuk, one of the principal proponents of the Consumer Protection Agency legislation and a strong advocate of a wide variety of regulatory laws designed to protect the health and safety of the public, has made the same point:

"'Consumer Protection' is a term that can be put out to pasture for several decades. It smacks of paternalism. For what consumers seek is not 'protection' from a benevolent 'big brother', but participation, Rules of Conduct in the marketplace which enable the consumer to help himself. The consumer wants essential information upon which to base decisions, so that he can fulfill his theoretical role as sovereign of the marketplace—not substituting government decision-making for individual choice; but making individual choice workable."[7]

These developments could not possibly have been foreseen even as short as two years ago.

In papers I delivered in September 1977 at MIT[8] and in February 1978 before the International Academy of Environmental Safety,[9] I explored some of the implications of these developments for the regulation of food safety. In this paper I will complete that analysis, and offer specific suggestions for future food safety policy in this country.

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[5] 42 *F. R.* 1996 (April 15, 1977); 42 *F. R.* 33768 (July 1, 1977).

[6] Kennedy, *Regulation, Self-Regulation, and Knowledge* 15-16 (April 7, 1978).

[8] Hutt, *The Basis and Purpose of Government Regulation of Adulteration and Misbranding of Food,* 33 CCH FOOD DRUG COSMETIC LAW JOURNAL 505, (1978).

I. A No-Risk Food Safety Policy Is Unattainable

Until quite recently, a no-risk food safety policy was widely thought to be an achievable goal. To be sure, there was some recognition of potential hazards of the food supply,[10] but they were not the subject of general public knowledge and were thought to be relatively few in number and controllable through appropriate regulatory measures.

In the past two years, however, there has accumulated substantial scientific evidence that carcinogens and other toxic substances pervade the entire food supply. It is now clear that it is literally impossible to eliminate all carcinogens from our food. Moreover, many of the substances which pose a potential risk are part of long-accepted components of food, and any attempt to prohibit their use would raise the most serious questions both of practicality in implementation and of individual free choice in the marketplace.

Common Carcinogenic Food Components

A partial list of common food components found to be carcinogenic in test animals[11] is sufficient to illustrate this problem:

Benz(a)anthracene in food[12]

Benzo(a)pyrene in food, including charcoal broiled steaks[13]

Benzene, 1, 2 (methylenedioxy)-4-propenyl in rootbeer, sarsaparilla[14]

Benz(e)acephenanthrylene in food[15]

Benzo(j)floruanthrene in food[16]

Bracken fern in greens or salads[17]

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[10] See "Human Health and the Environment—Some Research Needs," *Report of the Second Task Force for Research Planning in Environmental Health Science* 73-110 (1977).

[11] The Food and Drug Administration has also stated that such common food substances as beverage alcohol and aflatoxin (found in peanuts, corn, and milk) are proven human carcinogens. See 38 *F. R.* 10458, 10460 (April 27, 1973); 39 *F. R.* 42748 (Dec. 6, 1974).

[12] Van Duuren et al., *Initiating Activity of Aromatic Hydrocarbons in Two-Stage Carcinogenesis,* J. Nat'l Cancer Inst., *44:* 1167 (1970); International Agency for Research on Cancer, *Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man* (hereafter "IARC") *3:* 45 (1973).

[13] IARC, *3:* 91 (1973) National Institutes of Health, *Survey of Compounds Which Have Been Tested for Carcinogenic Activity* (1961-1967 ed.), (1970-1971 ed.), (1972-1973 ed.).

[14] IARC, *1:* 169 (1972).

[15] Wynder & Hoffman, *The Carcinogenicity of Benzofluoranthenes,* Cancer, *12:* 1194 (1959) IARC, *3:* 69 (1973).

[16] IARC, *3:* 82 (1973).

[17] Price & Pamukcu, *The Induction of Neoplasms of the Urinary Bladder of the Cow and the Small Intestine of the Rat by Feeding Bracken Fern (Pteris aquilina),* Cancer Res., *28:* 2247 (1968).

-- Van Duuren et al., *Initiating Activity of Aromatic Hydrocarbons in Two-Stage Carcinogenesis,* J. Nat'l Cancer Inst., *44:* 1167 (1970); International Agency for Research on Cancer, *Monographs on the Evaluation of Carcinogenic Risk of*

[17] Price & Pamukcu, *The Induction of Neoplasms of the Urinary Bladder of the Cow and the Small Intestine of the Rat by Feeding Bracken Fern (Pteris aquilina),* Cancer Res., *28:* 2247 (1968).

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Cadmium in food, water[18]
Caffeine in coffee, tea, cocoa[19]
Calcium in food[20]
Chloroform in water[21]
Carbon tetrachloride in water[22]
Cycasin in cycad nut[23]
Cyclochlorotine in rice[24]
Dibenz(a,b)anthracene in food[25]
Egg yolk and egg white[26]
Ergot in rye[27]
Indeno(1,2,3-cd)pyrene in food[28]
Isopropyl oils in water and fruit oils[29]
Lactose and maltose[30]
Luteoskyrin in rice[31]
Nickel as a contaminant in food, water[32]
Oil of Calamus as a flavoring agent in food[33]

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[18] Kolonel, *Association of Cadmium with Renal Cancer,* Cancer, *37:* 1982 (1976); IARC, *2:* 74 (1973).

[19] Press Release, *Japan Times,* September 22, 1977, quoting Japanese Cancer Research Inst.

[20] Krook, Lutwak & McEntee, *Guest Editorial: Dietary Calcium, Ultimobranchial Tumors and Osteopetrosis in the Bull,* Am. J. Clinical Nutrition, *22* 115 (1969).

[21] NCI, *Report On The Carcinogenesis Bioassay of Chloroform* (March 1, 1976); IARC, *1:* 61 (1972).

[22] Eschenbrenner & Miller, *Studies on Hepatomas: I. Size and Spacing of Multiple Doses in the Induction of Carbon Tetrachloride Hepatomas,* J. Nat'l Cancer Inst., *4:* 385 (1944).

[23] Crampton & Charlesworth, *Occurrence of Natural Toxins in Foods,* Br. [illegible] Research Inst.

[20] Krook, Lutwak & McEntee, *Guest Editorial: Dietary Calcium, Ultimobranchial Tumors and Osteopetrosis in the Bull,* Am. J. Clinical Nutrition, *22* 115 (1969).

[21] NCI, *Report On The Carcinogenesis Bioassay of Chloroform* (March 1, 1976); IARC, *1:* 61 (1972).

[22] Eschenbrenner & Miller, *Studies on Hepatomas: I. Size and Spacing of Multiple Doses in the Induction of Carbon Tetrachloride Hepatomas,* J. Nat'l Cancer Inst., *4:* 385 (1944).

[23] Crampton & Charlesworth, *Occurrence of Natural Toxins in Foods,* Br. Med. Bull., *31:* 209 (1975).

[24] IARC, *10:* 139 (1976).

[25] IARC, *3:* 178 (1973).

[26] Szepsenwol, *Presence of a Carcinogenic Substance in Hens' Eggs,* Proc. Soc. Exp. Biol. & Med., *37:* 1350 (1958); Szepsenwol, *Carcinogenic Effect of Hens' Eggs as Part of the Diet in Mice,* Proc. Soc. Exp. Biol. & Med., *102:* 748 (1959); Szepsenwol, *Carcinogenic Effect of Egg White, Egg Yolk and Lipids in Mice,* Proc. Soc. Exp. Biol. & Med., *112:* 1073 (1963); Szepsenwol, *Carcinogenic Effect of Ether Extract of Whole Egg, Alcohol Extract of Egg Yolk and Powdered Egg Free of the Ether Extractable Part in Mice,* Proc. Soc. Exp. Biol. & Med., *116:* 1136 (1964).

[27] Nelson et al., *Neurofibromas of Rat Ears Produced by Prolonged Feeding of Crude Ergot,* Cancer Res., *2:* 11 (1942).

[28] IARC, *3:* 178 (1973).

[29] IARC, *3:* 229 (1973).

[30] Japanese J. Cancer Res., *46:* 363 (1955); *48:* 556 (1957).

[31] IARC, *10:* 263 (1976).

[32] Sunderman, *A Review of the Carcinogenicities of Nickel, Chromium and Arsenic Compounds in Man and Animals,* Prev. Med., *5:* 279 (1976); IARC, *11:*

Peanuts, corn products, and milk containing aflatoxins[34]

Polyaromatic hydrocarbons in many plant foods[35]

Pyrrolizidine alkaloids in cereals[36]

Safrole in spices[37]

Selenium in food[38]

Peanuts, corn products, and milk containing aflatoxins[34]

Polyaromatic hydrocarbons in many plant foods[35]

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Tannic Acid in coffee, tea, cocoa[39]

Vitamin D_2[40]

This is merely a tentative list of some food constituents for which the evidence of carcinogenicity is most readily available. Under the Biomedical Research and Research Training Amendments of 1978, as reported by the House Committee on Interstate and Foreign Commerce,[41] the National Cancer Institute will be required to issue an annual report of all known or suspected carcinogenic agents, the nature of exposure and the approximate number of persons exposed to such agents, their relative toxicity, any synergistic action, the level of exposure from food, and the identification of subpopulations expected to be at higher than average risk. The report is intended to assist the public to reduce subsequent exposure to these agents. Accordingly, the public will have available to it in the future a comprehensive list of all potential or known carcinogens occurring in the food supply. Any pretense that food is without risk will thereafter be impossible.

Limitations on Government Protection

Because of the growing realization that all risks cannot be eliminated or even reduced, responsible public officials and scientists have begun to emphasize the limitations of government regulation in protecting the public. Senator Kennedy has pointed out that:

"We must begin educating the public to the reality that there is no such thing as absolute safety. Regulation can never completely and totally protect the

[34] IARC, *10:* 51 (1976).
[35] *Id.*
[36] *Id.*
[37] IARC, *10:* 231 (1976).
[38] 38 *F. R.* 10458 (April 27, 1973); 39 *F. R.* 1335 (Jan. 8, 1974).
[39] National Academy of Sciences, *Toxicants Occurring Naturally in Foods* 329-332 (2d ed. 1973); IARC, *10:* 253 (1976).
[40] Gass & Allaben, *Preliminary Report on the Carcinogenic Dose-Response Curve to Oral Vitamin D_2.* IRC J. Med. Sci., *5:* 477 (1977).
[41] H.R. Rep. 95-1192, 95th Cong., 2nd Sess. 28 (1978).

"Where it was once common to refer to 'no-effect doses' of chemicals and 'safe' doses, it is now more appropriate to speak of 'no-observed-adverse-effect' doses and 'acceptable risk' when describing permissible use or exposure to chemicals."[43]

The Committee recommended that "material should be assessed in terms of human risk, rather than as 'safe' or 'unsafe,'" because: "It is not possible to guarantee a risk-free society; nor is a risk-free society necessarily the best society."[44]

Other Common Risks

Our country has, of course, become accustomed to living on a daily basis with a wide variety of very real and very serious risks. Professor Richard Wilson of Harvard has recently performed a use-

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ful function by quantifying some of these risks, based upon actual mortality statistics.[45] Table I quantifies the annual risk of death to an individual from participating in various sports and recreational activities. Table II provides the annual risk of death to an individual from various common human activities and environmental effects. Table III states the annual risk of death to an individual from common occupations. It is important to appreciate that these risks are real risks, using known mortality figures, and are not estimates or extrapolations. Some of the risks shown in these tables are extremely high.

[42] Kennedy, *Risk/Benefit Decisions and the Public Health,* 124 Cong. Rec. E1310 (daily ed. March 15, 1978). The Acting Director of the FDA Bureau of Foods has stated that:

> "... we should stop pretending that absolute safety for food is possible. It isn't, for there is virtually no food that is without some risk to some person. We should acknowledge and explain this to the public."

Roberts, *The Economic Effects of Government Regulation on the Food Industry and the Consumer* 11 (May 24, 1978).

[43] National Academy of Sciences, *Drinking Water and Health* 24 (1977). See also Kraybill, *Pesticide Toxicity and Potential For Cancer: A Proper Perspective,* Pesticide Control 9 (December 1975).

[44] *Id.* at 57.

[45] Tables I—III are derived from Wilson, Direct Testimony before the Occupational Safety and Health Administration, OSHA Docket No. H-090 (February 1978). The bases for Dr. Wilson's calculations are set out in his testimony.

TABLE I

Annual Risk of Death from Sports and Recreational Activities

		Deaths 1975	Individual Participant Risk/Year
Football	Averaged		4×10^{-5} or 1/25,000

TABLE I

Annual Risk of Death from Sports and Recreational Activities

		Deaths 1975	Individual Participant Risk/Year
Football	Averaged over Participants		4×10^{-5} or 1/25,000
Automobile racing			1.2×10^{-3} or 1/830
Horse racing			1.3×10^{-3} or 1/770
Motorcycle racing			1.8×10^{-3} or 1/550
Power boating			1.7×10^{-4} or 1/5,900
Boxing (amateur)	40 hours/year engaged in sports		2.10^{-5} or 1/50,000
Skiing			3×10^{-5} or 1/33,000
Canoeing			4×10^{-4} or 1/2,500
Rock climbing (U. S.)			10^{-3} or 1/1,000
Fishing (drowning)	Averaged over fishing licenses	343	1.0×10^{-5} or 1/100,000
Drowning (all recreational causes)		4,110	1.9×10^{-5} or 1/53,000
Bicycling (assuming one person per bicycle)		1,000	10^{-5} or 1/100,000

Motor Vehicle (1975)	(Total	46,000	2.2×10^{-4} or 1/4,500
	(Pedestrian (involuntary)	8,600	4×10^{-5} or 1/25,000
Home Accidents (1975)		25,500	1.2×10^{-5} or 1/83,000
Alcohol—cirrhosis of the liver (1974)			1.6×10^{-4} or 1/6,250
Alcohol—cirrhosis of the liver (moderate drinker)			4×10^{-5} or 1/25,000
Air travel: one transcontinental trip/year			3×10^{-6} or 1/330,000
jet flying professor			10^{-4} or 1/10,000
Accidental poisoning—solids and liquids		1,274	6×10^{-6} or 1/170,000
gases and vapors		1,518	7×10^{-6} or 1/140,000
	(involuntary)	8,600	4×10^{-5} or 1/25,000
Home Accidents (1975)		25,500	1.2×10^{-5} or 1/83,000
Alcohol—cirrhosis of the liver (1974)			1.6×10^{-4} or 1/6,250
Alcohol—cirrhosis of the liver (moderate drinker)			4×10^{-5} or 1/25,000
Air travel: one transcontinental trip/year			3×10^{-6} or 1/330,000
jet flying professor			10^{-4} or 1/10,000
Accidental poisoning—solids and liquids		1,274	6×10^{-6} or 1/170,000
gases and vapors		1,518	7×10^{-6} or 1/140,000
Inhalation and ingestion of objects		2,991	1.4×10^{-5} or 1/71,000
Electrocution		1,157	5×10^{-6} or 1/200,000
Falls		16,339	7.7×10^{-5} or 1/13,000
Tornados		160	5×10^{-7} or 1/2,000,000
Hurricanes	(Average over (several years	118	4×10^{-7} or 1/2,500,000
Lightning		90	4×10^{-7} or 1/2,500,000
Air pollution (total U. S.) estimate (sulphates)		30,000	1.5×10^{-4} or 1/6,700
Vaccination for small pox (per occasion)			3×10^{-6} or 1/330,000
Living for one year downstream of a dam (calculated)			5×10^{-5} or 1/20,000

TABLE III

Annual Occupational Risk of Death

	Number of Fatalities (in 1975 unless stated)	Individual Risk/Year
Mining & Quarrying (accident only)	500	6×10^{-4} or 1/1,700
Coal mining—accident (average 1970-74)	180	1.3×10^{-3} or 1/770
—black lung disease (1969)	1,135	8×10^{-3} or 1/770
Agriculture—total	2,100	6×10^{-4} or 1/1,700
—tractor driver (one driver/tractor)		1.3×10^{-4} or 1/7,700
Trade	1,200	6×10^{-4} or 1/1,700
Manufacturing	1,500	8×10^{-5} or 1/12,500
Service	1,800	9×10^{-5} or 1/11,000
Government	1,100	1.1×10^{-4} or 1/9,100
Transportation & Utilities	1,600	3.3×10^{-4} or 1/3,000
Airline Pilot		3×10^{-4} or 1/3,300
Truck driver (one driver/truck)	400	10^{-4} or 1/10,000
Jet flying consultant & professor		10^{-4} or 1/10,000
Steel worker (accident only) (1969-71)	66	2.8×10^{-4} or 1/3,600
Railroad worker (1974) (all accidents excluding grade crossing)	688	1.3×10^{-3} or 1/770
Fire fighters (1971-72 average)		8×10^{-4} or 1/1,250

TABLE III

Annual Occupational Risk of Death

Modern technology has reduced our individual and societal risks, not increased them.

Nor is modern technology responsible for most of the current carcinogenic risk in the food supply. The aflatoxin in peanuts, corn, and milk occurs naturally. Nitrosamines are formed by a combination of naturally-occurring nitrites and amines, both of which are found in abundance in the foods that we consume every day. The benzo(a)-pyrene in charcoal-broiled steaks, the cadmium and other heavy metals in food, the calcium and vitamin D_2 in food, the egg yolk and egg white, the lactose and maltose derived from dairy products and starch, the safrole in nutmeg, and the tannic acid in coffee, tea, and cocoa, were not put there by man. They were put there by nature. They have been consumed for as long as man and animals

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There are, of course, many sources of cancer risk in our environment. Many risks of cancer are no more avoidable than any other risk we face in our daily living. Table IV shows, moreover, that cancer risks from food are no greater, and in many instances much smaller, than from other common sources and activities.[46]

[46] Table IV is derived from Wilson, *supra* n. 45.

TABLE IV

ANNUAL CANCER RISKS

	Individual Risk/Year
Cosmic ray risks*	
One transcontinental flight/year	1 in 2,000,000
Airline pilot 50 hrs./mo. at 35,000 feet	1 in 20,000
Frequent airline passenger	1 in 65,000

TABLE IV

ANNUAL CANCER RISKS

	Individual Risk/Year
Cosmic ray risks*	
One transcontinental flight/year	1 in 2,000,000
Airline pilot 50 hrs./mo. at 35,000 feet	1 in 20,000
Frequent airline passenger	1 in 65,000
Living in Denver compared to N.Y.	1 in 100,000
One summer (four months) camping at 15,000 feet	1 in 100,000
Other radiation risks*	
Average U.S. diagnostic medical x-rays	1 in 100,000
Increase in risk from living in a brick building	1 in 200,000
Natural background at sea level	1 in 65,000
Eating and Drinking	
One diet soda/day (saccharin)**	1 in 100,000
Average U.S. saccharin consumption**	1 in 500,000
Four tablespoons peanut butter/day (aflatoxin)*, **	1 in 25,000
One pint milk per day (aflatoxin)*, **	1 in 100,000
Miami or New Orleans drinking water***	1 in 800,000
½ lb. charcoal broiled steak once a week (cancer risk only; heart attack, etc. additional)****	1 in 2,500,000
Alcohol—averaged over smokers and non-smokers*	1 in 20,000
Tobacco	
Smoker, cancer only*	1 in 800
Smoker, all effects (including heart disease)*	1 in 300
Person in room with smoker**	1 in 100,000
Miscellaneous	
Taking contraceptive pills regularly*	1 in 50,000
Skin cancer (curable) from sunbathing, rock climbing, and other outdoor activities.*	1 in 200

* Linear extrapolation from human epidemiological data.
** Linear extrapolation from animal data.
*** Multi-stage extrapolation from animal data.
**** Based on equivalent concentration of benzo(a)pyrene in cigarette smoke.
* Human epidemiological data, no extrapolation.
** Based on equivalent concentration of benzo(a)pyrene in cigarette smoke.

the current no-risk food safety policy embodied in the Federal Food, Drug, and Cosmetic Act. And if the wording of the law itself is not changed, it is apparent that it must be reinterpreted by the FDA in its daily enforcement activities, because its former mandate can no longer be accomplished.

Limitations on Disease Prevention

It is currently popular to champion the cause of disease prevention in general, and cancer prevention in particular. Prevention of disease would, after all, be far more effective than any attempts to cure disease can ever hope to be. Very seldom, however, does any discussion of disease prevention focus upon the major reason why this approach has so often failed—the fundamental libertarian principle of freedom of individual thought and action that underlies the history and tradition of our country. Many of the major causes of

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The centerpiece of any future discussion of disease prevention through regulation of food safety must therefore be a very straightforward and realistic appraisal of the practicality of prevention techniques in light of the constitutional and ethical limitations imposed by our society, and the unwillingness of many citizens voluntarily to change their "vices." As Dr. Thomas Trotter said in 1778: "Mankind, ever in pursuit of pleasure, have reluctantly admitted into the catalogue of their diseases, those evils which were the immediate

offspring of their luxuries."[47] Quite obviously, things have not changed in the intervening 200 years.

This point is aptly illustrated by a Herblock cartoon that recently appeared in the Washington Post.[48] It shows two consumers facing three government scientists and regulators. The consumers carry two signs. The first says "Keep us informed of what we ought to know." The second says "But don't tell us things we don't want to hear."

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This point is aptly illustrated by a Herblock cartoon that recently appeared in the Washington Post.[48] It shows two consumers facing three government scientists and regulators. The consumers carry two signs. The first says "Keep us informed of what we ought to know." The second says "But don't tell us things we don't want to hear."

Focusing on the issue of "free choice" will, indeed, be very helpful in targeting those areas where prevention techniques can be very effective because they do not involve significant diminution of individual choice (such as, reducing water and air pollution), and where they will be of limited effectiveness because they depend upon individuals voluntarily changing their lifestyles when they do not wish to do so (such as, reducing caloric intake rather than consuming artificially sweetened food). It will also necessarily lead to consideration of alternative strategies in those areas where our tradition of civil liberties precludes direct government intervention in the individual's freedom of choice.

II. Legal Constraints Require the Development of a Consistent Food Safety Policy

The practical impossibility of implementing the present food safety provisions of the law is, in itself, sufficient to assure that Congress and the FDA begin to formulate a new food safety policy for the future. It is also useful to appreciate, however, that very important legal considerations provide an independent reason for fashioning new public policy in this area.

Constitutional Principles

Supreme Court decisions during the early 1930's invalidating government action on the ground that it violated "substantive" due process of law[49] have long since been repudiated.[50] With very rare exception, courts today are unwilling to second-guess Congress by striking down any form of government regulation, however outrageous it might be, on that particular constitutional ground. A num-

[47] Trotter, *Essay, Medical Philosophical and Chemical, on Drunkenness* (1778).

[48] Washington Post, May 28, 1978, page C6.

[49] E.g., *New State Ice Co. v. Liebman*, 285 U. S. 262 (1932).

[50] E.g., *Nebbia v. New York*, 291 U. S. 502 (1934); *United States v. Carolene Products Co.*, 304 U. S. 144 (1938).

are impossible.[58] The courts have demanded, however, that regulatory agencies "supply a reasoned analysis indicating that prior policies and standards are being deliberately changed, not casually ignored," where different principles are applied in similar situations.[59] If the FDA chooses to ban some carcinogens from the food supply, but not others, it must offer a reasoned analysis demonstrating why the situations are different, and thus articulate a rational food safety policy that can consistently be applied to the entire food supply. Current legal precedent will not tolerate ad hoc judgments or post hoc rationalizations that fail to adhere to a minimum standard of uniform applicability.

Faced with applying the impossible statutory standard of complete safety for all food ingredients, the courts are also likely to begin to interpret the basic safety provisions of the Federal Food, Drug, and Cosmetic Act in a different way than they have in the past. The Act has long prohibited any filth in food[60] in the same absolute terms that it requires that all food ingredients be safe. When provided irrefutable evidence that it is impossible to remove all filth from food, however, the courts have reacted in a common sense way and refused to impose such a standard, even when the FDA itself espoused it.[61] Reasonable tolerances for filth in food have been ordered by the courts under those circumstances, and reasonable tolerances for harmful substances could similarly be recognized by the courts even without amendment of the Act.

Recent court decisions affecting other regulatory agencies illustrate the reluctance of courts to endorse regulatory requirements that seem impossible or lack common sense.

In the *Aqua Slide* case, the court rejected a warning required by the Consumer Product Safety Commission (CPSC) on swimming pool slides when it was informed that:

"The risk of paraplegia from swimming pool slides, however, is extremely remote... the risk, for slide users, is about one in 10 million, less than the risk an average person has of being killed by lightning."[62]

[58] *Mary Carter Paint Co. v. FTC*, 333 F.2d 654, 660 (CA-5 1964) (Brown, J., concurring).

[59] *Greater Boston Television Corp. v. FCC*, 444 F.2d 841, 852 (CA DofC 1970). See also *Teamsters Local Union v. NLRB*, 532 F.2d 1385, 1392 (CA DofC 1976); *Distrigas of Massachusetts Corp. v. FPC*, 517 F.2d 761, 765 (CA-1 1975); *Marine Space Enclosures, Inc. v. Federal Maritime Comm'n*, 420 F.2d 577, 585 (CA DofC 1969); *FTC v. Crowther*, 430 F.2d 510, 514 (CA DofC 1970).

[60] 21 U. S. C. 342(a)(3).

[61] E.g., *United States v. 1500 Cases*, 236 F.2d 208 (CA-7 1956); *United States v. General Foods Corp.* (N. D. N. Y., February 9, 1978).

[62] *Aqua Slide "N" Dive Corp. v. CPSC*, 569, F. 2d 831, 840 (CA-5 1978).

secondary role in the determination of food safety policy for the future. Nonetheless, the constant pressure created by these legal doctrines requires that the FDA directly confront this problem and formulate a consistent rationale for resolving it.

III. Future Food Safety Policy in the United States

In fashioning food safety policy for the future, three essential areas must be explored. First, it is important to determine the sources of the data on which regulatory decisions will be made. Second, consistent rules must be established to guide the regulatory decisions that will be made for individual food components. Third, an appropriate procedure must be established to assure the participation both of qualified scientists and of the general public in the decision-making process.

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A. SOURCES OF DATA

There are three basic sources of data on which to base regulatory decisions respecting the safety of food ingredients: human epidemiology, animal experimentation, and *in vitro* testing.

Human Epidemiology

It is the rare exception when definitive data are available to establish, with a high degree of confidence, the actual human toxicity of a chemical. In most instances, regulatory decisions must be based upon incomplete information, largely from animal and *in vitro* testing. It is unlikely that this will change in the future.

The utility of human epidemiology studies in making regulatory

[63] *Id.* at 842.

[64] *Turner Co. v. Secretary of Labor,* 561 F.2d 82 (CA-7 1977); *AFL-CIO v. Brennan,* 530 F.2d 109 (CA-3 1975); *Florida Peach Growers Ass'n v. United States Department of Labor,* 489 F.2d 120 (CA-5 1974); *Industrial Union Department, AFL-CIO v. Hodgson,* 499 F.2d 467 (CA DofC 1974).

decisions about food ingredients is severely limited,[65] for several reasons. Epidemiological data are useful only where the ingredient in question has been used for a sufficiently long period of time to assure that any effects would have been manifested, the exposure has been sufficiently high to result in a discernible difference as contrasted with those who were not exposed, there are accurate records for many years that allow the experience of those exposed to the ingredient to be compared with the experience of other

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The food supply currently consists of an estimated 13,000 components.[66] It would be impossible for anyone accurately to recall in detail the components of his past diet, even for a very short period of time, much less for the decades that are thought to be required for a valid epidemiological study. In order to maintain a proper diary-based epidemiological record for the future that would permit statistically valid conclusions, it would be necessary for tens of thousands of individuals to record in minute detail the ingredient statement of every food they consume, over a period of many years, and to computerize all of this information. Even then, this information could cover only the estimated 3,000 direct food additives, and not the estimated 10,000 indirect food constituents or the unknown additional environmental contaminants. Thus, either retrospective or prospective epidemiological dietary studies of large human populations are impracticable for purposes of regulatory decision-making on food safety.

Even if such studies could be undertaken as a practical matter, their ability to distinguish effects caused by individual food constituents as contrasted with the diet as a whole is highly questionable. It is estimated that 60 percent of female cancer and 40 percent

[65] See, e.g., the discussion of the available epidemiological studies on saccharin, in the Food and Drug Administration notices on these studies, 42 *F. R.* 20001 (April 15, 1977) and 42 *F. R.* 33768 (July 1, 1977), and in Office of Technology Assessment, *Cancer Testing Technology and Saccharin* 26-28 (1977). See also National Academy of Sciences, 1 *Contemporary Pest Control Practices and Prospects* 61-64 (1975); National Academy of Sciences, *Drinking Water and Safety* 28 (1977).

[66] See "Food Additives: Competitive, Regulatory, and Safety Problems," Hearings before the Select Committee on Small Business, United States Senate, 95th Cong., 1st Sess. 42, 52, 57, 502-503 (1977).

stance used in food over a long period of time by a relatively small cohort may yield valid epidemiological data. Even here, however, it is likely that any epidemiological study would be regarded as sufficiently sensitive to be meaningful only if it found a positive result, but not to exonerate the substance if it failed to find an effect. And as industrial exposures are reduced by modern processing methods and occupational safeguards, the opportunity for this form of epidemiological study is correspondingly reduced.

Animal Experimentation

For these reasons, toxicological testing in animals has been, and remains, the primary source of information for food safety decisions. As long as this form of testing involved observation primarily for acute effects, it was realistic and manageable. With the recent advent

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For these reasons, toxicological testing in animals has been, and remains, the primary source of information for food safety decisions. As long as this form of testing involved observation primarily for acute effects, it was realistic and manageable. With the recent advent of lifetime in utero carcinogenicity testing in two rodent species, however, such a testing requirement is not practical for all components of the food supply either from an economic standpoint or in light of the available animal testing facilities in this country and other priorities for testing chemicals to which we are exposed. Tests using current government-required protocols cost over $500,000 per ingredient and take more than three years to complete.

Reliance upon animal testing for future regulatory decision-making is thus misplaced. Even if all animal testing facilities available in the country were deployed solely in testing the potential carcinogenicity of all food substances, it is unlikely that the project would be completed in our lifetime. It is therefore apparent that some other mechanism must be found.

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[67] The Deputy Director of the National Cancer Institute has testified that:

"In the United States, the number of cancer cases a year that appear to be related to diet are estimated to be 40 percent of the total incidence for males and about 60 percent of the total incidence for females."

U. S. Senate Select Committee on Nutrition and Human Needs, *Diet Related to Killer Diseases,* 95th Cong., 1st Sess. 166 (1977).

Nor are animal carcinogenicity studies necessarily correlated with human risk.[68] It is a logical and scientific non sequitur to argue, as many do, that because virtually all human carcinogens are also animal carcinogens, virtually all animal carcinogens are also human carcinogens. All that can properly be said at this time is that a substance which is shown, through proper testing, to be a carcinogen in test animals, has a greater probability of also being a carcinogen in humans than a

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In Vitro Testing

It is for this reason that the single most important priority for food safety policy in the future is the development, refinement, validation, and acceptance of a battery of new *in vitro* short-term carcinogenicity predictive tests,[69] on the basis of which sound regulatory decisions can be made. These tests are quite inexpensive and can be completed very quickly. Although they are presently too unpredictable to justify by themselves, regulatory decisions on the safety of food ingredients,[70] it is only a matter of time before their deficiencies are corrected and they become at least as reliable in predicting human carcinogenicity as animal studies. It is likely, indeed, that in time they will be perfected to a point where they are able to mimic human response far more accurately than animal testing.

Thus, it is apparent that the only realistic basis for systematic safety decision-making on food ingredients in the future lies in the use of short-term *in vitro* tests. Until these tests are perfected, of

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[68] Dr. Arthur Upton, Director of the National Cancer Institute, has testified that:

"The NCI animal bioassay effort for chemical carcinogens can merely detect a chemical's potential for causing cancer in humans. It [sic] results cannot tell us whether a particular chemical will cause human cancer, but they may alert us to a presumptive risk and this will serve as a basis for further studies of the chemical in question."

* * *

"Unfortunately, the science of the matter is not cut and dry. There are honest scientific differences of opinion about evidence and how one can interpret it."

Hearings before the Subcommittee on Oversight and Invesigations, Committee on Interstate and Foreign Commerce, Tr. at 14, 49 (January 23, 1978).

[69] See Subcommittee on Environmental Mutagenesis, DHEW Committee to Coordinate Toxicology and Related Programs, *Approaches to Determining the Mutagenic Properties of Chemicals: Risk to Future Generations* (1977); Saffiiotti & Autrup, *In Vitro Carcinogenesis: Guide to the Literature, Recent Advances and Laboratory Procedures,* NCI Carcinogenesis Tech. Rept. Ser. No. 44 (1978).

[70] Kennedy, *Animal Testing and Human Risk* 14 (April 1, 1978); J. Nat'l Cancer Inst., *58,* 463 (1977).

future food safety policy must involve an assessment of the degree of risk posed by any food substance, when compared with the risks posed by other food substances, by other consumer products, and indeed by all other human activity. It is insufficient, however, simply to state this proposition as a general principle. It is essential that specific rules for decision-making be established, in order to assure a rational basis for individual regulatory decisions.

Establishment of Priorities

A comprehensive approach to food safety evaluation must be preceded by a preliminary review of the relative risks presented by the present known component of the food supply—including all environmental contaminants, indirect constituents, and direct ingredients—in order to establish priorities for the study of individual food substances.[71] It seems reasonable to begin with the very lim-

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ited number of substances that are proven human carcinogens. Following that it would be appropriate to move on to proven animal oncogens, and then to suspect animal oncogens. When *in vitro* tests have become sufficiently perfected for their results to be considered reliable, they should similarly be incorporated into the prioritizing mechanism. Within each of these general categories, moreover, the substances should be ranked in order of priority according to their relative risk, taking into consideration the relative potency and the level and extent of human exposure through the food supply. On this basis, a systematic work plan can be developed.

Risk Assessment

The first step in the decision-making process for any individual food substance must be a risk assessment.[72] Without question, risk assessment at this time represents a highly uncertain science. It is,

[71] See, e.g., Jellinek, Direct Testimony before the Occupational Safety and Health Administration, OSHA Docket No. H-090, at 2, 6 (June 1978).

[72] See Kennedy, Direct Testimony before the Occupational Safety and Health Administration, OSHA Docket No. H-090, at 11-12 (April 1978); Jellinek, *supra* n. 71, at 2, 5. For a general discussion of risk assessment see National Academy of Sciences, *Drinking Water and Health* ch. 2 (1977).

however, the only means available to quantify the magnitude of risk represented by the use of a particular substance in a specific way in the food supply, and thus to permit comparison with the magnitude of other risks.

As already noted, evaluation of the potential carcinogenic risk of a substance today necessarily depends primarily upon animal testing. In order to determine whether a given substance may produce a carcinogenic

however, the only means available to quantify the magnitude of risk represented by the use of a particular substance in a specific way in the food supply, and thus to permit comparison with the magnitude of other risks.

As already noted, evaluation of the potential carcinogenic risk of a substance today necessarily depends primarily upon animal testing. In order to determine whether a given substance may produce a carcinogenic response, it is fed to a relatively small number of animals at a relatively high dose—the so-called "maximum tolerated dose." Thus, risk assessment must proceed in the following way. First, from the high doses at which the animals are exposed it is necessary to extrapolate the estimated effect of the test substance at the low doses to which humans are exposed. Second, it is necessary to compensate for the differences in size and dietary intake between the test animals and humans. Third, it is necessary to take into consideration the various differences between the exposure conditions in the animal experiment (such as lifetime daily feeding at specific levels under rigidly controlled conditions) and the exposure conditions for humans (for example, intermittent consumption of various possible amounts under various possible conditions).

Extrapolation Models and Scaling Factors

With respect to extrapolation from high doses to low doses, a variety of mathematical models has been advanced. The four most widely discussed models in descending order of conservatism are the linear,[73] multi-stage,[74] Mantel-Bryan,[75] and Cornfield[76] models. The risk estimates obtained by these four models vary dramatically.[77]

[73] Hoel et al., *Estimation of Risks of Irreversible, Delayed Toxicity*, J. Toxicol. Environ. Health, *1*, 133 (1975).

[74] Crump et al., *Fundamental Carcinogenic Processes and Their Implication for Risk Assessment*, Cancer Res., *36:* 2973 (1976); Guess & Crump, *Low Dose Extrapolation of Data from Animal Carcinogenicity Experiments—Analysis of a New Statistical Technique*, Math. Biosci., *32:* 15 (1976); Guess, Crump & Peto, *Uncertainty Estimates for Low-Dose-Rate Extrapolations of Animal Carcinogenicity Data*, Cancer Res., *37:* 3475 (1977).

[75] Mantel & Bryan, *"Safety" Testing on Carcinogenic Agents*, J. Nat'l Cancer Inst., *27:* 455 (1961); Mantel et al., *An Improved Mantel-Bryan Procedure for "Safety" Testing of Carcinogens*, Cancer Res., *35:* 865 (1975).

[76] Cornfield, *Carcinogenic Risk Assessment*, Science, *198:* 693 (1977).

[77] For saccharin, using the body surface area scaling factor, the linear and multistage models resulted in the following differences in the estimated new cancer cases per year:

linear	3,400
multistage	15

Office of Technology Assessment, *supra* n. 65, at 88. For aflatoxin, the Food and Drug Administration estimated the

(Continued on the next page.)

mates obtained by using these three scaling factors also vary dramatically.[78] Because human exposure conditions are unique for every particular food substance, there are no generalizable rules for taking these conditions into consideration.

Because there is presently no "standard" extrapolation model or scaling factor, different individuals within and outside the government have been conducting risk assessments using widely varying models and factors—often without even explaining exactly which ones were used—with a resulting welter of noncomparable and indeed uninterpretable conclusions. Until a single extrapolation model and scaling factor is adopted as the standard approach for all risk assessment, the present confusion will continue.

Need for Uniform Approach to Risk Assessment

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Need for Uniform Approach to Risk Assessment

It is undoubtedly true that there is inadequate experimental evidence to determine which mathematical extrapolation model more accurately portrays dose-response relationships at extremely low doses. Nor is this matter likely to be resolved in the near future. Like so many other scientific issues surrounding testing for carcinogenicity, it may well remain a matter of serious scientific dispute for years and perhaps for decades. In the meantime, clear rules must be formulated to guide regulatory decisions, even in the face of scientific uncertainty.

In this respect, the important difference between risk calculations obtained from epidemiological data, and risk estimates obtained by

(Footnote 77 continued.)
following ranges for the lifetime liver cancer rates per 100,000 using the Mantel-Bryan and Cornfield models:

Mantel-Bryan	30-1400 per 100,000
Cornfield	17-126 per 100,000

Food and Drug Administration, *Assessment of Estimated Risk Resulting from Aflatoxins in Consumer Peanut Products and Other Food Commodities* 2, 10-14 (1978).

[78] For saccharin, using the linear extrapolation model, the three scaling factors resulted in the following differences in the estimated new cancer cases per year:

mg./kg. body weight	600
body surface area	3,400
lifetime mg./kg. intake	15,000

Office of Technology Assessment, *supra* n. 65, at 88.

mathematical extrapolation from animal data, must be kept in mind. The former represent "absolute" risk calculations. They are based on actual mortality rates. Thus, the data given in Tables I through III, as calculated by Professor Wilson, provide the actual yearly risk involved for each of the activities specified.

In contrast, risk estimates obtained by extrapolation from animal data, regardless of which mathematical model is used, provide only "relative" information, not absolute information. These numbers, in and of themselves, are meaningless. They become meaningful only insofar as they can be compared with other risk estimates prepared using the identical mathematical model, scaling factor, and other assumptions.

In the area of carcinogenic risk, the government has consistently adopted the most conservative possible assumptions, in order to provide the greatest possible public protection. It is for that reason that regulatory agencies presently assume that there is no threshold level below which a carcinogen cannot assert its carcinogenic effects,[79] and will continue to make that assumption until there is adequate scientific evidence to refute it. For the same reason, it is likely that the government will adopt the linear mathematical extrapolation model,[80] which is the most conservative of the models that have been advanced. It is also likely that the government will adopt a body surface area scaling factor, which the NAS recently described as more accurate.[81] Standardization of all risk assessments utilizing this model and scaling factor would then permit the relative carcinogenic risk of all substances in the food supply, and indeed all chemicals in our environment, to be compared. The only procedure that would clearly be unjustified would be to use different mathematical models, scaling factors, or other assumptions to calculate the potential carcinogenic risk for different substances, because this would make any comparison of relative risk impossible.

[79] See, e.g., 42 *F. R.* 54148 (Oct. 4, 1977).

[80] The Food and Drug Administration adopted the Mantel-Bryan model in its regulation prescribing criteria and procedures for evaluating assays for carcinogenic residues in edible products of animals. See 42 *F. R.* 10412 (Feb. 22, 1977); Perez, *Human Safety Data Collection and Evaluation for the Approval of New Animal Drugs,* J. Toxicol. Environ. Health, *3:* 837, 853 (1977); In *Animal Health Institute v. FDA* (D. D. C., February 8, 1978), the court concluded that the procedure used by FDA to promulgate the regulation was legally deficient, and the regulation has therefore been withdrawn, 43 *F. R.* 22675 (May 26, 1978), and the matter is being reconsidered.

[81] National Academy of Sciences, *Drinking Water and Health* 31 (1977).

is the most conservative extrapolation. The
estimate obtained by it from animal data can be compared with the "absolute" risk calculations obtained from human epidemiological data for all other types of risks with assurance that the relative magnitude of the animal extrapolations is not understated. This affords an important bridge between these two different types of risk data and permits regulatory determinations to be made on a broad comparative basis.

Even if the linear model is adopted as the standard, moreover, this would not preclude also conducting risk assessments by other models that are thought to be more realistic. Indeed, it would always be possible to calculate a range of risks, using more than one extrapolation model. As long as one particular model is specified as the standard, however, a valid basis for making comparative risk determinations will always exist.

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Classification of Risks

The second step in this decision-making process is to classify the risk. In my prior papers, I have suggested the necessity of classifying risks into high, moderate, and low risks.

For high risks, society customarily enforces a ban. The examples that readily come to mind are attempted suicide, putting frank poisons in the food supply, and going over Niagara Falls in a barrel. The extraordinarily high risk involved in each of these activities has prompted our country to determine that the principle of freedom of individual choice simply cannot be allowed to prevail.

For a moderate risk, our country has decided that individuals should be educated and warned about the risk, and cautions should

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[82] The risk of liver cancer estimated by the Food and Drug Administration even using the Mantel-Bryan model for aflatoxin in peanuts substantially exceeded the actual total liver cancer in the United States from all causes, which prompted the Agency to conclude that:

"Possible explanations for these differences are: 1) the level of human exposure to aflatoxin has been overestimated; 2) the Mantel-Bryan extrapolation procedure is overly conservative in this case; and/or 3) rats may not be an appropriate model for predicting aflatoxin-induced primary liver cancer in humans."

Food and Drug Administration, *supra* n. 77, at 13-14.

be taken, but nonetheless the ultimate choice whether or not to accept the risk must be left up to each person. Depending upon our individual value judgments, each of us chooses among these risks as we go about our daily living.

For a low risk, our country generally imposes neither attempts to educate the public nor any form of restriction. These are the daily "background" risks about which we think very seldom, if at all.

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The same conceptual basis for classifying other risks into these three categories also exists with respect to the risks posed by food. Both because all foods pose some risk and because of our civil libertarian heritage, it simply is not possible to ban all food risks. Thus, only those substances that present a truly high risk should be banned outright from the food supply.

It is equally clear that the public should be warned only about significant food risks, not about all food risks. This principle was clearly enunciated by Congress in enacting the Federal Hazardous Substances Labeling Act in 1960. Concern about public disregard of warnings, if faced by a multiplicity of precautionary labeling about risks, led Congress to require warnings only for those household chemicals that represent a "substantial" danger rather than just a "minor hazard."[83] The identical concern was recognized by the Panel on Chemicals and Health of the President's Science Advisory Committee in 1972:

> "If the public is exposed to too many vivid accounts of nonexistent or very minor threats to health, its attention will be misdirected, its priorities will be confused, its responsiveness to important messages will be decreased."[84]

More recently, leaders in the fight against cancer have realized that bombarding the public with warnings against minor cancer hazards will render public educational activities "ineffective."[85] The numerous cartoons, editorials, and humorous satires that populate the news media, which depict everything as carcinogenic, indicate the real necessity of limiting public warnings only to significant cancer risks.

Three Classes of Risk

Perhaps the most difficult aspect of classifying food risks into high, moderate, and low risks, is in determining the appropriate dividing lines. Professor Wilson has suggested that, based upon

[83] P. L. No. 86-613, 74 Stat. 372 (1960); S. Rep. No. 86-1158, 86th Cong., 2nd Sess. 2 (1960).

[84] *Report of the Panel on Chemicals and Health* 2-28 (1972).

[85] Weisburger, *Social and Ethical Implications of Claims for Cancer Hazards,* Med. & Ped. Oncology, *3:* 137-140 (1977).

1,000,000) would be acceptable.[87]

Quite obviously, the dividing lines to be chosen will depend upon the mathematical model and scaling factor adopted as the standard. Because all extrapolation models produce only relative, rather than absolute, risk estimates, the level of acceptable risk must be tailored to the relative degree of conservatism built into the model. Thus, whereas 10^{-5} might well be an acceptable risk using the linear model, it might well not be acceptable using less conservative models.

It must also be recognized that risk assessment presently is sufficiently sensitive to differentiate among different orders of magnitude, but cannot distinguish between risks that are relatively close in magnitude. Thus, some degree of flexibility must necessarily be incorporated in any regulatory decision-making based upon risk assessment. Rigid adherence to specified cut-off levels simply is not feasible at the present.

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Ultimately, of course, it will also be necessary to establish an extrapolation model based upon short-term *in vitro* tests. That must come as part of the validation work that is presently in progress. Once again, it is likely that there will be scientific disagreement about the proper extrapolation method from *in vitro* testing, just as there is for animal testing. On the other hand, extrapolation from *in vitro* testing is more likely to yield uniform results, since the dosage involved can readily be varied to determine potency and thus the available data will be more complete than is presently possible from many animal experiments. Hopefully, a standard approach for extrapolation will develop more rapidly for *in vitro* testing than has been true for animal testing, and thus will allow prompt use of these data in regulatory decision-making.

Determination of the Regulatory Response

The third step in the decision-making process involves formulation of the specific regulatory response to the potential risk involved. This step in turn requires a detailed analysis based upon the magnitude of the risk involved and the nature of the risk.

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[86] See n. 45 *supra*.

[87] See n. 79 *supra*.

Reduction of the Risk

First, it is essential to determine the feasibility of reducing the risk. It is here, and only here, that the source of the risk becomes relevant. If the source of the risk is an environmental contaminant (such as aflatoxin in peanuts) or an indirect constituent purposely used in the production of food but that serves no purpose in the food itself (for example, a pesticide residue or a migrating packaging

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First, it is essential to determine the feasibility of reducing the risk. It is here, and only here, that the source of the risk becomes relevant. If the source of the risk is an environmental contaminant (such as aflatoxin in peanuts) or an indirect constituent purposely used in the production of food but that serves no purpose in the food itself (for example, a pesticide residue or a migrating packaging ingredient), it may well be possible to reduce the risk by eliminating or reducing the level of that contaminant or constituent. Under these circumstances, the feasibility of reducing the risk must be determined, taking into consideration current technological capabilities and the cost of such reduction, as compared with the magnitude of the reduction in the risk that would result. Without question, this involves both difficult calculations and ultimately a very complex judgmental decision. In general, any reduction in the total body burden of carcinogens should be undertaken where the cost is small. Where major costs are involved, on the other hand, the resulting reduction in risk must be sufficiently large to justify the expenditure.

If the source of the risk is a direct additive that is essential to, or an integral component of, the food itself (such as, saccharin in artificially sweetened soft drinks, safrole in nutmeg, or tannin in tea), on the other hand, it may well be impossible to reduce the risk involved. Under these circumstances, consideration of the appropriate regulatory action must proceed directly on the basis of the intended use of the food without any attempt to reduce that risk.

Some have suggested that different rules should apply with respect to environmental contaminants (such as aflatoxin in peanuts) as contrasted with substances used in the production of food (for example, packaging materials) or direct food ingredients (such as saccharin). There is, however, no conceptual or rational basis for this distinction. An environmental contaminant can be reduced or eliminated from the food supply just as easily as an indirect constituent or direct ingredient. There is nothing inherently different from eliminating saccharin (which would require removing artificially sweetened soft drinks from the food supply) or aflatoxin (which would require removing peanuts from the food supply). The fact that one is a processed food and the other is a raw agricultural product has no bearing whatever on the amount of economic impact, the health effects, the reduction in consumer choice, or any other relevant consideration. Thus, the regulatory construct for food

a substantially smaller risk. Obviously, there is no single
tute for peanuts, nutmeg, or, at the present time, saccharin. Indeed, it is unlikely that there is a fungible substitute for any raw agricultural commodity or other substance that is used as a characterizing ingredient in food.

In some instances, however, there are fungible substitutes for functional chemical food components designed for such uses as stabilizers, emulsifiers, thickeners, preservatives, and other technological purposes. It is largely in this area of chemicals used at relatively small levels for technical and functional purposes in food production and food formulation that fungible alternatives may exist which have a substantially lower risk, and thus where elimination of one of a number of alternatives will involve no loss of free choice in the marketplace.

Adoption of Regulatory Action

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Adoption of Regulatory Action

Third, based upon the foregoing analysis, it is then possible to determine the appropriate regulatory action.

For a high risk which cannot be reduced to a moderate or low risk, the appropriate regulatory response is a total ban. Only in very rare circumstances, involving overwhelming benefits, would this large magnitude of risk ever be justified in a food product. It is, indeed, impossible to imagine this kind of exception in the general food supply. Nor is it likely that any such large risk exists today in the food supply, or it would have become apparent before now.

For a moderate risk, any cost-justified reduction should be required. Appropriate labeling or other information should then be disseminated to inform the public of the nature and the magnitude of the risk involved. It is particularly important that this warning and other information provide full and accurate information about the risk, rather than simply a one-sentence scare statement of the kind recently required by Congress for saccharin under the Saccharin Study and Labeling Act.[88]

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[88] *Supra* n. 4. The statutorily-required warning states:

"Use of this product may be hazardous to your health. This product contains saccharin which has been determined to cause cancer in laboratory animals."

21 U. S. C. 343(o)(1).

Indeed, one can scarcely imagine a more uninformative and misleading warning than the one required by Congress for saccharin. It gives no information whatever about the relative magnitude of the risk involved.[89] One could easily gain the impression that saccharin is one of the major sources of cancer in this country, particularly because the only other consumer product that bears a similar warning is cigarettes.

Indeed, one can scarcely imagine a more uninformative and misleading warning than the one required by Congress for saccharin. It gives no information whatever about the relative magnitude of the risk involved.[89] One could easily gain the impression that saccharin is one of the major sources of cancer in this country, particularly because the only other consumer product that bears a similar warning is cigarettes.

The government must be certain, in the future, to avoid warnings which are, in themselves, grossly misleading to consumers. This is particularly true now that the Supreme Court has ruled that manufacturers have a constitutional right to provide accurate and truthful information directly to the public, even over the objections of the government.[90] If future warnings imposed by the government are inadequate fully to convey the nature and magnitude of the risk involved, the food industry may exercise its constitutional right to provide that information to consumers even if it appears to contradict the required government warning.

Informing Consumers About Moderate Risks

The concept of providing informative labeling to consumers about moderate risks in food rests, of course, upon the principle that individual consumers are then entitled to make their own personal benefit/risk decision by exercising their free and fully-informed choice in the marketplace. In three special circumstances, however, questions may arise when the consumer is in fact making a conscious choice.

It has been suggested that, where the substance is an inherent component of the food, the consumer does not make a conscious choice to consume that particular component when the entire product is purchased. This point was made during the debates on saccharin, where it was suggested that the consumer only makes a truly deliberate choice when forced to add saccharin to food directly, and not when purchasing a product that already contains saccharin. This analysis, however, rapidly breaks down in virtually all practical situations, and particularly those involving environmental contaminants or indirect food ingredients. Saccharin is the rare exception. In virtually all other situations, the risk arises from an ingredient that cannot be separated from the food. If environmental contaminants

[89] The potency of carcinogens varies over a millionfold. See Office of Technology Assessment, *supra* n. 65, at 22-24.

[90] See cases cited notes 53 & 54 *supra*.

It has also been suggested that some individuals deserve special protection, such as the uneducated and children, as well as the unborn fetus. Short of a total ban on all ingredients and products that pose any risk whatever, however, this is not feasible. Our society has uniformly relied on parents to protect the interests of both live and unborn children. Our national emphasis on public eduction is the only mechanism that has been devised to protect the uneducated. For example, there is no mechanism whatever, at this time, for protection of these special groups from food allergies other than ingredient labeling—which depends, of course, upon the availability of parents to protect their children and the willingness of the uneducated to become literate.

Similarly, some have questioned how this reliance upon labeling will be helpful to the ever-increasing number of people who consume a major portion of their daily diet in restaurants and other institutions, where the labeling cannot be seen. This matter could, of course, be handled in two ways. It would be possible simply to ban all food which presents a moderate risk from being sold without appropriate accompanying information. It is doubtful, however, that the public would stand for this type of cumbersome approach. Instead, it seems preferable to rely on the fact that the public will become accustomed to seeing labeling with warnings and other similar information associated with particular types of food products and food ingredients, and thus will associate that information with those products and ingredients even when they are consumed in a setting where that labeling is not immediately visible. This is, of course, the way that food ingredient labeling is presently handled today. People with allergies who eat in restaurants either depend upon their own knowledge of food composition or ask appropriate questions.

It has also been suggested that the government has a right to intervene in the individual consumer's choice of food, and to make a societal benefit/risk decision rather than to allow each consumer to make his own personal benefit/risk decision, because the public ultimately pays for at least part of the consequences of any disease that may result from an individual's wrong choice. This patently

fallacious argument represents the ultimate in government paternalism. It would permit the government to impose mandatory prevention measures and involuntary treatment for every known human disease or disability and thus to intrude upon private decisions and personal liberty in a way wholly repugnant to the Constitution.

Further Reduction of Low Risks

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Further Reduction of Low Risks

For a low risk, which involves a magnitude that ordinarily justifies no public warnings or education, no restrictions would ordinarily be justified. Nonetheless, the question necessarily arises whether it would be reasonable to require a further reduction in risk, from an environmental contaminant or an indirect constituent, where it can readily be reduced without any significant cost. Once again, it seems reasonable to require that the total burden of carcinogens be reduced in our environment whenever that can easily be accomplished. Where a low risk is involved, however, the cost of reducing that risk must be shown to be trivial before a still further reduction should be required.

C. PROCEDURAL REQUIREMENTS

In numerous papers presented during the past six years, I have pointed out that the processes by which safety decisions are made by the FDA are at least as important as, and perhaps more important than, the ultimate substantive decision on any particular issue at hand.[91] As Mr. Justice Frankfurter stated, "The history of liberty has largely been the history of observance of procedural safeguards."[92]

This does not mean that, by observing proper procedure, controversy or concern about food safety issues will be eliminated in the future. It does mean, however, that by opening up food safety decisions to greater scientific and public participation, there will be a more widespread understanding of the complexity of food safety issues, the lack of certainty in food safety decisions, the subtle and difficult judgments that comprise the ultimate regulatory decision,

[91] *Public Information and Public Participation in the Food and Drug Administration,* 36 Q. Bull. Ass'n of Food & Drug Officials of U. S. 212, 216-220 (1972); *Safety Regulation in the Real World,* 28 CCH Food Drug Cosmetic Law Journal 460, 469-472 (1973); *Balanced Government Regulation of Consumer Products,* 31 CCH Food Drug Cosmetic Law Journal 592, 600-604 (1976); *Public Participation in Toxicology Decisions,* 32 CCH Food Drug Cosmetic Law Journal 275 (1977); *The Citizen and the Expert,* in National Academy of Sciences, *Science: An American Bicentennial View* 67 (1977).

[92] *McNabb v. United States,* 318 U. S. 332, 347 (1943).

Use of such advisory committees as part of the regulatory mechanism for reviewing the safety of other products regulated by the Food and Drug Administration has substantially enhanced Agency decisions in terms of substance, credibility, and public acceptance.

As I have repeatedly pointed out, it is equally important for the FDA clearly to articulate the basis for its decisions on the safety of food ingredients and food products, in a way that is not presently required: "The public cannot be expected to understand and accept decisions that are nowhere explained. Both the rationale for each decision and any underlying documentation must be laid bare to critical scrutiny."[94] These are improvements that are well within the current capability of the FDA, and indeed are consistent with its present regulatory philosophy.

IV. Conclusion

This analysis essentially completes the construct begun in my

decisions in terms of substance, credibility, and public acceptance.

As I have repeatedly pointed out, it is equally important for the FDA clearly to articulate the basis for its decisions on the safety of food ingredients and food products, in a way that is not presently required: "The public cannot be expected to understand and accept decisions that are nowhere explained. Both the rationale for each decision and any underlying documentation must be laid bare to critical scrutiny."[94] These are improvements that are well within the current capability of the FDA, and indeed are consistent with its present regulatory philosophy.

IV. Conclusion

This analysis essentially completes the construct begun in my paper at MIT and continued in my paper before the International Academy of Environmental Safety. It is intended to provoke new thought about the regulation of food safety in this country, not to provide a definitive answer. Public policy does not change quickly, particularly when it rests on a 70-year-old statutory and administrative history and tradition. Thus, I do not expect revolutionary changes to occur immediately.

It is apparent, however, that new public policy analysis is critically needed in this area. While administrative patchwork can continue to hold together the present statutory policy, and prevent it from disintegrating altogether, it is essential that Congress, the FDA, the regulated industry, consumer advocates, the professional societies, and the public at large, begin a spirited and searching debate about these matters. It is through this process that new public policy on food safety will emerge in this country and will gain widespread acceptance. **[The End]**

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[93] See Hutt, *Safety Regulation in the Real World,* 28 CCH Food Drug Cosmetic Law Journal 460, 464-468 (1973); Hutt, *The Future of the Food and Drug Administration,* CCH Food Drug Cosmetic Law Journal 694, 702-705 (1975).

[94] Hutt, *Safety Regulation in the Real World,* 28 CCH Food Drug Cosmetic Law Journal 460, 471 (1973).

Annual Report
1977-1978

The Center for the Study of Drug Development

University of Rochester Medical Center
School of Medicine and Dentistry
Rochester, New York 14642

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Report for fiscal year ending July 1, 1978.

LETTER FROM THE CHAIRMAN

TO FRIENDS OF THE CENTER:

The recently concluded year has seen our Center's activities grow in scope and importance.

We have been fortunate to have the advice and help of a distinguished Advisory Board, to which a new member was added last fall-Dr. Renée Fox, Professor of Sociology in the Departments of Sociology, Psychiatry, and Medicine and Chairman of the Department of Sociology at the University of Pennsylvania.

Several foundations have joined our current supporters, including the Ford Foundation, the Edna McConnell Clark Foundation, and the John M. Olin Foundation to which we are particularly grateful for the receipt of an unrestricted gift in November 1977.

Dr. Mohammed Hassar has been appointed as the Center's second adjunct scholar. Dr. Hassar is the Head of the Preclinical Science Department, Faculté de Médecine in Rabat, Morocco, and Chairman of the Committee on Drugs at the Moroccan Ministry of Health. He adds to the Center's resources expertise in the field of tropical disease therapies and in the medical and pharmaceutical problems of developing countries.

The Center's impact is being felt within our University, throughout the U.S., and abroad as well. My only regret is that our limited staff and resources prevent us from doing more.

We look forward to an even better 1979.

Louis Lasagna

Louis Lasagna, M.D.

DIRECTOR'S SUMMARY

During the year ending June 30, 1978, the workload of our small Center staff was heavy. We realized that to keep up with our project commitments and to initiate new projects we needed to expand. As a result we have two full-time research associates: Dr. Jean DiRaddo assumed responsibility for managing many of the projects in 1977, and Dr. Martin Eisman joins us in a similar capacity in July 1978. We have added a secretary to our office staff and will be replacing Jeanne Herzog, a technical associate who has left for graduate school. In September a part-time consultant in political science, Dr. Lynda Powell, will also join our staff.

In addition to increasing the size of our staff, we have expanded into additional offices in another part of the Medical Center. Although the two parts of our Center are separated physically, we now have the personnel and

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In addition to increasing the size of our staff, we have expanded into additional offices in another part of the Medical Center. Although the two parts of our Center are separated physically, we now have the personnel and facilities to proceed more efficiently with our work.

The sections of this report describe various aspects of the Center's activities and output. Our work is being recognized and cited both in this country and abroad. The publications of the Center have elicited many favorable responses and several journals have requested permission to reprint these articles. The usefulness and comprehensive nature of our research data and analyses are attested to by the fact that they have been relied upon and quoted by those testifying for the government, for academia, and for industry at congressional hearings. With respect to our teaching activities, we have had such a good response to the announcement of the 1978 Postgraduate Course in Clinical Pharmacology that we expect to be teaching the largest group in our history this October.

In August 1978 we will begin work on two foundation grants. We will analyze the recent history and current trends in the rate of development of systemic contraceptive new chemical entities for the Ford Foundation, and we will analyze innovation in chemotherapy for tropical diseases for the Edna McConnell Clark Foundation.

The Center is a subcontractor to the University of Pittsburgh in their contract with the National Cancer Institute to study "The Effect of Regulations on the Conduct of Cancer Treatment Research." We will be obtaining data from the NCI on their development of new anticancer drugs and will analyze these data together with the data from the pharmaceutical industry. Work on this project will begin in October 1978.

A BBC television crew taped in our offices a section of an episode that will be shown by the Public Broadcasting System in 1979 in a series moderated by Dr. Milton Friedman, a Nobel Prize winner in economics.

As I review the past year I am proud of the accomplishments of the Center for the Study of Drug Development, and look forward to an equally rewarding year ahead.

William Wardell

William Wardell, M.D., Ph.D.

Foundation, was described in detail in the Annual Report of 1976-77. The final report, completed during 1978, contains detailed information on the five major fields of the study: 1) NCE flow in the U.S.; 2) "drug lag" update; 3) national origin of U.S. marketed NCEs; 4) measures of therapeutic significance of U.S. marketed NCEs; and 5) economic studies. Several papers have resulted from this project and have appeared in scientific and academic journals; others are scheduled for early publication. (See "Publications" Section.)

REGULATION AND COMPETITION IN THE PHARMACEUTICAL INDUSTRY

This study was performed for the Federal Trade Commission's Bureau of Competition, which requested that the Center study the effect of regulation on competition and monopoly in the research-based pharmaceutical industry. The study was outlined in the Annual Report of 1976-77 and was completed in October 1977.

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CASE STUDIES OF REGULATORY DECISION-MAKING IN SCIENCE AND MEDICINE AND OTHER ISSUES RELATING TO DRUG DEVELOPMENT

Saccharin. Dr. Irving Kessler, Professor of Epidemiology at Johns Hopkins University School of Hygiene and Public Health,* wrote a paper for the Center outlining his suggestions for improving the scientific basis for regulating food and drugs--using saccharin as an example. His paper was published by the Center in October 1977.

Triazure. Mr. Seymour Shubin, a free-lance scientific writer, carried out a detailed research project on the approval and subsequent withdrawal of azaribine (Triazure) for the treatment of psoriasis. His paper will be published in 1978 in *Perspectives in Biology and Medicine.*

Spray Adhesives. Dr. Ernest Hook, Associate Professor of Pediatrics at Albany Medical College, is continuing his inquiries into the withdrawal of spray adhesives from, and their subsequent reinstatement to, the marketplace following erroneous mutagenicity reports.

*Dr. Kessler is now at the University of Maryland.

Phenformin. Dr. Rachmiel Levine, Medical Director of the City of Hope National Medical Center, is studying the imminent hazard clause of the Food, Drug and Cosmetic Act and its application to phenformin.

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Orphan Drugs. A variety of drugs with significant therapeutic potential but limited commercial interest have had difficulty in acquiring industrial sponsorship; these have been called "orphan drugs." The existence of such compounds suggests that the drug development system may be inadequate in certain circumstances. The purposes of this project are to elucidate the factors that have impeded the development of potentially useful drugs, to examine some existing mechanisms for expediting the development or clinical availability of orphan drugs, and to suggest improvements in the development process for these drugs. A monograph on this subject is being edited for the Center by Dr. Fred E. Karch of the University of Rochester School of Medicine and Dentistry.

Drug Shortages. Dr. Michael Schwartz, Dean of the School of Pharmacy, University of Florida, Gainesville, has completed his review of the effects on public health of shortages of such drugs as quinidine, opium, and heparin. His monograph will be published by Marcel Dekker, Inc. in early 1979.

Drug Prices. Dr. W. Duncan Reekie, Department of Business Studies, Edinburgh University, has completed his research on the relationship of prices to the therapeutic significance of drugs. His paper, "Price and quality competition in the U.S. drug industry," was published in the *Journal of Industrial Economics* in March 1978.

Patient Package Inserts. Associate Professor Fred Pyrczak, School of Education, California State University at Los Angeles, has completed a paper on the application of readability research principles to the preparation of patient package inserts. In his study of the new estrogen insert he found that it requires a 9th to 10th grade reading ability. He feels that improvements in the wording of the inserts are necessary, and has made several suggestions for increasing their readability. His paper will be published by the Center in the fall.

Too Many Drugs? Dr. Michael Halberstam, Assistant Clinical Professor of Medicine at George Washington Medical School, will soon complete a paper on the question of whether or not there are too many drugs on the market, in which he reviews the adequacy of marketed drugs from the point of view of the practicing physician.

RESEARCH RESOURCES

Computerized Library. The Center's Library of reprints and other literature resources on Drug Development and Regulation has grown to 6,000 entries, all listed on a computerized data file by title, author, and code assignment to enable efficient computer searching. The Library is open to any interested researcher and continues to be used regularly by workers both in and outside the Rochester area.

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New Chemical Entity (NCE) Data Bases. The Center continues to expand and update its unique data bases on the R&D and regulation of both marketed and investigational NCEs. Data from U.S. firms are being updated, and complete data (from 1963 on) from British firms are being obtained. The major Swiss firms have agreed to submit pertinent information, and plans for the addition of the Swiss data are under way. The addition of the Swiss and British information will provide us with the only data bank of its kind in the world. It will enable us to analyze the recent history of worldwide drug development, and will provide the first scientific baseline against which future changes in drug development in the major drug-developing countries can be measured. It will also enable us to perform international comparisons to elucidate the effects of national influences on drug development. In the future, if our efforts are successful, we will expand our data bases to include comparable information on NCEs from Germany and Japan.

ACADEMIC ACTIVITIES

Teaching continues to be an integral part of the Center's activities and takes place at all collegiate levels: undergraduate, graduate and postgraduate.

Rochester Plan. The Rochester Plan is a program of the University of Rochester, supported by the Commonwealth Fund. Its purpose is to improve education in the health professions and health sciences. A cooperative degree program leading to a Master of Science in Public Policy with a specialty in pharmaceutical policy issues has been established. This M.S. degree program in Public Policy Analysis is offered by the Department of Political Science (College of Arts and Science) and starting in September 1978, a substantive area of study may be taken within the Department of Pharmacology and Toxicology (School of Medicine and Dentistry). The program will include both formal coursework in pharmacology and a research project which will utilize the facilities and resources of the Center.

There is a great need today for people knowledgeable in both science and policy-making. The Public Policy program will provide students with a unique training in advanced analytic skills and with an awareness of the political system, while the Center's resources will enable students to learn about and perform research in the substantive area of pharmaceutical policy issues. The Center's role in this program represents a major and important teaching activity.

Annual Course on the Evaluation of Drugs in Man. An annual course for medical students, pharmacology graduate students, and postdoctoral clinical pharmacology fellows is given on the design and evaluation of drug studies in man. It covers scientific, medical, industrial and regulatory aspects of drug development.

Guest Lecturer. In October the Center co-sponsored, with the George W. Corner History of Medicine Society, a lecture by Professor James Harvey Young, Chairman of the Department of History of Emory University. Professor Young's field is American social, intellectual, and medical history. He is the author of several books including *The Toadstool Millionaires* and *The Medical Messiahs*. His lecture topic was "The Climate of Food and Drug Regulation: Then and Now," a review of the circumstances and achievements of early food and drug legislation and regulation. He was well received by a large audience made up of medical school faculty and staff, medical students, pharmacology graduate students, undergraduate students from the University's History Department, and Center personnel.

Corner History of Medicine Society, a lecture by Professor James Harvey Young, Chairman of the Department of History of Emory University. Professor Young's field is American social, intellectual, and medical history. He is the author of several books including *The Toadstool Millionaires* and *The Medical Messiahs*. His lecture topic was "The Climate of Food and Drug Regulation: Then and Now," a review of the circumstances and achievements of early food and drug legislation and regulation. He was well received by a large audience made up of medical school faculty and staff, medical students, pharmacology graduate students, undergraduate students from the University's History Department, and Center personnel.

Annual Postgraduate Clinical Pharmacology Course. The Annual Postgraduate Course in Clinical Pharmacology was well received in 1977, as evidenced by the number of participants (27) and their positive evaluations. The intensive one-week course, designed for M.D.s and Ph.D.s entering government and industrial positions requiring a knowledge of clinical pharmacology, consisted of a full schedule of lectures and workshops on clinical pharmacology, drug development, experimental design, and clinical trials.

The faculty consisted of the University of Rochester's School of Medicine faculty plus several visiting professors. The latter included Dr. Maurice Cuthbert, Principal Medical Officer of the Committee on Review of Medicines (U.K.); Dr. M.N.G. Dukes, Deputy Chairman of the Netherlands Board for the Evaluation of Medicine; Dr. E. Richard Dorsey, Group Director, Psychotherapeutic Research, Merrell-National Laboratories; and Thomas Athridge, Esq. of the Federal Trade Commission. Drs. Cuthbert and Dukes outlined the systems of drug regulation in Britain and Western Europe and related the British and European experiences with postmarketing surveillance. Dr. Dorsey lectured on the design and management of successful psychotropic drug studies.

101 Signatures. The HEW Review Panel on New Drug Regulation completed its work in mid-1977, and upon its publication the FDA requested comments on the final report. Dr. Lasagna, feeling that comments of a group of experts might carry more weight than those of an individual, sent the summary report and recommendations to each of over 125 experts in the United States. A

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Health-Oriented Foundations. The Drug Regulation Reform Act of 1978 which is before Congress states: "The Secretary [of HEW] shall obtain and consider recommendations from health care providers, scientific investigators and organizations interested in public health, particular diseases, or consumer affairs." The Center felt that organizations interested in particular diseases might not be aware of this provision in the bill. True consumer representation in pharmaceuticals has become a subject of increasing interest during the past year, as shown by the debate over who actually does represent the "consumer." It was therefore decided to send to the 40 largest health-oriented foundations in the country a mailing which included reprints of two articles on the subject (Halberstam, Michael J.: Power to patients, *Modern Medicine* 9/15/77; and Lasagna, L.: Wanted: A new type of consumer advocate for drugs, *New England Journal of Medicine* 4/20/78). This was sent in June 1978. A list of responses and recommendations is being compiled and will be reported within the coming year.

Drug Regulation Reform Act of 1978. The new drug bill has been under consideration in the House and Senate in 1978. In May, the Center contacted several experts in clinical pharmacology, drug development, and government, suggesting that they might constitute a small one-day working conference focusing on those portions of the new bill that will have the greatest impact on drug development. The response to the invitation was excellent. The participants will include the three immediate former FDA commissioners; the two immediate former FDA chief counsels; several lawyers, including two professors of law and the counsel for the House Subcommittee on Health and the Environment; the Director of the Bureau of Drugs; economists; clinical pharmacologists; and government employees. The Center will make a summary of the meeting available this fall.

following:

DR. LASAGNA

Lectures and Papers Presented

National Conference on Clinical Trials Methodology, Fogarty International Center of NIH. "Problems in Publication of Clinical Trial Methodology."

University of Pennsylvania. "The Scientific and Social Interdependence of Animals and Man."

University of Minnesota School of Medicine, "Bias in Selection of Patients

DR. LASAGNA

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University of Pennsylvania. "The Scientific and Social Interdependence of Animals and Man."

University of Minnesota School of Medicine, "Bias in Selection of Patients for Clinical Trials" and "Factors Affecting Chlorpromazine Blood Levels."

Italian Pharmaceutical Association of Small Manufacturers (CRI), Rome, Italy. "Toxicological Barriers to Providing Better Drugs."

Public Responsibility in Medicine and Research, Boston, Mass. "FDA, Drug Research and the Patient."

Testimony

FDA, Washington. Re protocol design at the OTC Panel on Anti-Flatulents.

FDA, Washington. Testimony at hearings on amphetamines.

The White House, Washington. Met with DEA and NIDA representatives on amphetamines.

Senate Subcommittee on Health and Scientific Research, Committee on Human Resources. Testimony on 1978 Drug Regulation Reform Act.

GAO, Washington. Panel member on Advisory Panel on Drug Lag Investigation.

GAO, Washington. Panel member on Advisory Panel on Drug Lag Investigation.

Joint Commission on Prescription Drug Use, Kansas City. Invited testimony.

House Subcommittee on Health and the Environment; Committee on Interstate and Foreign Commerce, Washington. Testimony on Drug Regulation Reform Act of 1978.

Participation in Meetings, etc.

Hoover Institution, Stanford University, California. Participant in round table discussion on Innovation and Health.

FDA, Washington. Committee member of GI Drugs Advisory Committee, Subcommittee on Hepatotoxicity.

Clinical Faculty Association of the University of California at San Francisco. Presented six lectures as the first Visiting Professor of the C.F.A.

Public Broadcasting System, Buffalo, N.Y. Taped a program on medical ethics.

Liver Toxicity Conference of Fogarty International Conferences, Washington, D.C. Participant.

Lasker Foundation. Member of jury for Lasker Awards.

City College of New York. Lectures to pharmacology class of 2nd year medical school students.

University of Wisconsin School of Medicine. Visiting Professor in Clinical Pharmacology for one week.

American College of Physicians annual meeting, Boston. Speaker and panel participant.

PMA of Canada, Montreal. Symposium participant on "Postmarketing Surveillance and ADR Reporting."

WPIX, New York. Television interview.

Graduate School of Management, UCLA: Seminar on the Economics of the Pharmaceutical Industry. "History and Development of Pharmacology, Therapeutics and Drug Regulation."

Pharmaceutical Manufacturers Association, meeting on Developments in the U.S. Health Care System. "Prospects and Future Problems in Drug Development and Regulation."

International Meeting on Comparative Therapeutic Trials, Institut de Cancerologie, University of Paris, France. "Scientific and Ethical Problems Posed by Regulatory Requirements for Proof of Efficacy" and "Appropriate and Inappropriate Use of Controlled Trial Designs by Regulatory Authorities."

American Society for Clinical Pharmacology and Therapeutics 79th Annual Meeting, Atlanta, Georgia. "How Can One Measure the 'Therapeutic

Pharmaceutical Manufacturers Association, meeting on Developments in the U.S. Health Care System. "Prospects and Future Problems in Drug Development and Regulation."

International Meeting on Comparative Therapeutic Trials, Institut de Cancerologie, University of Paris, France. "Scientific and Ethical Problems Posed by Regulatory Requirements for Proof of Efficacy" and "Appropriate and Inappropriate Use of Controlled Trial Designs by Regulatory Authorities."

American Society for Clinical Pharmacology and Therapeutics 79th Annual Meeting, Atlanta, Georgia. "How Can One Measure the 'Therapeutic Significance' of Marketed Drugs in Evaluating the Results of Pharmaceutical Innovation?"

College of Physicians and Surgeons, Columbia University. Symposium on FDA Medical Device Regulation. "Estimating the Impact of Medical Device Legislation and Regulation: Analogies from the Field of Drugs."

The University of Berne, Switzerland. Postgraduate course in Methods in Clinical Pharmacology. Lecture: "How to Judge Publications About Controlled Clinical Trials." Workshops on "The interpretation of controlled clinical trials."

Testimony

FDA, Rockville, Maryland. Testified as Chairman of the Drug Regulatory Committee of the American Society for Clinical Pharmacology and Therapeutics on the Drug Regulation Reform Act of 1978 (S.2755).(Jointly with Dr. Gilbert McMahon.)

House Subcommittee on Health and the Environment; Committee on

House Subcommittee on Health and the Environment; Committee on Interstate and Foreign Commerce, Washington. Testimony on Section 108 of the Drug Regulation Reform Act of 1978.

House Subcommittee on Health and the Environment; Committee on Interstate and Foreign Commerce, Washington. Testimony on the Drug Regulation Reform Act of 1978 (H.R. 12980) as Chairman of the Drug Regulatory Committee of ASCPT. (Jointly with Dr. Arthur Hayes.)

PROFESSOR HANSEN

UCLA and Institute for Health Economics and Social Science joint seminar on Economics of the Pharmaceutical Industry. "The Pharmaceutical Development Process: Estimates of Current Development Costs and Times and the Effects of Regulatory Changes."

Southern Economics Association and Society of Government Economists Annual Meetings, New Orleans. "Drug Discovery, Use, and Regulation: A Problem of Information."

FDA, Washington. Public Hearing on the Final Report of the Review Panel on New Drug Regulation. Testimony on the proposed changes in the FDA's trade secrets policy.

Using the saccharin controversy as a starting point, Dr. Kessler (Professor of Epidemiology at Johns Hopkins University School of Hygiene and Public Health) discusses the general problem of regulation and public protection.

Hansen, Ronald. Comments on the Proposed Changes in FDA's Trade Secrets Policy. PS 7706

This paper is based on the author's testimony at an FDA hearing on the HEW Review Panel's Final Report, and addresses the economic implications of the changes in FDA's trade secret policy that were proposed by the Review Panel.

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This paper is based on the author's testimony at an FDA hearing on the HEW Review Panel's Final Report, and addresses the economic implications of the changes in FDA's trade secret policy that were proposed by the Review Panel.

Remington, Richard D. Post-Marketing Surveillance: A Comparison of Methods. PS 7811

Dr. Remington (Dean of the University of Michigan's School of Public Health) discusses a revision of our drug evaluation procedures so that beneficial and adverse responses are studied and reported simultaneously. He reviews various methodologies for post-marketing evaluation, and suggests a system suitable for prompt implementation.

Crout, J. Richard. The Nature of Regulatory Choices. PS 7812

Dr. Crout (Director of FDA's Bureau of Drugs) outlines the difficult issues involved in the saccharin ban and in the Laetrile question. He describes the role of health regulatory agencies today as not only law enforcement, but also judicial. They have the power to issue regulations, to enforce laws, and to resolve conflicting views--a microcosm of government itself.

*Consists of Publication Series (PS); Reprint Series (RS); and Working Papers (WP).

Swisher, Scott. The Introduction of Adenine Fortified Blood Preservatives: Introduction and an Interpretation of its History. RS 7814

Swisher, Scott. The Introduction of Adenine Fortified Blood Preservatives: Introduction and an Interpretation of its History. RS 7814

Dr. Swisher, a distinguished hematologist, presents an account of the introduction of blood preservatives which has interesting parallels with drug development and regulation.

Lasagna, Louis. Testimony of Louis Lasagna, M.D. on Drug Regulation Reform Act of 1978 before the Subcommittee on Health and Scientific Research, 12 April 1978. PS 7815

Landau, Richard. What You Should Know About Estrogens or The Perils of Pauline. PS 7816

Professor Landau writes a critique on the controversial subject of the use of estrogens for menopausal women. He includes the science, the medicine, and the politics of estrogen prescribing in an article filled with wisdom and wit.

Wardell, William. Excerpts from Monograph Entitled, CONTROLLING THE USE OF THERAPEUTIC DRUGS: AN INTERNATIONAL COMPARISON. RS 7817

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