THE PHARMACOLOGY AND TOXICOLOGY OF THE ENVIRONMENT[1]

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INTRODUCTION

The environment, by definition, is the aggregate of all the external conditions and influences affecting the life and development of an organism. It includes but is not limited to factors which affect the organism through chemical actions, as do drugs administered deliberately to modify favorably certain bodily functions; or poisons which, whether administered deliberately or otherwise, interfere with or abolish essential bodily functions.

In the pharmacological sense, the environment of man consists of the food he eats, the water he drinks and the air he breathes, since these are the vehicles by which the pharmacologically active components of the environment are introduced into his body. Man has been able to reach his present state of development because of his ability to adapt to his environment and to live harmoniously with it, and in this he does not differ from other living creatures. The organism which does not adapt to its environment perishes. The Darwinian terms "struggle for existence" and "survival of the fittest" attest the fact that the environment poses hazards which man and other organisms must continually combat and adapt themselves to in order to survive.

The present and rapidly increasing population of man attests to a successful biological adaptation to the present conditions of life. He has increased in stature, if not in wisdom, and currently enjoys a longer average expectation of life than his ancestors of a few centuries ago. The death rate from all causes for American men has been decreasing slowly since 1900 (1). He has controlled many devastating diseases by increased awareness and application of sanitary practices, and also by discovering agents for combating important diseases of specific etiology. He has expanded the production of food to meet the needs of his rapidly expanding numbers, and has discovered ways of preserving it and packaging it so that it can be transported to and distributed within the rapidly growing urban centers of population.

The literature concerning the pharmacology and toxicology of the environment is vast and found in many places outside the bounds of the usual pharmacological literature. This is perhaps because the social and behavioral aspects of the problem have had a greater impact on the literature than the pharmacological aspects. So many books, articles, and official reports have

[1] The survey of the literature pertaining to this review was concluded in July 1962.

been written that this review can only scratch the surface and refer the reader to sources of further information.

Pharmacology and Toxicology of Food

It is clear that an adequate diet consisting only of natural foodstuffs provides more than the substances required for growth, maintenance and repair, and reproduction of the organism. Bicknell (2) devotes a chapter of his book to naturally occurring poisons (in food). A recent example is also given by Kline *et al.* (3) who observed during a chronic feeding study involving reproduction in rats, that several of the rats delivered dead pups or pups that died within two or three days. Investigation revealed that the toxicity was due to the alkaloid solanine contained in sprouts on potatoes which were a part of the rats' diet. The effect could be duplicated by adding pure solanine to a diet of commercial laboratory chow.

Today the diet of man in an industrial culture contains not only naturally occurring substances capable in sufficient dosage of producing pharmacologic and toxic effects, but also a great many "chemical additives" placed there by man in the course of producing, processing, packaging and distributing food. Some of these chemical additives have nutritional value; others do not, and have given rise to a concern that they too may exert adverse pharmacologic and toxic effects. The chemical additives may be classified broadly as follows:

(*a*) Chemicals used to increase production of raw agricultural commodities, e.g., fertilizers, growth promoters, pesticides, herbicides.

(*b*) Chemicals added to food to improve nutritional value or preserve desirable qualities while the food is in the channels of distribution, e.g., vitamins, minerals, antioxidants, antimycotics, antimicrobials.

(*c*) Chemicals added to food to achieve an esthetic effect, e.g., flavors, colorants, thickeners, emulsifiers; or to improve convenience of food preparation in the home.

(*d*) Chemicals present in food unintentionally because they are extractable from materials used in processing, handling and packaging the food.

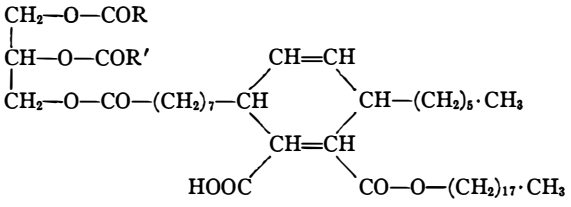
(*e*) Accidental additives with no functional role in the production, processing or distribution of food, e.g., pollutants of air and water.

The total number of chemicals added directly or indirectly to food is large, perhaps numbering several thousand. On the other hand, the concentration in which the vast majority of these additives appear in food is usually minute, of the order of parts per million. A pertinent question is whether the net effect of these additives is adverse or beneficial. Two types of adverse effects might be postulated, i.e., acute pharmacologic or toxic effects, and chronic toxic effects resulting in specific tissue injury, adverse effects on reproduction or resistance to disease, increased incidence of cancer or harmful mutations.

There have been few examples of acute toxic effects from chemical additives in food other than those attributable to carelessness, negligence or

accident. One recent incident occurred in Europe, however, which presents many interesting features. This is the so-called Planta disease, attributed to the ingestion of margarines containing an emulsifier known as ME-18. Reith (4) has given a detailed account of the epidemiology and etiology of the disease.

The compound ME-18 was produced in 1958 by the Oelwerke at Brake in the Federal Republic of Germany. Its published formula is as follows:



where R and R′ are fatty acids from soybean oil. According to Reith, ME-18 was in fact a mixture of uncertain and perhaps unpredictable composition. It is an emulsifier of weak activity designed to reduce the spattering of soy oil margarines during cooking.

Two manufacturers in the Federal Republic of Germany added 0.1 per cent ME-18 to margarine during the period July 7, 1958 to November 7, 1958. Wherever the margarine was sold, illness presenting mainly dermatological symptoms occurred, of which it is estimated that some 30,000 to 50,000 cases occurred in West Berlin alone. The disease was considered to be of virus or bacterial origin and the patients recovered although they continued to eat the margarine. In 1959 a large lot of margarine containing 0.1 per cent ME-18 was again sold in West Berlin but only a few cases of dermatitis were reported.

In 1960, ME-18 in concentration of 0.1 to 0.2 per cent was added to Dutch Planta margarine and there followed an estimated 50,000 cases of the syndrome among some 800,000 consumers of the product. This time the ingestion of Planta margarine was definitely associated with the occurrence of the disease and the addition of ME-18 was halted. Doeglas, Hermans & Huisman (5) have given a detailed description of the clinical features of the Planta disease.

While the epidemiological evidence strongly linked the Planta disease to the ingestion of margarine containing ME-18, the specific etiology of the disease remained obscure. It was not, according to Reith (4) a clear case of chemical toxicity. Why did the disease clear up spontaneously in patients who continued to eat the margarine? Why the apparent immunity in West Berlin in 1959? Reith lists the following working hypotheses concerning the etiology of Planta disease:

(*a*) ME-18 or a decomposition product is toxic or acts as an antigen.

(*b*) ME-18 or a decomposition product reacts with another substance to form a product which is toxic or acts as an antigen.

(*c*) ME-18 facilitates the absorption of a compound of the intestinal tract which is not normally absorbed.

(*d*) ME-18 facilitates the absorption of a certain type of bacteria through the intestine.

(*e*) ME-18 renders a certain type of bacteria or virus temporarily noxious.

(*f*) ME-18 produces a photosensitivity.

None of these hypotheses, however, had been confirmed at the time of Reith's review.

While it would be interesting to know what toxicological investigations of ME-18 were made prior to marketing, they are not described by either Reith, or Doeglas, *et al.* Reith does comment, however, that the toxicity of ME-18 would not have been revealed by the procedures recommended by Lehman, *et al.* (6), or by the Food and Agricultural Organization of the World Health Organization (7). It is, in any event, clear that ME-18 presents a case of bizarre and atypical acute toxicity, related in some way to its use as a food additive.[2]

The other type of concern, often expressed today, relates to the hypothesis that chemical additives in food may be producing adverse chronic effects as yet unrecognized, and which might not become apparent for decades or generations. Recent books by Bicknell (2), Herber (8), and Carson (9) argue the case that chemical additives in food are endangering human health. These and similar reviews give scant consideration to the beneficial effects of the chemical additives or to measures that have been taken to insure their safe use. Nor do they relate quantitative intake of the chemicals to the probable adverse effects. Counter arguments which consider the beneficial effects of chemical additives may be found in pamphlets published by Darby & Lam (10), Decker (11), the Manufacturing Chemists' Association (12), and the National Agricultural Chemists' Association (13).

Neither government, industry, nor the scientific community have ignored the problems of acute or chronic toxicity from chemical additives in food. While recognizing that the food supply must be safe, it has become apparent that no simple solution like banning the use of chemical additives in the production, processing, and distribution of foods is practicable—at least at this time.

Pharmacologists have relied on the principle that for drugs there are safe doses and dangerous doses; effective doses and non-effective doses. For each drug, the goal is to find a dose large enough to be effective and small enough to be safe. The same principle applies to chemical additives, and as Mrak (14) has recently reiterated: "there are no harmless substances, only harmless ways of using substances." On this basis it is impossible, no matter

[2] A recent review article by Simons (83) rejects the hypotheses that the "so-called margarine illness in Holland" (Planta Disease) resulted from the direct or indirect toxic effects of the margarine or the emulsifier.

how desirable, to classify chemical additives per se as those which are poisonous or deleterious, and those which are harmless.

The concern of the scientific community and of industry is made evident by the formation in 1950 of the Food Protection Committee under the auspices of the Food and Nutrition Board of the National Academy of Sciences—National Research Council. The Food Protection Committee has issued a series of publications (15 to 20) relating to the principles and procedures for evaluating the safety of chemical additives in foods. The Food and Agricultural Organization of the World Health Organization has also been active in issuing similar publications (7, 21 to 24). To these may be added the review articles of Lehman, *et al.* (6, 25 to 28) on testing procedures, the review article of Barnes & Denz (29) on the determination of chronic toxicity, of Hayes (30) on pesticides in relation to public health, of Reith (31) on the relationship between food chemistry and toxicology, and papers by Frazer (32, 33) on pharmacological aspects of chemicals in food, Gaddum (34) on the estimation of the safe dose, Barnes (35) on research vs. testing, and many others.

Hueper (36) reviewed the question of possible carcinogenic effects from chemical additives to food and postulates the existence of these effects. The Food Protection Committee of the National Academy of Sciences—National Research Council has discussed problems in evaluating carcinogenic hazards from the use of food additives (37). One conclusion of the Food Protection Committee report was that:

> Information obtained from dose-response curves prepared from data obtained in animal experiments appears of little practical use in evaluating carcinogenic hazard for man. The apparent lack of quantitative correspondence in the carcinogenicity of a substance for different mammalian species and the other complicating factors that have been discussed make meaningful extrapolation from the "no-effect" level on the dose-response curve to a "safe level" of use by man currently impossible. It seems reasonable to infer, however, that a no-effect level exists for man as well as for laboratory animals.

Until some means for establishing a "no-effect" or "safe" level for specific carcinogens in the diet of man is achieved, it is anticipated that the law will continue to forbid any finite level of a chemical additive which is found to induce cancer when ingested by man or animals.

Alexander (38) has questioned whether some chemical additives may be capable of producing harmful genetic mutations. Carson (9) reiterates this concern. Alexander stresses the difficulty of testing genetic effects of chemicals on mammals and points out:

> Nothing comparable to the huge mouse 'factory' of the United States Atomic Energy Commission at Oak Ridge, in which a hundred thousand animals are used for just one experiment on radiation mutagenesis, is available for testing of chemicals." He adds: "At the present time it is impossible to calculate whether chemical mutagens introduced by man into his environment constitute a genetic danger.

And:

It may be that all the possible embryonic and genetic hazards can, on investigation, be discounted one by one. Let us hope so, but instead of merely hoping, let us find out.

In summary, much concern has been voiced concerning possible pharmacologic and toxic effects from chemicals reaching man via his food supply. Much work has also been done to evaluate this potential hazard and to control it. The success of these evaluation and control measures is witnessed by the fact that most of the concern has had to be focussed on adverse effects which might—perhaps—occur at some time in the future. The problem remains, however, as one which will continue to require serious attention from all those concerned with public health, along with constant refinement and improvement of methods for evaluating the safety of food additives.

The Pharmacology and Toxicology of Water

Water is an essential medium for conveying substances into and out of the body; for distributing substances within the body; the medium in which most of the reactions of metabolism are carried out; and a heat transfer agent. Yet in one sense man only borrows it for a short time since over the long run his daily input of water is matched by his daily output.

Pure water, as H_2O, is not found in nature, and all natural waters contain dissolved and suspended materials, organic and inorganic. Nor has it been possible to specify completely the composition of the "ideal" water for human consumption, except to say that it is not pure H_2O; rather it is a very dilute aqueous solution of desirable trace substances, attractive in appearance, pleasant in taste, free from odor, and noninjurious. Suggested new United States Public Health Service Standards for potable water have been published in the Federal Register (39).

It has long been recognized that natural waters can be vehicles for substances producing beneficial pharmacologic as well as toxic effects. Thus, the fluoride ion in certain natural waters was associated with the prevention of dental caries and has led to extensive programs of artificial fluoridation. On the other hand, the occurrence of excessive nitrate ion in natural water has been associated with numerous cases of methemoglobinemia in infants (40).

A great many industrial processes also use water as a medium for transporting materials into, through and out of the industrial plant; as a chemical reaction medium; and as a heat transfer agent. Where natural water is abundant it is often most convenient and inexpensive to discharge plant wastes into the nearest stream, even as a great many communities find it most convenient and inexpensive to discharge raw human wastes into the nearest stream. With a low population density and an abundant water flow, such practices have seemed both tolerable and logical. With increasing

population density and industrialization along with concomitant increase in withdrawals from natural water sources there has occurred a great increase in the amount of waste-contaminated water returned to the natural sources from which man must again borrow water for his daily needs. The increasing use of pesticides on agricultural lands has also resulted in contamination of water sources through "run-off."

The increasing burden of contaminants in natural waters, both from human wastes, industrial wastes, and from pesticides, has resulted in many expressions of concern about their adverse effects on plant and animal life as well as their possible adverse effects on man (8, 9, 41 to 45).

The rise in nuclear technology has added a new problem in water quality—the control of contamination by radioactive wastes. There is no argument over the potential harmful effects of such contamination if it reaches significant levels. Consequently the disposal of radioactive wastes into water sources in the United States is strictly regulated by the United States Atomic Energy Commission and, frequently, by local authorities as well. Abee & Cottrell (46) describe the results of surveys of the radioactive levels in the Tennessee River system used for disposal of liquid radioactive wastes from the Oak Ridge National Laboratory. It was found that these levels were well below the maximum safe limits, but: "It should be noted that, while there are fluctuations in the level of activity, the general trend is in an increasing direction." If, as Bronowski (47) predicts, the trend of the future in energy production may be toward relatively small but widely scattered nuclear energy plants, the health effects of radioactive contaminants of water may well assume a new importance in many sections of the world.

As with contaminants of food and air, acute pharmacologic and toxic effects from chemical contamination of water are rare. Aside from nitrate poisoning, complaints have usually referred to bad taste or odor, or to foaming attributable to detergent residues. The latter phenomenon has elicited many expressions of concern, but the toxicity of the detergents in question (i.e., the alkyl benzene sulfonate type) has been rather thoroughly studied (48 to 50) and the evidence suggests that no adverse health effects are to be expected from the residues which have been found in water to date.

Hueper (36) has called attention to several reports of the presence of various carcinogens in raw waters. While there is no evidence which establishes a cause-and-effect relationship between these water contaminants and human cancers, it is nevertheless apparent that water might, if allowed to do so, develop into a carcinogenic hazard for man.

On the other side of the coin, some natural contaminants of water exert beneficial chronic pharmacologic effects. Thus, Schroeder (51, 52, 53), and Morris, *et al.* (54) have called attention to a significant negative correlation between the hardness of water (mineral content) and the incidence of cardiovascular disease. Strokinger (40) points out that vanadium in trace quantities lowers serum cholesterol; that vanadium is present in ppb range in

certain New Mexico waters; and that New Mexico has the lowest incidence of male mortality from coronary heart disease. The effect of other trace elements in water is being investigated (40).

At least passing mention should be made of fish kills resulting from the intentional use of pesticides or from the accidental contamination of water with piscides (55). Most fish succumb to much lower doses of pesticides than do mammals, but their death does indicate a certain degree of water contamination and points to the necessity for care in the use of pesticides in and around water sources.

The laboratory evaluation of the effects of water contaminants does not differ in principle from that involved in the evaluation of the effects of chemical food additives, which has been discussed above. Stokinger & Woodward (56) have called attention to ways in which existing toxicological data might be applied for the specific purpose of establishing drinking water standards, as well as to the limitations of such data.

It is obvious that pharmacologic and toxic effects from water pollutants cannot be ignored and that this field will require more attention from pharmacologists and toxicologists in the future than it has received in the past. Stokinger (40) makes the grim prediction that: "These problems and others to come will provide enough grist for toxicologic milling for more toxicologists than are presently available." It is encouraging, however, to note that pure water can be prepared—for a price—from even heavily contaminated sources. The technology for purifying nonpotable water exists, but the cost is high compared to that of natural water.

The Pharmacology and Toxicology of Air

The atmosphere is the immediate source of oxygen and CO_2 on which life depends. It extends several hundred miles outward from the surface of the earth and weighs some 5×10^{15} tons. It is essentially stable in composition because of natural equilibria and it is usually in motion.

Because of its size and motion, the atmosphere has been used as a dilution reservoir to dispose of volatile waste products, e.g., the smoke from man's fires, without materially changing its composition—at least, up to the beginning of the Industrial Revolution. Two variables, both increasing rapidly for the past hundred years, population and industrialization, have made it possible for man to effect local and even general changes in the composition of the atmosphere.

Thus, the concentration of CO_2 in the air has been steadily increasing during this century due to increased burning of fossil fuels, and the concomitant limitations of the surface absorption of CO_2 by green plants [Chambers (57); Bonner (58)]. The air now bears a burden of radioactive particles due to nuclear weapons testing. Locally, pollution of the air with the waste products of technology has effected changes readily detectable by the eyes and nose, which have at times resulted in irritation and have been associated with tissue damage and an increased death rate.

We have thus reached a state where the American Association for the Advancement of Science in its charge to its newly formed Air Conservation Commission (59) could say:

> We now possess the capacity to determine whether the atmosphere shall be used in such a way as to preserve its ability to sustain life or whether man's atmospheric environment shall continue to deteriorate to the detriment of his health and his way of life. The future of mankind depends on the wisdom with which we conserve our atmospheric resources.

In view of the above it is not surprising that pollution of the atmosphere has been charged with responsibility for both acute and chronic pharmacologic and toxic effects.

Most citations of acute toxic effects attributable to air pollution refer to episodes which occurred in the Meuse Valley in 1930; in Donora, Pa. in 1948; and in London in 1952 (60 to 63). On each of these occasions: (*a*) local meteorological conditions resulted in an accumulation of pollutants in the atmosphere which persisted for several days; (*b*) irritation of the mucous membranes was experienced; and (*c*) there was a sharp rise in the death rate from cardiovascular and pulmonary disease, particularly among the aged.

That there is a cause-and-effect relationship between air pollution and these excess deaths seems certain, but it is not the simple relationship between dose and a specific toxic action which is familiar to pharmacologists. Thus Hatch (64) states:

> It is improper perhaps to conclude that air pollution has been the cause of the reported excess deaths and to search therefore for direct cause-and-effect relationships. The polluted air has acted rather as a secondary insult, operating to produce serious illness in individuals who had arrived at their crippled states for a variety of reasons." Dubos (65) takes a similar point of view: "There is no doubt that heart disease is extremely widespread and has many different origins, and that bronchitis is associated with the activity of viruses and bacteria ubiquitous in all human communities. What then are the causes of deaths which follow smogs? The vascular lesions which are so common in modern man? The bacteria or viruses which almost everyone carries in his respiratory tract? Or the poisonous substances in the air which reach everybody but kill only a few?

Regardless of the specific etiology of the excess deaths, it seems reasonable to predict that a repetition of the conditions which prevailed in the Meuse Valley in 1930, in Donora, Pa. in 1948, or in London in 1952, would again be attended by a sharp rise in death rate from pre-existing cardiovascular and respiratory disease. The same kind of increase, however, is also evoked by prolonged hot spells (66) without air pollution. This suggests, at least, that the smog functioned more as a nonspecific stress than as a specific toxicant.

That air pollution can produce direct irritant effects on mucous membranes seems firmly established. Thus, Los Angeles smog consistently elicits

complaints of eye irritation, the cause of which is one or more of the products of vehicular exhaust gases modified by photochemical reactions (61, 67, 68). Both Stokinger (68) and Heiman (63) discuss the problem of defining more precisely the pharmacology of these complex mixtures of air pollutants. In addition, mechanism of action needs to be elucidated for those compounds which have a radiomimetic effect and those which appear to have an immunochemical action [Stokinger (40)].

With respect to chronic toxic effects of air pollution, attention has centered primarily on its association with chronic respiratory obstructive diseases (asthma, bronchitis, emphysema), and lung cancer. Extensive laboratory studies with animals have been carried out using both single contaminants and combinations (68 to 70). The results, while interesting as toxicologic investigations, have not been decisive with respect to air pollution toxicity. One reason, perhaps, is that laboratory animals do not smoke cigarettes. However, there are other reasons, and these relate to species variations and differences among individuals of the same strain as well as factors due to length of exposure and concentration profile of inhaled materials.

In any assessment of the causes of either chronic obstructive respiratory disease or lung cancer, smoking habits must be taken into account (1, 71). The problem is to determine how much, if any, responsibility for these conditions is attributable to air pollution per se.

Chronic bronchitis is a disease of high prevalence in Great Britain and ranks among the more prominent causes of death. Morbidity studies (72, 73) have associated the occurrence of chronic bronchitis with air pollution. Higgins & Cochran (74), however, have suggested that the effect of air pollution on chronic bronchitis may be less than previous work had indicated. A more recent study based on a national survey and reported by Fletcher, *et al.* (71) concludes that the occurrence of chronic bronchitis correlates with smoking, with place of residence (i.e., air pollution) and with social status. It was concluded that:

> There are significant differences between rural and urban males in their smoking habits, but as Table XI shows, these differences in themselves cannot explain the rural:urban gradient in male morbidity. Similarly, Table XII shows that although there are small but significant differences in smoking habits between social classes, again these have no material effect on the social-class gradient in chronic bronchitis. These results in the age group 40 to 64 thus confirm the independent effect of social class differences and cigarette smoking on bronchitis prevalence found in men over 60 by Edwards, *et al.* (75).

Thus, air pollution may be one of several factors contributing to chronic bronchitis, but its specific role remains obscure.

The relationship of air pollution to lung cancer is equally difficult to elucidate. Lung cancer is increasing at a more rapid rate than other forms of cancer in all countries where adequate mortality statistics exist. [Hammond

(1)]. Urban air has been shown to contain small amounts of polycyclic aromatic hydrocarbons, some of which are known carcinogens, e.g., 1:2 benzanthracene and 3:4 benzypyrene [Kennaway & Lindsey (76), Sawicki, *et al.* (77)]. It is tempting, therefore, to speculate that air pollution may be an important cause of the observed increase in lung cancer [Hueper (78), Kotin (79)].

While the evidence does not eliminate air pollution as a contributory cause of lung cancer it does suggest that cigarette smoking far outweighs it in importance [Kennaway & Lindsey (76), Hammond (1), Royal College of Physicians of London (80), Dorn (81)]. There appears to be no evidence that air pollution in and of itself has caused lung cancer in man.

In summary, acute effects from the inhalation of polluted community air so far have been infrequent. When they have occurred, the effects have been limited to mucous membrane irritation and, in rare instances, an increase in mortality from pre-existing cardiovascular and respiratory disease. Experimentally, the effects of prolonged inhalation of single contaminants and of contaminant mixtures is being actively explored but without, as yet, decisive results.

The effects of prolonged exposure to low levels of contaminants is in need of investigation. Pharmacologically, this is an area complicated by; (*a*) host variability due to heredity or acquired resistance; (*b*) possible adaptation, mutation, or both; (*c*) effects of ageing; (*d*) biological stress periods, such as reproduction and growth; (*e*) intercurrent disease; (*f*) exposure to varying mixtures; and, (*g*) cigarette smoking.

Basically, there is no reason why the air could not serve as a vehicle for conveying substances with pharmacologic or toxic effects into the body of man. Thus, while the problem has not yet proved to be urgent, except in widely isolated instances, it is obvious that the potential pharmacologic and toxic effects of air contaminants should continue to receive serious attention and study.

SUMMARY

In view of the fact that the environment of man, his food, air, and water, can serve as a vehicle for conveying to him materials which might under some circumstances exert adverse pharmacologic and toxic effects, and since examples can be cited where hazardous amounts of contamination of food, air and water have occurred at some time and in some place—it is obvious that man should be concerned about the safety of his environment.

One solution to the problem has been the demand for legislative prohibition of the pollution of food, air, and water by any chemical additives other than those put there by nature. While this is indeed a solution to the problem it unfortunately interacts with the solution to other problems of equal scientific, social, and political importance. Could one, after abolishing pollution of food, air, and water, feed the current and ever-expanding population; or provide the kind of transportation mobility to which the current

economy is geared; or provide employment at even the present scale; or defend the nation against aggressors; or maintain an acceptable standard of living; or raise sufficient taxes? These too are questions of prime importance.

The interaction of the pharmacologic problem with other problems is well illustrated by a quotation from Dorn (82) "The future may witness a dramatic increase in man's ability to control his environment, provided he rapidly develops cultural substitutes for those harsh but effective governors of his high reproductive potential—disease and famine—that he has so recently learned to control."

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