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- Can vitamin C work to both cure and CAUSE cancer?
- Does vitamin E operate both for and against sexual potency?
- When might vitamin A act to prevent breast cancer and when act to CAUSE it?
- When will zinc suppress the immune system and when strengthen immunity?
- Could strenuous exercise help CAUSE cancer and reduce longevity?

For answers see the
BIG BOOK, *The Reverse Effect*

"I am impressed with Heiby's attempt, when reviewing a particular issue, to find balance in various observations, while at the same time to keep an open mind about the possible. That is the stuff of good science." - T. Colin Campbell, Ph.D. (animal nutrition), Prof. Nutritional Biochemistry, Cornell Univ.; NIH res. career devel. award; Sr. Adv., Amer. Instit. Cancer Res.; Vis. Scholar, Univ. Oxford, Eng. Authority on nutrition-toxin interactions; nutrition and cancer.

"There is supposedly a Hindu proverb which tells us that we can drown in nectar. The idea is that if a little is good, a lot is not necessarily better. This is the principal message of *The Reverse Effect* and it is an important and timely message indeed. Walter Heiby has compiled and annotated a valuable catalog of the positive and negative sides of a variety of dietary substances including vitamins and minerals. The book demonstrates clearly why we so often get mixed messages regarding effects of specific minerals, vitamins or drugs. This readable book has a thorough bibliography and the citations and quotations are accompanied by the author's pithy comments. The book should be required reading for people practicing medicine or consulting on nutrition. It would actually be a useful addition to anyone's library." - David Kritchevsky, Ph.D. (Chem.), Prof. and Assoc. Dir., Wistar Institute; visiting prof. at Royal Society of Medicine, London, Eng. Authority on lipid metabolism, fiber, atherosclerosis and nutrition.

"*The Reverse Effect* is an exceedingly valuable and important contribution to the often seemingly confusing and contradictory fields of immunology and physiological homeostasis. An error regarding whether an epidemiologic relationship reflects cause or symptom can be very important; the difference is between hazard and benefits! Thus, severe problems exist in biomedical and in epidemiological literature regarding use and misuses of statistics. *The Reverse Effect* will be quite helpful in resolving conflicts and errors that result from abuses and misuses of statistics, epidemiology, and science." - Richard J. Hickey, Ph.D. (Biophysical Chemistry), Senior Research Investigator (retired) Dept. of Statistics, Wharton School, Univ. of Pa. Authority on mutagenesis, cancer, radiation hormesis, epidemiology, scientific malpractices.

"It is a well known pharmacological fact that drugs have more than one effect depending on the dose. Drugs can be ineffective at small doses, effective at therapeutic doses and toxic at large doses. *The Reverse Effect* extensively documents similar phenomena in the case of vitamins and minerals." - Julius Axelrod, Ph.D. (Chem pharmacol). Authority on noradrenaline; drug and hormone metabolism. Nobel Laureate, Medicine & Physiol., 1970.

LIBRARY LOVERS: PAGE 101

BETTER HEALTH

and the

REVERSE EFFECT

by

WALTER A. HEIBY

This is a sampler consisting of material from the BIG book *The Reverse Effect: How Vitamins and Minerals Promote Health and CAUSE Disease* by Walter A. Heiby. In addition to acting as an introduction to the reverse effect, it is designed to aid scientists in formulating protocols for proposed studies.

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The Reverse Effect

is similarly growing in acceptability. Our concept of pleasure today should not be unduly limited.

An important key to living healthfully and youthfully all one's life is to maximize the number of experiences that are apt to be worth experiencing. Perhaps to be most healthy we must continually experience the greatest joys of all. And what are the greatest joys of all? Each of us will have different ideas of such joys, but perhaps you'll agree with mine: the giving and receiving of love to and from a very special person and helping that person and all others with whom I come in contact to live happier, more meaningful lives. (If the health benefits of love could be provided by a pill, that pill would outsell all the vitamins and drugs on the shelves of drugstores and of health food suppliers.) In our giving and receiving happiness we should strive to achieve in ourselves, and foster in others, peace of mind.*

The *pleasure concept* of health deserves our attention not only in terms of *thought* but in terms of *action*. A most important prescription for health and longevity is to *determine what you like to do—what makes you very happy—and then find lots of opportunities to do it!*

Pleasure must, however, be subject to the dictates of the Greek principle of the *golden mean*. The *golden mean* recognizes that there is a position between "too little" and "too much" that is often superior to either extreme. Not only in the case of pleasure but in the case of various other phenomena, including the action of toxins and of nutrients, there is a *golden mean* that may be more healthful than either extreme. Science has a lot to learn about the quantities of nutrients or of toxins which are likely to lead to either health benefits or health threats. Like the love-hate duality to which human love affairs are subject, so there is a love-hate body reaction that may be exhibited by foods, vitamins, minerals, alcohol, coffee and other substances.

* An important step toward achieving and maintaining peace of mind is to keep a list of jobs to be done. Work on each item in the sequence of its time-order importance. Keep at the top of the list the never-finished project entitled: "Make love, not war."

The Reverse Effect

The *theory of the reverse effect* states that there is a good probability that any activity or any substance that is health-promoting or health-destructive in a given concentration may, on occasion, reverse its role and become respectively health-destructive or health-promoting at a different concentration. Furthermore, the same activity or the identical dosage of a substance may sometimes show an opposite effect in different persons or animals. What I term a *reverse effect* is not always a matter of going from enhancement to inhibition, but may simply be a trend reversal from increased enhancement to lesser enhancement or from increased inhibition to lesser inhibition. The action will be modulated* not only by the amounts of the chemical or other entity being considered but by the species involved, its health-disease state and its environment. In some cases (e.g., vitamins C and E) the *reverse effect* may involve a change in role from that of antioxidant to pro-oxidant. Perhaps the *theory of the reverse effect* will remind some of my readers of the statement of J. B. S. Haldane: "Nature is not only queerer than we suppose, but queerer than we can suppose."

The toxicologist, M. Alice Ottoboni⁵² is referring to the phenomenon I call the *reverse effect* when she writes:

Every toxicologist who has been engaged for any period of time in research into chronic toxic effects of chemicals has observed, more often than not, that animals in the group with the lowest exposure to the test chemical grew more rapidly, had better general appearance and coat quality, had fewer tumors, and lived longer than the control animals. I know from personal experience that novice

* Note my use of the word *modulated*. If the *reverse effect* concept proliferates, I suspect that, in the absence of dose-response data on a given substance relative to a given disease, scientists and physicians will increasingly employ the words *modulate* or *modulated* when an effect is apparent but it is not known if a given dosage works as a cause or as a cure or acts to exacerbate or to mollify.

The Reverse Effect

toxicologists usually consider such observations as aberrations in their data or the result of some flaw in their experimental design or conduct. They are usually loath to call attention to such findings, perhaps because to do so might bring their competence into question, or because they are unable to explain the reason for such findings. It is only with the confidence that comes with experience that the research toxicologist can comfortably acknowledge the occurrence of such results in his own experiments and broach the subject with his colleagues. The reaction from his fellow toxicologists is usually one of, "You, too?"

The phenomenon of beneficial effects from trace exposures to foreign chemicals, although often a subject of conversation among toxicologists, particularly with regard to why such effects occur, is rarely mentioned in the scientific literature. If the phenomenon does occur in a chronic toxicity experiment, the text of the paper reporting the results will seldom mention the fact. It is only by careful perusal of the data tables and figures presented in the body of the text that the phenomenon is revealed. Such subtleties are lost on people who read only the abstracts of scientific papers. Unfortunately, there are some scientists who may be counted among the abstract-only readers.

The doctrine of "sufficient challenge" of H. F. Smith, Jr.¹⁴ was introduced in a subnote earlier in this chapter. This doctrine is based on the concept that an unused function atrophies. Ottoboni⁵³ quotes Smith as saying: "I think that most of the small non-specific responses which we measure in chronic toxicity studies at low dosages are readjustments or adaptations to sufficient challenge. I interpret them as manifestations of the well-being of our animals, healthy enough to maintain homeostasis. They are beneficial in that

How to Use the Reverse Effect

they exercise a function of the animal. Only when challenge becomes overwhelming does injury result." The doctrine of "sufficient challenge" obviously casts doubt on the attitude expressed by the Delaney Clause. The Delaney Clause is based on the idea that if a substance is carcinogenic in large dosages it may also be dangerous in small dosages and it should therefore not be permitted as a food additive. *The Federal Register*⁵⁴ perpetuates the line of reasoning behind the Delaney Clause by saying, "The exposure of experimental animals to toxic agents in high dosages is a necessary and valid method of discovering possible carcinogenic hazards in man." Those fostering the Delaney Clause are not concerned with the possibility that such "carcinogens" might, at certain dosages, constitute a "sufficient challenge" and offer protection against cancer. We will consider the Delaney Clause again later in this chapter.

In this book I will report on much research suggesting that large amounts of vitamins and minerals may at times be harmful. Conversely, I speculate that small quantities of toxins may beneficially stimulate the liver to be more efficient just as muscles become stronger when they are occasionally exercised.* The advice to eat a well-balanced diet may be good information not only in order to achieve a broad spectrum of needed nutrients but because it introduces the body to a well-balanced but minor intake of toxins, at least some of which in small amounts might actually be beneficial. Nutrition and pharmacology must become sciences, not merely of nutrients, drugs and toxins, but sciences of dose-response relationships.

Thus, I am suggesting that we do not always know which constituents are good and which are bad for the body. *That which is good may be bad; that which is bad may be good.* It depends on the circumstances and one of the circumstances is the quantity of the presumed nutrient or presumed poison that is involved. W. W. Duke,⁵⁵ three-quarters of a century ago, tested the effects on blood platelets of many different agents such as toxins, bacteria, a chemical

* The rationale for this proposed action may involve stimulation of the liver's microenzyme cytochrome P-450. This will be discussed in Chapter 3 (references 129b-d of Chapter 3).

The Reverse Effect

Alice Ottoboni¹⁰⁴ tells about a "megamouse" study of the National Center for Toxicological Research (NCTR)¹⁰⁵ involving more than 24,000 mice and the carcinogen 2-acetylaminofluorene (AAF). A committee of the Society of Toxicology¹⁰⁶ reviewed the NCTR report.¹⁰⁵ Ottoboni, in citing from this review, said:

The Society's review points out that the statistical model used for extrapolating effects from very low doses "provides statistically significant evidence that low doses of a carcinogen are beneficial...."

"If the time-dependent low-dose extrapolation models are correct," the Society states, "then we must conclude that low doses of AAF protected the animals from bladder tumors." However, the Society also asserts, "...not only is the simple model used by NCTR statisticians inappropriate to the data, but most of the models that have been proposed in the statistical literature are also inappropriate." They urge a "profound rethinking of the entire problem of chemical carcinogenesis and low-dose extrapolation."

The *theory of the reverse effect* suggests just the opposite of the standard line of reasoning. Small doses of a huge-dose cancer-causer might protect against cancer! Tomorrow's statements of physiological interactions with drugs and nutrients are likely to be elucidated in dose-response tables rather than in simple sentences.

Then too, the fact that many drugs have side effects corresponding with the same condition for which they are curative provides many examples of the *reverse effect*. This fact also serves as a warning that drugs must be carefully studied for dose-responses and possible *reverse effects* that can be exacerbative rather than curative. If you study several drugs in the *Physicians' Desk Reference*¹⁰⁷ you will probably discover that, for at least a few of them, the list of side effects contains a symptom for which the drug

How to Use the *Reverse Effect*

is sometimes curative. The diazepam, Valium® is one such drug.* Among the indications for its use is included "management of anxiety disorders or for the short-term relief of the symptoms of anxiety." Among its adverse reactions are included "hyperexcited states" and "anxiety."^{107b} The barbiturate, Nembutal® Sodium is used as a "sedative hypnotic." Among its side effects are "agitation," "nightmares," "nervousness" and "anxiety."^{107c} Quinidine sulphate (Quinora®) is used for "paroxysmal atrial tachycardia" and "paroxysmal atrial fibrillation" and "paroxysmal ventricular tachycardia when not associated with complete heartblock." Among its adverse effects are "ventricular tachycardia and fibrillation" and "paradoxical tachycardia."^{107d} The rauwolfia product, Harmonyl® is employed for its "antihypertensive effects" and it also displays "sedative and tranquilizing properties." Among its adverse effects are "nervousness," "paradoxical anxiety" and "nightmares."^{107e} To cite a final example, Asellacrin®, a growth hormone (somatropin or somatotrophin) which is used in treating short children in the attempt to increase their height, may sometimes be subject to a *reverse effect*. The *Physicians' Desk Reference* relates that "bone age must be monitored annually during Asellacrin® administration, especially in patients who are pubertal and/or receiving concomitant thyroid replacement therapy. Under these circumstances, epiphyseal maturation may progress rapidly to closure."^{107f} In other words, sometimes there is a *reverse effect* and, instead of the child growing taller, his epiphyses close and he completely stops growing.

In each of these drugs the normal action shows a *reverse effect* at some concentrations in some persons. A *reverse effect* of the drug diphenylhydantoin (Dilantin®), alias phenytoin, involving vitamin D is shown in Chapter 4 and, in connection with hypertension (in the potassium section of Chapter 7), we will note the *reverse effect* shown by hydrochlorothiazide. At a given dosage a

* The patent on Valium® has recently run out, so there are likely to be many more diazepam drugs to offer it competition. Horrobin^{107a} speculates that diazepam and possibly the benzodiazepines, including chlordiazepoxide hydrochloride (Librium®), may promote tumor growth. (Tumor promoters do not usually cause cancer when used alone but can enhance the effect of a cancer initiator.) Is it possible that diazepam and/or benzodiazepines at some dosage might show a *reverse effect* and act to cure cancer?

were performed at various toxic and nontoxic levels. However, I think the entire group of 300 extracts should be studied for *reverse effects* and possible antitumor action at some yet-to-be-discovered dosages.*

The Reverse Effect as a New Therapeutic Paradigm

Thomas S. Kuhn has thrown interesting new light on the ways in which various sciences evolve. Paramount to Kuhn's viewpoint is the role in scientific research played by "paradigms" which he defines as "universally recognized scientific achievements that for a time provide model problems and solutions to a community of practitioners."^{108c}

Kuhn develops the thesis that "normal science," as he calls it, presupposes one or more paradigms which are accepted by practicing scientists as being beyond questioning. Thus, research tends to be looked upon as an act of puzzle-solving that occurs within the bounds set by a paradigm rather than as a free-wheeling exploration of the unknown. Kuhn, in his thought-provoking book *The Structure of Scientific Revolutions*, says:

...normal science repeatedly goes astray. And when it does—when, that is, the profession can no longer evade anomalies that subvert the existing tradition of scientific practice—then begin the extraordinary investigations that lead the profession at last to a new set of commitments, a new basis for the practice of science. The extraordinary episodes in which that

* D. R. Stoltz et al.^{108a} found that 22 fruits and vegetables had mutagenic activity. Grapes, onions, peaches, raisins, raspberries and strawberries showed the most potent mutagenicity. Could components (perhaps flavonoids) from these six be concentrated to act as anticancer agents, as the *reverse effect* suggests? Many flavonols found in foods are mutagenic and references for this finding are found in Chapter 6. I have not seen studies indicating that 3,4'-dimethoxy-3',5,7-trihydroxyflavone and centaureidin are mutagenic and/or carcinogenic. However, S. Morris Kupchan and E. Bauerschmidt^{108b} found that these flavonols from the plant *Baccharis sarothroides* showed significant inhibitory activity against cells derived from human carcinoma of the nasopharynx carried in cell culture.

shift of professional commitments occurs are the ones known in this essay as scientific revolutions. They are the tradition-shattering complements to the tradition-bound activity of normal science.^{108d}

Kuhn, in further development of his view of "normal science," goes on to say:

Few people who are not actually practitioners of a mature science realize how much mop-up work of this sort a paradigm leaves to be done or quite how fascinating such work can prove in the execution. And these points need to be understood. Mopping-up operations are what engage most scientists throughout their careers. They constitute what I am here calling normal science. Closely examined, whether historically or in the contemporary laboratory, that enterprise seems an attempt to force nature into the preformed and relatively inflexible box that the paradigm supplies. No part of the aim of normal science is to call forth new sorts of phenomena; indeed those that will not fit the box are often not seen at all. Nor do scientists normally aim to invent new theories, and they are often intolerant of those invented by others. Instead, normal-scientific research is directed to the articulation of those phenomena and theories that the paradigm already supplies.^{108e}

Thus, dramatic new breakthroughs can occur only through the process of overthrowing well-established doctrines. The doctrine that extrapolation can predict effects in nutrition and in medicine must be viewed as being obsolete. A *reverse effect* might be present and produce a reaction quite the opposite from what data extrapolation would suggest—perhaps even a cure from a known disease-causer. I

Healthful Thoughts and Other Supplements

This book deals not only with the prevention of *disease*, but also with far more. Beyond just prevention of disease, this book relates to the building of *health*. Health is a state of well-being which is far superior to the mere absence of disease and relates to joy, happiness and the enhancement of life; and remember this: joy, happiness and the enhancement of life cannot only be the *result* of superior health but a *cause* of superior health. Most persons now believe in the reality of psychosomatic disease. Why not also believe in the reality of psychogenic health? You can think yourself into better health. Do it!

Often the comment is heard that if one eats good food, then supplementation is unnecessary. There are several reasons why this doctrine is apt to be false. Try as we can, it is unlikely that all our foods will be grown on rich soil, and thus at least some of these foods are less likely to contain the healthful array of minerals our ancestors enjoyed. Even if our foods were all grown on rich soil, many would still be irrigated with polluted waters and exposed to air pollution. Furthermore, we are breathing that polluted air and we are subjected not only to toxic chemicals in our foods but to those in cosmetics, cleaning compounds, and so on. Then too, our society subjects us to many mental stresses which may, if we let them influence us negatively, deplete vitamin and mineral stores as the body attempts to compensate for those stresses.

G. Brubacher et al.¹¹⁸ make the point that borderline vitamin deficiency exists in many population groups and in single persons even in industrialized countries. Their studies demonstrated that the avoidance of pork and whole wheat bread can lead to a borderline vitamin B₁ deficiency. Similarly, their studies have shown that avoidance of other items can lead to other vitamin deficiencies. Most persons who have fully operational food-assimilational and enzyme systems can probably get their vitamin and mineral needs from their diet if their objective is an *average* state of health. Those less efficient in food assimilation and in enzyme production or those with unusual

diets (such as those who avoid pork and whole wheat bread) or those desiring superlative health may require supplements.* Moreover, R. L. Gross and P. M. Newberne,¹¹⁹ in citing C. M. Leevy et al.^{119a} who studied a selected municipal hospital population, say:

These studies of isolated vitamin deficiencies lead to the inescapable conclusion that a single nutrient deficiency can result in profound impairment of specific immunologic processes—a concept that has not yet received widespread attention or general acceptance. This inattention may be having important clinical results, since the immunologic defects resulting from even marginal deficiencies may significantly alter disease course and/or therapeutic response. The incidence of hypovitaminosis discovered in a randomly selected U. S. hospital population in the 1960's dramatically illustrates that this is not an exclusive problem of underdeveloped countries. In this study, only 12% of the 120 patients had normal serum levels of all vitamins tested; 88% had at least one deficiency, and 59% had two or more biochemical deficiencies. There appeared to be no consistent trend with regard to sex, age, or racial group. Only 39% of the deficient patients had any history of dietary deficiency, the other 61% consuming what was considered a normal U. S. diet. Clinical signs of deficiency were present in only 38%; the remainder had deficiencies falling into the subclinical or marginal categories.

The elderly may be especially prone to vitamin deficiencies. D. J. Smithard and M. J. S. Langman¹²⁰ found subclinical vitamin C

* On the other hand, it may be possible that food itself could sometimes supply a dangerous *excess* of vitamins. Certainly, Eskimos consuming bear liver have been known to get dangerous excesses of vitamin A. Kummerow maintains, as we will see in Chapter 4, that foods may contain unhealthful excesses of vitamin D.