An Overview of Chemoprevention: Current Status and Future Prospects (44163)

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Abstract. **The optimal way of dealing with any disease is by prevention. This is particularly true of cancer, with all of its complexities. A major problem that exists for cancer prevention is that we do not know the cause of over 50% of cancers. Even when causes are known, serious difficulties often exist in removing them. To the extent that causality cannot be dealt with effectively, other strategies merit consideration. One is chemoprevention. A great strength of chemoprevention is that a large number of compounds can prevent the occurrence of cancer, and a variety of mechanisms exist for producing such protection. Much of this review deals with efficacy, toxicity, and mechanisms of action of chemopreventive agents. Gap areas in information are discussed, as well as opportunities for producing compounds with optimal attributes. Chemoprevention is not simple, and successes may not come quickly. However, for both the general population and, even more urgently, for individuals at high risk, chemoprevention has the potential of providing an important means for cancer prevention.** [P.S.E.B.M. 1997, Vol 216]

The optimal way of dealing with any disease is by prevention. This is particularly true of cancer, with all of its complexities. This goal is forgotten quickly. Prevention often is difficult, long term, and undramatic. However, in reality it is the most important accomplishment that can be made. One of the problems that exist for cancer prevention is that we do not know the causes of over 50% of cancers. Even in those cases for which this information is available, serious difficulties can exist in removing causes or preventing exposures to them. One such case is when causation is related to genetics. Lack of effective action can also occur under conditions in which the high risk has strong lifestyle or societal connections, as with cigarette smoking and improper diet.

Given the extent that causality cannot or has not been dealt with effectively, what comes next? There are several strategies. One is to rely primarily on early diagnosis and therapy. While this is a useful backup, it has a basic fault in that the pathologic process is allowed to proceed in the individual. This is undesirable in principle and in reality. If the early diagnosis is missed either by neglect or unavailability of the necessary procedures, or if the technique lacks the capacity to detect lesions at the time when protection can be achieved, then the individual is at risk. A different type of strategy is to carry out intervention(s) aimed at obtaining prevention. Chemoprevention is one such intervention strategy. It entails the administration of one or several compounds to prevent the occurrence of cancer. Other strategies entail dietary manipulations involving control of consumption of major nutrients such as fat and also control of caloric intake. Programmed physical activity also can have preventive effects. These various strategies can be combined.

This review focuses on chemoprevention (1–5). Cancer is a slow, multistep process. Frequently, the time period over which it develops is on the order of decades. Thus, at any point in time, a large number of individuals are at risk. For use in estimating the size of this group in the United States, a time interval on the order of 20 years can serve for making rough calculations. This interval is based on studies of individuals with heavy exposures to industrial carcinogens, on clinical observations of the progression of premalignant to malignant lesions, on the age of onset in individuals genetically at high risk of cancer, and also on other clinical observations (6–11). In the United States, approximately 550,000 people were expected to die of cancer in 1996 (12). If the 20-year latency period is multiplied by the number of deaths from cancer in 1996, the figure of 11,000,000 is arrived at. This is approximately the number of people who are currently in some phase of the evolution

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0037-9727/97/2162-0133$10.50/0

of a carcinogenic process that ultimately will be lethal. In addition, there is a somewhat greater number of individuals who will develop cancer but will either be cured or will die of some other cause. Combined, these two groups contain more than 22,000,000 people (12). These individuals are a major target for chemoprevention.

Characteristics of Chemoprevention for Individuals at Different Risks

There are two types of subject categories for chemoprevention. One is the general population and the other is individuals for whom there is a known increased risk of cancer. Table I depicts some of the parameters pertaining to each category. For a chemopreventive agent to be used in the general population, it must have exceedingly little toxicity. Encouragement for the prospects of success in this area comes from observations that diets rich in vegetables and fruit reduce the risk of cancer. In addition to epidemiological studies showing this relationship, a large number of naturally occurring compounds in vegetables and fruits have been shown to have efficacy as chemopreventive agents (13–15).

The "high-risk" groups designated in Table I represent a spectrum ranging from moderately high risk to extremely high risk. As with chemoprevention for the general population, toxicity of chemopreventative agents for high-risk individuals is a major issue, but to a somewhat lesser extent. Chemopreventive agents generally are given to individuals who are functional and going about their daily lives even though they may be at increased risk for cancer. Anything that significantly threatens their lifestyle or makes them feel ill becomes unacceptable. However, some risk of toxicity may be allowable depending upon the severity of the risk. The selection of individuals at high risk is a clinical one. In some cases it will be made on the basis of medical findings or exposures histories. Increasingly, it will be based on genetics. In addition, as predictive biomarkers of the likely occurrence of cancer become more accurate these will come into play in the clinical setting. It is likely that, within the next decade or so, when individuals go for a routine physical examination it will entail evaluation of their risk of developing cancer. Potentially, on the basis of this evaluation the selection of which chemopreventive agents to use could be made.

Categories of Chemopreventive Agents

A great strength of chemoprevention has been that a large number of compounds can prevent the occurrence of cancer and that a variety of mechanisms for producing such protective effects exist. This information provides a major foundation for chemoprevention as it exists now. Chemoprevention has been obtained in several hundred animal studies. Human intervention trials also have shown efficacy. For purposes of conceptualization, many chemopreventive agents can be placed into broad categories (4, 5). The first category is "blocking agents." These compounds prevent carcinogenic agents from reaching or reacting with critical target sites. They exert a barrier function. A second category of compounds decreases the vulnerability of target tissues to carcinogenic stimuli. The final category is "suppressing agents." These compounds prevent the evolution of the neoplastic process in tissues that otherwise would become malignant.

Blocking Agents. There are three major mechanisms by which blocking agents act. Some blocking agents prevent activation of carcinogens or tumor promoters requiring metabolic activation. A second group of blocking agents are effective by virtue of their capacity to enhance detoxification systems. A third group of blocking agents trap reactive carcinogenic species before they reach critical target sites. Much of this has been described in detail previously (1–5). Blocking agent that enhance the activity of systems detoxifying carcinogenic chemicals are of special interest. These systems are inducible, and, in many instances, induction of increased activity has been shown to be protective against the occurrence of cancer. Phase II enzymes, which are involved in conjugation and excretion reactions are particularly important in terms of their protective capacities. Probably the single most critical system in this regard is glutathione-*S*-transferase (3, 15, 16). Many Phase II–inducing compounds occur as non-nutrients in vegetables and fruits, and may be responsible for some of the protective effects that are obtained as a result of consuming diets containing relatively large quantities of these types of foods (3, 13).

Among the synthetic inducers of Phase II enzymes, one that is the focus of considerable attention is the compound Oltipraz. Oltipraz is a drug that has bee used in treating large numbers of humans with schistosomiasis. Its potential as a chemopreventive agent was first suggested by the late

Table I. Chemoprevention in Different Risk Categories

Parameter	Risk category	
	General population	High risk
Allowable agent toxicity	Trivial or none	Slight (magnitude dependent on risk)
Selection method	Public health	Clinical
Additional considerations	Use of dietary supplements may be particularly applicable	Development of accurate diagnostic and predictive testing is critical

Dr. Earnest Bueding. In the initial studies of the protective effects of Oltipraz in experimental animals, the ability of the compound to inhibit benzo[*a*]pyrene (BP)-induced pulmonary adenoma formation and formation of forestomach tumors in mice was demonstrated (17). In more-recent work, Oltipraz has been found to be very effective in inhibiting aflatoxin-induced carcinogenesis (18). Plans are in progress to determine the efficacy of Oltipraz as a protective agent in areas of the world in which aflatoxin represents a serious environmental carcinogen. A third way in which blocking agents can work is by trapping reactive carcinogenic species (19). Endogenous thiols, particularly glutathione, are important in this regard. *N*-Acetylcysteine is a chemopreventive agent that has favorable attributes which potentially make it applicable for use in humans. The compound has efficacy as a trapping agent *in vivo* and has very low toxicity (20).

The trapping of oxygen radicals has received a great deal of attention. This is a very complex area because many antioxidants are multifunctional and have been used at high concentrations in *in vivo* studies. Oxygen radicals are produced *in vivo* under many conditions, prominent among them being inflammatory reactions. These radicals are capable of attacking DNA (21, 22). Frequently, the production of oxygen radicals is part of a complex process in which several events occur simultaneously, making it difficult to evaluate mechanisms of inhibition by antioxidants, particularly when used in high concentrations. There have been a number of publications on this topic (23–25).

Chemopreventive Agents Decreasing Tissue Vulnerability to Carcinogenesis. This group of chemopreventive agents is not well defined, but they are extraordinarily interesting. The effects of the compounds falling into this category are to make tissues less vulnerable to carcinogenesis. This increased resistance can be brought about in at least three ways. One is by virtue of the compound's producing cellular maturation. A second is to decrease function or activity of target cells. A third is to decrease cell proliferation.

The most extensively studied tissue for demonstrating protective effects of cellular maturation is the female breast. Decreasing the vulnerability of the breast to neoplasia has been studied in detail in the rat. The terminal end-buds of the mammary gland are vulnerable to carcinogenic stimuli. They can be matured by pregnancy or hormonal stimulation. The matured glands show a marked reduction in tumor formation resulting from administration of carcinogens (26, 27). There is a human counterpart to these animal experiments. Epidemiological studies have shown that an early age of first pregnancy results in a lesser risk of breast cancer (28). It can be decreased by 50% or more when the first pregnancy occurs in very young women. The animal and human data raise the issue of the possible use of chemopreventive agents that bring about maturation of the glands of the breast for prevention of breast cancer in women at particularly high risk of malignancy.

A second way of increasing resistance of a tissue to carcinogenesis is to decrease tissue function. Castration results in prevention of cancer of sex hormone–dependent tissues. However, a realistic situation for possible application to chemoprevention is derived from data showing that there is an approximately 50% decrease in ovarian cancer in women who use steroid contraceptives that contain estrogen. Although a clearly defined relationship between cancer prevention and suppression of ovarian function has not been demonstrated, the speculation is that such suppression is, in fact, the cause of the decreased ovarian cancer.

The third mechanism for potentially increasing resistance of a tissue to carcinogenesis is to decrease cell proliferation in the target tissue. Cell proliferation can be a risk factor for response to carcinogenic stimuli. Reduced cell proliferation can be brought about by dietary manipulation. Studies of this nature have been carried out by Newmark, Lipkin, and their colleagues (29, 30). These investigators compared the carcinogenic response in animals fed a diet similar to the Western diet to those receiving a diet with optimized composition. The Western diet contains high fat, low calcium, marginally low phosphorous, and low vitamin D. Animals fed this diet have a high mitotic activity in the glands of the large bowel compared with animals fed an optimal diet. Mitotic activity can be reduced by simply changing the dietary composition. Thus, a decreased risk can be produced by a relatively simple means without incurring any toxicity. In more recent studies, a similar strategy has been shown by these investigators to be effective for breast and prostate.

In summary, increasing the resistance of tissues to carcinogenic challenge may be an effective way of achieving prevention. This strategy has received only limited investigation. Positive attributes of this strategy are the relatively short period of chemopreventive agent administration in the case of tissue maturation effects and the little toxicity from dietary controls of cell proliferation. These approaches certainly merit further exploration.

Suppressing Agents. Suppressing agents prevent the evolution of the neoplastic process in cells that otherwise would become malignant (3, 5). A list of such compounds is provided in Table II. It is evident that a substantial number and variety of such compounds have the capacity to act as suppressing agents. Whereas the conceptualization of mechanisms of action of blocking agents is quite clear, although many of the details are complicated, the mechanisms of action of suppressing agents are frequently poorly defined. This is partly due to the fact that they entail effects on mechanisms in the carcinogenic process that are incompletely understood.

Several means by which suppressing agents produce their effects are known (5). Some suppressing agents act by producing differentiation. Others are directed specifically at counteracting the consequences of genotoxic events, in particular oncogene activation. Beginning efforts aimed at remedying defects in suppressor gene activity are emerging in which vectors bearing a normal suppressor gene are em-

Table II. Some Suppressing Agents

Compounds	Compounds
Vitamin A and retinoids[a]	Protease inhibitors[a]
Vitamin D and related compounds	Selenium (inorganic and organic)[a]
Monoterpenes (perillyl alcohol)[a]	Dehydroepiandrosterone and analogs
Hormone antagonists[a]	Inositol and phytate
Hormone metabolism inhibitors[a]	Glucocorticoids
Difluromethylornithine[a]	Chalcone
Arachidonic acid cascade inhibitors[a]	Nerolidol
Polyphenolics	Sodium cyanate

[a] Clinical trials in progress or pending.

ployed (31). A third group of suppressing agents focuses on selective inhibition of proliferation of potentially malignant cells.

There is a fourth group, which does not fit into any of the above. Included are a large number of compounds that have as a common feature the capacity to inhibit components of the arachidonic acid cascade (32–34). Some are medicinals, in particular nonsteroidal anti-inflammatory compounds. Others are phenolic compounds, which occur naturally in plants. Numerous experiments have been carried out in which the suppressing effects of nonsteroidal anti-inflammatory compounds such as piroxicam, sulindac, indomethacin, and aspirin have been investigated in experimental animals. Experimental work has shown that piroxicam, sulindac, and indomethacin have the important attributed of inhibiting neoplasia when administered late in the premalignant stages of the carcinogenic process. Sulindac can produce regression of adenomatous polyps of the large bowel in human subjects with multiple polyposis (35). In addition to the above, there are other suppressing agents of interest. Some are dietary constituents. These include protease inhibitors. A focus of particular attention has been the Bowman-Burke protease inhibitor (36, 37). Another group of suppressing agents occurring in the diet is the inositols. A considerable amount of work on the inhibitory capacities of these compounds has been carried out by Shamsuddin and his colleagues (38). These investigators have been particularly interested in phytate (inositol hexaphosphate), which inhibits carcinogenesis of the large bowel in mice and rats. A second compound, *myo*-inositol inhibits pulmonary adenoma formation in mice as well as carcinogenesis of the large bowel (38–41). Glucocorticoids also have been shown to suppress carcinogen-induced pulmonary tumor formation in mice (41). The suppressing agents are the lead compounds now being explored for chemoprevention in human subjects (Table II). Some are currently being used in intervention trials. Others are being prepared for such use. This is an area of research in the field of chemoprevention that is very promising.

Chemoprevention by Non-Nutritive Constituents of Foods of Plant Origin

An interesting observation that has been made repeatedly is that individuals who consume relatively large amounts of vegetables and fruits are at decreased risk of cancer of many organs. Thus, in a report by Block *et al.* 24 of 25 epidemiological investigations showed that consumption of relatively large amounts of vegetables and fruits was associated with decreased incidence of lung cancer (42). Comparable relationships were found for cancers of the larynx and oral pharynx, and also for the gastrointestinal tract and pancreas. Similar findings were reported by Steinmetz and Potter (43).

Supporting the results obtained in the epidemiological investigations are data obtained from animal experimentation. A number of studies have shown that animals fed crude diets containing vegetables, grains, and other natural products have a decreased carcinogenic response compared with animals fed semipurified diets consisting of purified compounds such as starch, casein, and others. The nutrient constituents of the two types of diets used in these experiments are the same, but the non-nutrients differ, being much greater in the crude diets. An early study of this type employed mice that develop hepatomas without any administration of carcinogen. The animals were placed on two diets, one semipurified and the other crude. The two were matched in terms of both major and minor nutrients. Mice fed the crude diet had half as many hepatomas as those fed the semipurified diet (44). The results of this experiment indicate that substances present in the crude diet other than nutrients can produce substantial prevention. Of importance is that this prevention is obtained without causing any toxicity.

In a more recent study, the effects of two diets that currently are used extensively in animal experiments were studied (i.e., the semipurified diet AIN-76 and the crude diet NIH-7). Pulmonary neoplasia was produced in mice by administrations of the tobacco carcinogen, NNK. A marked reduction of tumor formation in the mice fed the crude diet (NIH-7) was found (45). Other experiments have been reported showing similar results (i.e., reduced carcinogenic response in animals fed crude diets compared with semipurified diets). The third body of data relating to protective capacities of foods of plant origin has been the actual identification of a large number of non-nutritive constituents in foods of plant origin. These include both blocking and suppressing agents (3, 15). We now know that foods of plant origin contain many chemopreventive substances.

Applications of Chemoprevention to Humans

At the present time, we have a hierarchy of chemopreventive agents in use in intervention studies in humans or in preparation for such studies. This does not necessarily mean

that these ultimately will prove to be the best, but they are compounds that have been studied extensively and at present appear most promising. There are three major groups: vitamin A and the retinoids, compounds that alter hormonal metabolism and hormone antagonists, and nonsteroidal anti-inflammatory compounds.

Breast. Of all major organ sites for cancer, the one that appears most likely to be responsive in the near future to chemoprevention with agents currently available is the female breast. Two promising groups of chemopreventive agents exist for prevention of mammary carcinogenesis. These are hormone antagonists, the most noteworthy of which is tamoxifen, and retinoids. The supporting animal data are excellent for both groups of compounds (46). In addition, in the case of tamoxifen, data from clinical studies in the human offer encouragement for likely efficacy. Of particular importance have been observations that use of tamoxifen as an adjuvant therapy in women who have had one breast removed for cancer resulted in a reduced incidence of the occurrence of a second cancer in the remaining breast (47, 48). Chemopreventive studies with tamoxifen as a sole agent or in combination with a retinoid are now beginning. Some trials with retinoids are in their late phases. Even if this next round of intervention trials is not entirely favorable, the use of these two categories of compounds ultimately is very likely to produce effective chemoprevention.

Additional agents may also become important for chemoprevention of breast cancer. One group, the monoterpenes, which include perillyl alcohol, have been shown to have good chemopreventive efficacy against mammary carcinogenesis in the rat (49). These compounds have the important attribute of inhibiting the late stage of mammary carcinogenesis and also of producing regression of some mammary tumors (49, 50). Chemoprevention brought about by altering steroid metabolism is another potential means of preventing breast cancer. Indole-3-carbinol has been studied for this purpose (51). Although this compound itself has some negative attributes, in particular the risk of acting as a tumor promoter in other tissues, its capacity to inhibit mammary carcinogenesis might be used in specific instances. An additional means of protecting the breast from carcinogenesis is to induce maturation of the terminal endbuds. The strategy might be of assistance in chemoprevention for women at very high risk of breast cancer. Programed physical activity also offers a further modality that can add to a total preventive regime (52). One of the advantages in the study of breast cancer has been the availability of good animal models for identifying and evaluating potential efficacy of chemopreventive agents. A deficiency in the overall program for the chemoprevention of breast cancer is the lack of good intermediate end points that could be used for studies of promising agents or agent combinations prior to commitment of major resources for human intervention studies in which cancer is the end point.

Prostate. There are some similarities between chemoprevention of mammary carcinogenesis and chemoprevention of prostatic cancer. For both tissues, the exploitation of hormonal dependence can be employed as a chemopreventive strategy (53). In animal experiments, retinoids have also been reported to prevent the occurrence of prostate cancer. The slowly evolving nature of prostatic carcinogenesis is a special feature of this particular target site, which might be exploited. The development of chemoprevention for prostatic cancer has lagged behind that for carcinogenesis of the breast. A major problem in studies of chemoprevention of the prostate has been the lack of good animal models. Recently, several transgenic mouse models have been developed (54, 55). They offer promise for use of developing chemopreventive agents in this tissue.

Ovary. Epidemiological studies have shown that women who have used oral contraceptives are at decreased risk of developing ovarian cancer. These observations offer a basis for developing chemoprevention of this organ (56). However, a major problem for studying chemoprevention of ovarian cancer by hormonal manipulation as well as other agents has been a total lack of an experimental model of ovarian cancer in experimental animals.

Large Bowel. There are a number of studies in animals and humans indicating that chemopreventive efficacy can be obtained in the large bowel. The nonsteroidal anti-inflammatory compounds appear to be effective agents for preventing cancer in this tissue (1). The animal data are excellent in this regard. In the human, there are a number of epidemiology studies that show protection by the use of nonsteroidal anti-inflammatory compounds (57, 58). However, whereas this protection is shown in most studies, exceptions exist (59). Clinical investigations have shown that polyp regression can be brought about by administration of sulindac, a potent nonsteroidal anti-inflammatory compound (35). There is a cautionary note pertaining to the nonsteroidal anti-inflammatory compounds. They can have irritant effects on the large-bowel mucosa so that their use merits close observation.

Lung. Chemoprevention of the lung largely has been ineffective. One study has been reported in which retinyl palmitate was administered to subjects that had undergone resection of a small primary tumor of the lung. A modest reduction of occurrence of second pulmonary cancers was found (60). There are three major histologic types of cancer of the lung (i.e., adenocarcinoma, squamous-cell carcinoma, and small-cell carcinoma). A number of agents show efficacy for chemoprevention of adenocarcinomas of the lung (1, 3, 39–41). Thus far, none have reached the point of clinical trials. A problem retarding development of chemoprevention of squamous-cell carcinoma of the lung is that there is not a good animal model. In addition, there is no model for small-cell carcinoma. It is unfortunate that for these two important types of lung cancer such experimental deficits exist. Studies of chemoprevention of head and neck

cancers by Hong and his colleagues have shown some success by using retinoids as the chemopreventive agents (61). Because of etiological relationships, particularly causation by cigarette smoking, attention has focused on the use of retinoids for preventing bronchogenic carcinoma.

Further Identification of Chemopreventive Agents and Their Development

General Comments. Essential to an effective chemoprevention program is the availability of agents that have two major attributes, efficacy and lack of toxicity. A third attribute is desirable, namely human experience with intake of the compound, as is the case for dietary constituents and medicinals. In addition to providing information as to likely adverse effects under conditions of chronic intake, introduction for human use is facilitated. While desirable, it is important that this last attribute not discourage development of new, innovative agents.

Below are some recommendations of areas of research that appear promising as effective chemoprevention applicable to humans. Some of these agents have been discussed in part previously in this review. These recommendations are derived from epidemiological investigations in humans, studies showing chemopreventive effects in whole animal experiments, intervention trials in humans, and mechanistic data.

Areas of Opportunity for Future Development of Chemopreventive Agents. *Surrogate for the naturally occurring chemopreventive compounds occurring in vegetables and fruits.* An area of research that could yield extraordinarily useful results is based on the studies showing that diets containing relatively large amounts of foods of plant origin have substantial capacities to prevent cancer. As discussed previously, the epidemiological studies in this area are numerous and the results impressive. In addition, a large number of chemopreventive agents have been identified in foods of plant origin.

There are two ways of obtaining the preventive effects from chemopreventive compounds occurring in foods of plant origin. One is by making dietary recommendations for their consumption. The other is by using dietary supplements containing the protective substances occurring in foods of plant origin. These supplements would very likely be taken on a daily basis. Although reliance on dietary recommendations seems simple and logical, obtaining lifestyle alterations for health purposes has proved to be very difficult and uncertain. Additional disadvantages of relying on dietary recommendations to achieve chemoprevention is that the chemical composition of dietary constituents, as well as the size of food portions and manner of food handling and preparation, varies. Thus, there is no certainty of the quantity of protective materials that would be consumed. The use of standardized defined supplements would be a desirable means of achieving the preventive effects of diets rich in constituents of plant origin. Developing such dietary supplements is by no means a simple endeavor. It requires considerably more information on the preventive capacities of compounds present in foods of plant origin. Almost certainly, the prevention that occurs is the result of combinations of compounds rather than a single compound. The further development of this area will require rapid means of evaluating specific dietary constituents singly and in combinations for their chemopreventive efficacy. The natural diet achieves protection against cancers of major organ sites in the general population and without toxicity. These are highly desirable attributes. The formulation of a supplement or supplements with comparable properties is a formidable undertaking, but one which certainly merits a very high priority.

Hormonal chemoprevention. Hormonal chemoprevention is an areas that is well developed and very active, as described above. A pragmatic problem that has existed in research in hormonal chemoprevention is the lack of useful animal models for carcinogenesis of several of the organ sites involved, in particular ovary and uterus. One would hope that transgenic animals can be developed for these two organ sites. Until recently, experimental models for studying prostatic cancer have been poor. Several transgenic models have been developed (54, 55). Whether or not these resemble the human disease, particularly in terms of hormonal response, remains to be determined.

Chemopreventive contraceptive regimes. A special area of hormonal chemoprevention pertains to chemoprevention by contraceptive regimes. Efforts at this endeavor have received considerable attention by Henderson, Pike, and others (56). It has the advantage of combining prevention with the chronic intake of compounds that are being used by women for another beneficial purpose. Such a combination would enhance usefulness and compliance. Organs that could be protected are major sites of cancer in women.

Retinoids and deltanoids. Retinoids and deltanoids are very promising groups of compounds that have been studied extensively. They have been discussed previously in this review. Their continued study promises to produce effective agents.

Polyphenolics including those in tea. There is an extensive literature showing that polyphenolic compounds can inhibit carcinogenesis when administered in the post-initiation period. Polyphenolics occur in a variety of foods of plant origin, and also in tea (1, 62–65). Polyphenolics as such are poorly absorbed from the gastrointestinal tract. They can be extensively modified prior to absorption. A full knowledge of their metabolism has not been elucidated, and their mechanism(s) of action is not understood. This is an area of considerable interest because of the magnitude of the data showing preventive effects by these compounds.

Protease inhibitors. The protease inhibitors are an intriguing group of chemopreventive agents that have been studied for a long time by Kennedy, Troll, and others (36, 37). The basic data obtained suggest that they could be extremely effective chemopreventive agents.

Arachidonic acid cascade inhibitors. Arachidonic acid cascade inhibitors, in particular the nonsteroidal anti-inflammatory compounds, have been under investigation as chemopreventive agents for large-bowel carcinogenesis (1–3, 32–35). The fact that a drug as widely used as aspirin has chemopreventive potential has stimulated great interest in this group of compounds (33). A reality is that there is an enormous gap of knowledge pertaining to the arachidonic acid cascade itself and the ramifications of inhibition of its various components. This is a complicated set of metabolic interactions that is difficult to handle in the laboratory. A great deal more has to be done to understand fully the cascade itself and mechanism(s) by which it can alter neoplastic response. If not properly investigated, it is likely their potential utility will not be realized. In addition, adverse effects might compromise benefits that could be obtained.

Selenium compounds. Selenium compounds are among the oldest chemopreventive agents identified. Recent attention has focused on organoselenium compounds (1, 46, 66). Little is known about their mechanism(s) of action. There have been numerous problems in the development and application of selenium compounds to chemoprevention in human subjects. A major problem with their use pertains to toxicity. Recent work on the use of organoselenium compounds with improved attributes is promising as well as the data from the intervention studies by Clark and colleagues (67). This is an important area that could have a good payoff if successfully pursued.

Glucocorticoids. The glucocorticoids are effective in preventing carcinogenesis in a number of different organ sites, including the lungs, in whole animal experiments (2, 39, 41). A major problem with the glucocorticoids pertains to their adverse effects. Most glucocorticoids have substantial systemic effects. However, in recent years a number of topically active glucocorticoids with minimal systemic effects have been developed initially for use on the skin. Some newer compounds have topical effects in the respiratory tract and are being used in treating bronchial asthma under conditions in which systemic glucocorticoid effects are minimal. These compounds have potential use in chemoprevention of airway carcinogenesis.

Monoterpenes. The monoterpenes are an interesting group of compounds that can prevent cancer of the breast in the rodent and have been extensively studied for this purpose (49, 50). They are novel compounds and could provide distinctive mechanisms of inhibition.

Surrogate agents for physiological compounds produced as a result of caloric restriction and weight loss regimes that prevent cancer. There are a large number of animal experiments showing that caloric restriction has an inhibitory effect on the occurrence of cancers in experimental animals (68). Many biochemical alterations occur under these conditions (69, 70). Which of these (or some as yet unidentified entity) or which combination results in cancer prevention is not known. Prevention of cancer by this means has the positive attribute that it occurs in many organs. Although it has been studied for many years, the understanding of the mechanism(s) has proved elusive. The problem merits reevaluation because our information base has been increasing so rapidly. Newer data may help in elucidating the mechanism(s) involved and provide useful surrogate agents for bringing about the same protective effects on carcinogenesis.

Decreasing tissue vulnerability to carcinogenesis. An area of chemoprevention that has received relatively little attention, except for carcinogenesis of the breast, is the development of strategies for reducing the number of high-vulnerability target cells. This strategy has been discussed previously. A potential advantage of this particular approach is that it can entail a relatively brief period of agent administration and the effect could be permanent.

Additional Items Pertaining to Agent Identification and Testing. *In vitro test systems for identification and evaluation of chemopreventive agents.* The development of a variety of *in vitro* techniques that can be used as initial indications of likely chemopreventive efficacy of compounds is important. It merits considerable effort and constant reevaluation. This research is an area in which there is a particularly rapid accumulation of new information on basic mechanisms of carcinogenesis. Many scientists have the capacity of making major contributions to this endeavor if they are aware of how their work can be applied to it. An important point is that the translational implications of their basic work be understood and vigorously pursued.

Animal models for evaluating chemopreventive agents. Developing animal models for evaluating chemopreventive agents is an area of research that may improve dramatically by the use of transgenic animals. As mentioned previously, there is an appalling lack of animal models that can be used for studies of chemoprevention in some important humans cancers, including those occurring in the lung, ovary, uterus, and brain. Animal models are critical for evaluating the efficacy of chemopreventive agents and for providing a means of carrying out preclinical studies.

Predictive biomarkers. The term "biomarker" is currently being used to include a number of different types of parameters. One group of biomarkers provides information on dosimetry of carcinogen exposure, others are used for diagnosis, and still others (prognostic biomarkers) for following the course of cancers that are under treatment. There is an additional group which can be termed "predictive biomarkers." These are biomarkers that can predict the likely efficacy of chemopreventive agents. There are two major types. One evaluates a sequence of risk parameters that potentially can be reversed or held in check by a chemopreventive agent. Examples of this type of biomarkers are cell proliferation, hyperplasias, dysplasias, and/or their corresponding biochemical counterparts. A second group of biomarkers reflect early mutagenic events occurring in pre-

neoplastic cells. The disappearance of the cells bearing the markers or the lack of appearance of additional mutagenic events indicating progression can be used to assess potential chemopreventive efficacy. The development of predictive biomarkers is in the major line of basic research being carried out by many gifted investigators in cancer research and related fields. It is important that a constant search for such potential biomarkers be maintained and that basic scientists understand the potential translational implications of the basic work they might be carrying out. The validation of the reliability of the predictive biomarkers obviously is critical.

Short-term intervention trials using predictive biomarkers. A problem with conventional intervention trials is the relatively long time periods required for such trials and the large amount of resources required. The use of short-term intervention trials with biomarker end points could be extraordinarily useful. Trials with predictive biomarker end points can be carried out in a relatively short time (i.e., several months) and with relatively few subjects. For such studies to give the maximum amount of information, it would be useful to have corresponding animal models in which it had been shown that the reversal or lack of progression of the biomarker reflects cancer prevention. The use of short-term intervention trials using predictive biomarkers has the potential of providing a means of determining likely efficacy for larger trials using intermediate end points or cancer as the end point. In addition, prior to the start of longer trials, they would provide a means of determining optimal dosage regimes, agent combinations, and other information that could enhance the likelihood of success.

Summary

In this review, an effort has been made to provide a sense of what chemoprevention is, its potential, areas of opportunity, and gap areas that should be addressed in order to move the field forward. Chemoprevention is not simple, and success may not come quickly. However, prevention is the best way of dealing with cancer. Chemoprevention is one of the strategies that may be effective in this regard.

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