Chemoprevention of Cancer is a means of cancer control in which the occurrence of this disease is prevented by administration of one or several chemical compounds. This Perspective deals with the areas in cancer control that this field addresses, the promise that it holds, and the problems that must be solved in order to realize its goals. The most desirable way of eliminating the impact of cancer in humans is by prevention. The first set of strategies for achieving this objective is to remove the causative agents. In some instances, as with cigarette smoking, it is possible to eliminate the etiological agent. However, in others it is not. The causes of most cancers in the human are not known. Under some circumstances, even when causative factors are known, neoplasia may have been initiated, and prevention now falls into the realm of suppressing the evolution of the neoplastic process. Individuals already exposed to carcinogens fall into this category as do individuals at high risk to cancer because of genetic factors. Finally, there are a considerable number of suspect carcinogens in the environment that have been identified by virtue of mutagenicity testing. Many of these mutagenic substances occur in food. The carcinogenic potential of these compounds for the human is not clear. If they do in fact play a role in the occurrence of cancer, it would be exceedingly difficult to remove them from the environment. Flavones in food are an example of a class of compounds that are mutagenic and that would be virtually impossible to remove because of their ubiquitous distribution. Likewise, if exposure to oxygen radicals and epoxides poses a hazard, as has been suggested by some investigators, such exposures would be difficult to prevent. While removal of causative agents is the primary goal of cancer prevention, for the foreseeable future it is likely to be incomplete. Accordingly, the development of a second line of prevention based on chemoprevention assumes considerable importance.

The human constituencies that would be the target for chemoprevention vary. Two extremes are apparent, but in all likelihood a continuum exists between them. At one extreme are individuals at very high risk of developing cancer because of genetic predisposition or exposure to carcinogens. At the other end of the risk spectrum are individuals lacking any evidence of an increase in risk factors. The strategies for dealing with groups at varying risks differ. As the risk for developing cancer increases, the compounds likely to be most effective are those that suppress evolution of the neoplastic process. The permissible risk of toxicity from the chemopreventive agent also will increase. In contrast, when one considers chemopreventive agents to be directed at populations with no enhanced risk from cancer, protection against attack from compounds that are involved in the causation of cancer assumes a greater importance. For this population group, little risk of toxicity from a chemopreventive agent can be justified. Thus, when one evaluates a chemopreventive compound, considerations of its projected use are highly relevant. If the compound is very potent but has significant toxicity, it may nevertheless be useful for high-risk individuals but not for the general population. If a compound has modest protective effects and little toxicity, considerations of its primary use for individuals at lesser risk to neoplasia would be appropriate.

Chemopreventive Compounds

One of the most impressive findings in the field of chemoprevention is the very large number of compounds that have been demonstrated to prevent the occurrence of cancer. Compounds belonging to over 20 different classes of chemicals have been shown to have chemopreventive capacities (Tables 1 and 2). The great chemical diversity is a positive feature in that it indicates the likelihood that a variety of approaches can be made to prevention and that the options for selecting optimal compounds will be large. Some of these inhibitors are naturally occurring constituents of food (Table 1). Chemopreventive agents can be placed into 2 broad categories. The first category includes compounds that are effective against complete carcinogens. The second includes compounds effective against tumor promoters. Some compounds fall into both categories. As more data become available, this organization will almost certainly be modified. Nevertheless, it is useful for the present.

Inhibitors Effective against Complete Carcinogens

The mechanisms of action of most inhibitors of carcinogenesis, both synthetic and naturally occurring, are poorly understood. This lack of information makes it difficult to organize them into a cohesive pattern. One means of providing an organizational framework is to classify inhibitors according to the time in the carcinogenic process at which they are effective. Utilizing this framework, inhibitors of carcinogenesis can be divided into 3 categories (Chart 1). The first consists of compounds that prevent the formation of carcinogens from precursor substances. In the second are compounds that inhibit carcinogenesis by preventing carcinogenic compounds from reaching or reacting with critical target sites in the tissues. These inhibitors are called "blocking agents," which is descriptive of the mechanism of action. They exert a barrier function. A third category of inhibitors acts subsequent to exposures to carcinogenic agents. These inhibitors are termed "suppressing agents" since they act by suppressing the expression of neoplasia in cells previously exposed to doses of a carcinogenic agent that will cause cancer.

Compounds Inhibiting the Formation of Carcinogens

A major focus of this group of inhibitors has been on prevention of the formation of nitroso carcinogens from the reactions of pre-
CHEMOPREVENTION OF CANCER

Table 1
Inhibitors of carcinogen-induced neoplasia

<table>
<thead>
<tr>
<th>Category of inhibitor</th>
<th>Chemical class</th>
<th>Inhibitory compounds</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compounds preventing formation of carcinogen from precursor compounds</td>
<td>Reductive acids</td>
<td>Ascorbic acid</td>
<td>31, 32</td>
</tr>
<tr>
<td></td>
<td>Tocopherols</td>
<td>α-Tocopherol, γ-tocopherol</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Phenols</td>
<td>Caffeic acid, ferulic acid, gallic acid, propyl gallate</td>
<td>21, 38</td>
</tr>
<tr>
<td>Blocking agents</td>
<td>Phenols</td>
<td>2(3H)-Fert-butylhydroxyanisole, butylated hydroxytoluene, hydroxyanisole, allylic acid, caffeic acid, ferulic acid, p-hydroxynimonic acid, and others</td>
<td>24, 34, 44, 56, 67, 69, 71-73, 75</td>
</tr>
<tr>
<td></td>
<td>Indoles</td>
<td>Indole-3-acetonitrile, indole-3-carbinol, 3,3'-dindolylmethane</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Aromatic isothiocyanates</td>
<td>Benzyl isothiocyanate, phenethyl isothiocyanate, and phenyl isothiocyanate</td>
<td>66, 68</td>
</tr>
<tr>
<td></td>
<td>Coumarins</td>
<td>Coumarin, limetin</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Flavones</td>
<td>β-Naphthoflavone, α-naphthoflavone, quercetin pentamethyl ether</td>
<td>10, 66, 77</td>
</tr>
<tr>
<td></td>
<td>Dithiobenzenes</td>
<td>4-(2-Pyrazinyl)-4-methyl-1,2-dithiol-3-thione, 3-(p-methoxyphenyl)-1,2-dithiol-3-thione</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Diterpenes</td>
<td>Kahweol palmitate</td>
<td>71, 76</td>
</tr>
<tr>
<td></td>
<td>Dithiocarbamates</td>
<td>Tetraethylthiuram disulfide (disulfiram), sodium diethyldithiocarbanate, bis(ethylxanthogen)</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Phenoxyhazines</td>
<td>Phenoxyazine</td>
<td>67, 69</td>
</tr>
<tr>
<td></td>
<td>Barbbiturates</td>
<td>Phenobarbital</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>Trimethylquinolines</td>
<td>6-Ethoxy-1,2-dihydro-2,2,4-trimethylquinoline (ethoxyquin)</td>
<td>67</td>
</tr>
<tr>
<td>Suppressing agents</td>
<td>Retinoids and carotenoids</td>
<td>Retinyl palmitate, retinyl acetate, 13-cis-retinolic acid, ethyl retinamide, 2-hydroxyethylretinamide, retinyl methyl ether, N-(4-hydroxyphenyl)retinamide, other synthetic retinoids, β-carotene</td>
<td>33, 45, 48, 52-54</td>
</tr>
<tr>
<td></td>
<td>Selenium salts</td>
<td>Sodium selenite, selenious acid, selenious acid, sodium selenide</td>
<td>4, 14, 17, 18, 28</td>
</tr>
<tr>
<td></td>
<td>Protease inhibitors</td>
<td>Leupeptin, antipain, soybean protease inhibitors</td>
<td>16, 41, 83</td>
</tr>
<tr>
<td></td>
<td>Inhibitors of arachidonic acid metabolism</td>
<td>Indomethacin, aspirin</td>
<td>25, 35, 37</td>
</tr>
<tr>
<td></td>
<td>Cyanates and isothiocyanates</td>
<td>Sodium cyanate, tert-butyl isocyanate, benzyl isothiocyanate</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Phenols</td>
<td>2(3H)-Fert-butylhydroxyanisole</td>
<td>27, 75</td>
</tr>
<tr>
<td></td>
<td>Plant sterols</td>
<td>β-Sitosterol</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Methylene xanthines</td>
<td>Caffeinate</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>Dehydroepiandrosterone, lumaric acid</td>
<td>22, 46</td>
</tr>
</tbody>
</table>

a Naturally occurring compound present in food.
b Synthetic antioxidant used as a food additive.
c The closely related compounds tangeritin and nobiletin occur in citrus fruits.
d E. Bueding, unpublished results.

courser amines or amides with nitrite. Ascorbic acid is effective in inhibiting formation of these carcinogens both in vitro and in vivo (31, 32). Animals given appropriate precursor compounds form nitroso carcinogens in vivo and subsequently develop neoplasms. Under these conditions, addition of ascorbic acid to the diet will prevent formation of the nitroso compounds and the occurrence of neoplasia. α-Tocopherol and phenols also have the capacity to inhibit formation of nitroso compounds (Table 1). A somewhat different type of inhibition potentially can occur within the large bowel. The large bowel flora can form electrophiles from precursor compounds. In one such study, 4-isothiocyanato-4'-nitrophenylenamine was fed to 6 species of animals. In each instance, the large bowel flora converted the parent compound to a mutagen. This did not occur in germ-free rats and could be prevented in animals with a normal microbial flora by administration of antibiotics (1). In humans, the fecal flora produces mutagenic compounds termed fecapentaenes (15, 60). The implication of these mutagens for humans has not been established. If they do represent a hazard, their synthesis potentially could be controlled by compounds altering availability of precursor compounds or modifying the intestinal microbial flora.

Blocking Agents. General Consideration. Blocking agents prevent carcinogens from reaching or reacting with critical target sites. A large and diverse group of compounds both naturally occurring and synthetic falls into this category of inhibitors (Table 1). An understanding of their mechanisms of action is based on the contributions of the Millers and others to the field of chemical carcinogenesis (29, 30). A vast amount of information has been accumulated which demonstrates that chemical carcinogens act via common mechanisms. The ultimate carcinogenic forms of carcinogens are positively charged electrophilic species. Some carcinogens, termed "direct acting," exist in this form or assume it in solution. Others require metabolic activation. Blocking agents can be placed into 3 groups according to their mechanism of action. One group acts simply by inhibiting the activation of a carcinogen to its ultimate carcinogenic form. An example of this type of inhibition is the prevention of symmetrical dimethyldihydrazine-induced neoplasia of the large bowel by disulfiram (65). This compound inhibits the metabolism of symmetrical dimethyldihydrazine to its carcinogenic metabolites (11). Inhibitors in this group are effective only against carcinogens requiring activation. A second group of blocking agents is effective by virtue of inducing increases in activity of enzyme systems having the capacity to enhance carcinogen detoxification. The inhibitors in this group are of particular interest because they have the capacity to inhibit a wide range of carcinogens. They will be discussed more in detail in the next paragraph. The third group of blocking agents has the capacity to act by scavenging the reactive forms of carcinogens. Physiological nucleophiles, such as GSH, fall into

The abbreviations used are: GSH, glutathione; BP, benzo(a)pyrene; DMBA, 7,12-dimethylbenz(a)anthracene; TPA, 12-O-tetradecanoylphorbol-13-acetate.
CHEMOPREVENTION OF CANCER

Table 2

<table>
<thead>
<tr>
<th>Class of inhibitor</th>
<th>Compound</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinoids</td>
<td>All-trans-retinoic acid, 13-cis-retinoic acid, ethyl-8-(4-methoxy-2,3,6-trimethoxyphenyl)-3,7-dimethyl-trans-2,4,6,8-norretinone</td>
<td>62, 63</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Tosyl lysine chloromethyl ketone</td>
<td>57, 59</td>
</tr>
<tr>
<td></td>
<td>Tosyl arginine methyl ester</td>
<td>57, 59</td>
</tr>
<tr>
<td></td>
<td>Tosyl phenylalanine chloromethyl ketone</td>
<td>57, 59</td>
</tr>
<tr>
<td></td>
<td>Leupeptin</td>
<td>16</td>
</tr>
<tr>
<td>Inhibitors of arachidonic acid metabolism</td>
<td>Dexamethasone</td>
<td>57, 62</td>
</tr>
<tr>
<td></td>
<td>5,8,11,14-Eicosaatrynoic acid</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Fluorocitone acetone</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Fluoronide</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Fluorocitone acetone</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Indomethacin</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Nordihydroguaiaretic acid</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>1-Phenyl-3-pyrazoledine</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>p-Bromophenacyl bromide</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Dibromomacetophenone</td>
<td>13</td>
</tr>
<tr>
<td>Phenyis</td>
<td>p-Methoxyphenol</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>2-tert-Butylhydroxyanisole</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>3-tert-Butylhydroxyanisole</td>
<td>49</td>
</tr>
<tr>
<td>Synthetic compound with superoxide dismutase activity</td>
<td>Copper(ll) 3,5-diocepropylsalicylic acid</td>
<td>20, 50</td>
</tr>
<tr>
<td>Cyclic nucleotides or inhibitors of phosphodiesterase activity</td>
<td>Cyclic AMP</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>3-isobuty1-1-methykanethene</td>
<td></td>
</tr>
<tr>
<td>Polymamines</td>
<td>Putrescine</td>
<td>78</td>
</tr>
<tr>
<td>Modulation of calcium metabolism</td>
<td>1α,25-Dihydroxyvitamin D3</td>
<td>30</td>
</tr>
<tr>
<td>Benzoazepines</td>
<td>Diazepam</td>
<td>12</td>
</tr>
<tr>
<td>Others</td>
<td>Quercetin, α-difluorocetylornithine</td>
<td>19, 55</td>
</tr>
</tbody>
</table>

Inhibitors Preventing Formation of Carcinogens

Blocking Agents

Suppressing Agents

Neoplastic Manifestations

This group. Recently, xenobiotic compounds present in plant constituents of the diet have been shown to scavenge the ultimate carcinogenic form of BP. Ellagic acid has been shown to be highly potent in this regard (81). Among compounds that can scavenge carcinogens, one group is potentially of considerable interest, namely, those that would be effective in inhibiting gastrointestinal neoplasia. High-molecular-weight compounds that are not absorbed from the gastrointestinal tract and accordingly could scavenge the reactive form of carcinogens occurring within the lumen of the alimentary tract fall into this category.

Blocking Agents That Increase the Activity of Systems That Can Enhance Carcinogen Detoxification. One group of blocking agents that inhibit chemical carcinogens induces multiple enzymatic alterations. Before proceeding to further considerations of these inhibitors, a brief discussion of detoxification of xenobiotic compounds is relevant. In general, the overall metabolism of foreign compounds is directed towards producing chemical species that can be excreted. Two classes of enzyme systems have been used by Williams (79) for the metabolism of xenobiotic compounds to excretory metabolites. These are termed Phase I and Phase II reactions. Phase I reactions introduce polar groups into xenobiotic compounds. Most are oxidative reactions. A few are reductive. The enzyme system most frequently involved is the microsomal monoxygenase system. The presence of a polar group on a xenobiotic compound provides a means by which a subsequent conjugation reaction can occur, leading to excretion. Phase II reactions, for the most part, are conjugating reactions such as formation of glucuronides, GSH conjugates, and sulfates. The reactions detoxifying foreign compounds are exceedingly important in preventing toxicity from a wide variety of xenobiotic compounds including chemical carcinogens. With the vast variety of reactions catalyzed by the Phase I and Phase II enzymes, it might be anticipated that some adverse reactions occur. Such is the case, but overall this complex system is highly protective (67, 68).

Two general categories of blocking agents that enhance carcinogen detoxification systems have been identified in studies of inhibition of carcinogenesis. They are designated type A and type B inhibitors. Others almost certainly exist. In many instances, insufficient data are available to classify a particular inhibitor as being type A or type B. Both type A and type B inhibitors induce an increase in activity of multiple enzymes, presumably by reacting with receptors. A receptor has been demonstrated for some type B inhibitors but not as yet for type A inhibitors (43, 69, 71). The induction of increases in activity of multiple enzymes with coordinated function is in accord with a receptor mechanism. The type A inhibitors induce an increase in Phase II enzymes, i.e., conjugating enzymes and some related systems (71). A prominent feature of these enzymatic inductions is a marked increase in GSH S-transferase activity (2, 3, 7). UDP-glucuronosyltransferase activity is also enhanced as is epoxide hydrolase and NAPD(P)H quinone reductase activity (5, 6). Other features of type A inhibitors include an alteration in microsomal metabolism in which there is little change in activity but a pronounced alteration in metabolite pattern as demonstrated with BP as the substrate (23). In addition to enzymatic changes, an increase in the levels of GSH in tissues is also found (1, 2). Type A blocking agents have been shown to inhibit carcinogenesis resulting from administration of BP, BP-7,8-dihydrodiol, DMBA, dibenz[a, h]anthracene, diethylnitrosamine, 4-nitroquinoline N-oxide, uracil mustard, urethan, methylazoxymethanol acetate, and trans-5-amo-3-[2-(5-nitro-2-furylvinyl)]-1,2,4-oxadiazole (69).

Type B inhibitors characteristically induce pronounced increases in microsomal monoxygenase activity. A prototype of this class of inhibitors is β-naphthoflavone. Subclasses exist dependent upon differences in the species of cytochrome P-450 induced. Type B inhibitors also enhance the activity of major
conjugating systems such as GSH S-transferase and UDP-glucuronosyltransferase. Type B inhibitors have been shown to inhibit the occurrence of neoplasia resulting from administration of BP, DMBA, 3'-methyl-4-dimethylaminoazobenzene, N-2-fluorenlyacetamide, 4-dimethylaminostilbene, urethan, and aflatoxin (68). These inhibitors are complicated in that this microsomal monooxygenase system can both activate and detoxify chemical carcinogens. The classic example of this is with the aromatic amines. With these compounds, ring hydroxylation results in detoxification, whereas hydroxylation of the nitrogen is an activation reaction. In most instances, when tested in experimental animals, type B inhibitors have been found to inhibit chemical carcinogenesis (68). Presumably, the overall inductive effects on both Phase I and Phase II systems in aggregate result in enhanced carcinogen detoxification. However, the fact that one component of the enzyme induction can increase carcinogen activation makes it possible that conditions may exist in which enhancement of carcinogenesis might occur. A concern with both type A and type B inhibitors is that the particular compound will have multiple biological effects, some of which are noxious.

The resolution of the implications for the human of blocking agents that act by virtue of enzyme induction is likely to reside in 2 areas. The first is epidemiology. Since a large number of these blocking agents are naturally occurring constituents of food, it may be possible eventually to assess the role that these compounds play in inhibiting the occurrence of neoplasia in specific population groups. The second is likely to come from much more effective basic experimentation than has been carried out thus far on the mechanism(s) of enzyme induction. As discussed above, there is evidence that this class of inhibitors acts by virtue of reacting with receptors. If this is the case, then the critical information will reside in defining the specific responses to activation of particular receptors and the structural characteristics of the ligands for these receptors. With such information, one might be able to design ligands with minimal or no other biological effects, particularly adverse ones. In addition, the potential would exist for selecting the receptor providing the most favorable aggregate of enzyme responses appropriate for maximum detoxification capacity and minimum for confounding noxious side effects.

Detection and Identification of Blocking Agents. Blocking agents that act by virtue of their ability to inhibit activation of a carcinogen to its ultimate carcinogenic form can be detected by studies of the effects of test compounds on the activating system. Initial work of this type can be done with in vitro systems, but ultimately it is necessary to determine the effects of the test compounds in vivo (11). The blocking agents that act by inhibiting enzymatic activation of carcinogens are relatively specific. In contrast, inhibitors that act by virtue of their capacity to induce increased activities of multiple enzymes with the capacity to detoxify chemical carcinogens have been shown to inhibit a wide variety of carcinogens. The diverse chemical structures of blocking agents that act by this type of mechanism indicate that compounds in addition to those already identified will almost certainly exist. A means of identifying these inhibitors in complex mixtures such as dietary constituents is by virtue of the capacity to induce increased activity of enzymes that can detoxify chemical carcinogens. This is particularly true for induction of Phase II enzymes which is a characteristic of both type A and type B inhibitors. Induction of increased GSH S-transferase activity by crude materials and the subsequent identification of the inducing compounds using GSH S-transferase induction as an assay system for monitoring the purification process has been used successfully for identifying new blocking agents (71, 76).

The detection and identification of blocking agents that act by virtue of their capacity to trap reactive species of carcinogens can be identified by several techniques. One of these is to determine the specific reaction of the putative inhibitor with the carcinogen as has been done with diethylnitrosamine and BP-7,8-diol-9,10-epoxide (81). A more general type of testing entails the inhibition of binding of the carcinogen to DNA by the test compound. Inhibition of mutagenesis in the Ames system can also be used. Ultimately, in vivo studies should be performed since the complex conditions occurring in vivo may be very different than those existing for in vitro test systems.

Suppressing Agents. Suppressing agents are compounds that inhibit carcinogenesis when administered subsequent to a course of carcinogen administrations that would result in the occurrence of cancer. The number of classes of compounds that act as suppressing agents is smaller than that of blocking agents. Unlike the situation existing for blocking agents, there are no generic short-term test systems indicating the likelihood that a compound is a suppressing agent. Thus, they are more difficult to identify. The most extensively studied suppressing agents are the retinoids. These compounds have been reviewed recently (33, 52–54). There are several salient points that should be made concerning the retinoids: they can be highly effective as suppressing agents; individual retinoids target to specific tissues rather than on all tissues (some tissues such as the large bowel appear to be particularly refractory); in general, the effects of the retinoids are reversible; the compounds have toxic properties; and their mechanisms of suppressing action have not been clearly elucidated. The current status of information about these compounds indicates that they are likely to be most suitably utilized for groups or individuals at high risk to the occurrence of cancer. Major efforts are in progress worldwide to produce more effective retinoids and to determine their mechanism or mechanisms of action. β-Carotene, which can be metabolized to retinol, has been reported to have a suppressive effect on DMBA-induced mammary neoplasia (45, 47).

Selenium salts are an exceedingly interesting group of suppressing agents. These compounds have been found to inhibit a considerable variety of experimental neoplastic systems. Included are the inhibition of virus-induced neoplasia of the mammary gland in mice as well as carcinogenesis resulting from administration of chemical carcinogens to both mice and rats (9, 14, 18). Epidemiological data have been interpreted by some investigators as indicating that a low selenium consumption may increase the occurrence of neoplasia in certain human populations (9). There are 2 pressing problems in the available information concerning selenium inhibition of neoplasia. The first has to do with the mechanism or mechanisms by which selenium acts. Unfortunately, very little information exists on the mechanism(s) by which selenium inhibits the occurrence of neoplasia. The second problem, which is related, concerns the relationships between species, dose, and effectiveness of selenium as an inhibitor. Good information on the relationships of dose to protection against neoplasia is not available for different species of experimental animals and likewise for the human. Since selenium can have toxic effects, a major defect in currently available
information is the inability to predict the dose level in the human that would give maximum protection without producing toxicity (9). Dehydroepiandrosterone is an interesting inhibitor in that it has been shown to suppress neoplasia in several experimental systems (46); the mechanism of this suppression is not known. The number of investigators who have carried out experiments with this and related compounds as inhibitors of carcinogenesis has been very small. The use of protease inhibitors and inhibitors of arachidonic acid metabolism as inhibitors of carcinogenesis is under investigation by several groups of workers. The number of target sites at which inhibition has been demonstrated is relatively small for both of these classes of compounds as well as other remaining suppressing agents listed in Table 1.

A series of experiments has been published recently by Nomura et al. (40) showing that caffeine, antipain (a protease inhibitor), and retinoic acid can inhibit urethane-induced teratogenesis and in some instances teratogenesis resulting from administration of other carcinogens. Information concerning any common features between the mechanisms of suppression of neoplasia and teratogenesis could prove to be of importance.

Compounds Inhibiting Tumor Promotion

In Table 2, 9 classes of compounds that inhibit tumor promotion are listed. In some instances, a class contains a sizable number of inhibitors; and in others, there is one compound. The vast majority of these studies have focused on inhibition of promotion of epidermal neoplasia in the mouse as a result of topical administration of TPA. A few studies have used other tumor promoters. Of particular interest in this latter group have been experiments in which the tumor promoter used was benzyol peroxide. A major hypothesis concerning tumor promotion has been that attack by oxygen radicals may play a role in its causation (49, 58). In accord with this hypothesis has been the demonstration of oxygen radical formation in the mouse epidermis following application of TPA. Several groups of inhibitors that overall prevent attack by oxygen radicals inhibit tumor promotion. Phenolic antioxidants inhibit tumor promotion by benzyol peroxide (49). Protease inhibitors prevent formation of oxygen radicals by TPA and inhibit tumor promotion (58). A synthetic compound with superoxide dismutase activity, i.e., copper(II) 3,5-diisopropylsalicylic acid, inhibits tumor promotion (20, 50). Thus, there is a body of evidence indicating the possibility that one mechanism of inhibition of tumor promotion may reside in a "blocking action" in which the tissues are protected from attack by oxygen radicals.

A comparison of compounds listed in Tables 1 and 2 show that members of 3 major groups, i.e., retinoids, protease inhibitors, and inhibitors of arachidonic acid metabolism, which have the capacity to act as suppressing agents following administration of a full course of carcinogens also are inhibitors of TPA-induced promotion of epidermal neoplasia. An example of the former type of experiment is one in which a single dose of DMBA is given to Sprague-Dawley rats and inhibition is brought about by feeding a retinoid in the diet starting 1 week after the administration of the carcinogen (33). An example of inhibition of TPA-induced tumor promotion by a retinoid entails the administration of the retinoid prior to each of multiple administrations of TPA to the skin of the mouse (82). The observation that members of 3 major groups of inhibitors will inhibit the occurrence of neoplasia in both types of experimental models suggests the possibility of some common mechanism. Studies of inhibition of tumor promotion in target tissues other than skin and with a variety of tumor promoters are badly needed.

Compounds Inhibiting Neoplasia When Administered Shortly before Exposure to a Carcinogenic Compound

Compounds that exert inhibitory effects when administered shortly before exposure to a compound involved in the causation of cancer have implications that merit separate consideration. Some inhibitors are effective if administered during a time interval ranging from several minutes to several hours prior to the cancer-causing agent. In interpreting epidemiological data as well as for consideration of deliberate intervention strategies, short-time interval effects could be of importance. In general, epidemiological studies of the relationships of diet to cancer do not deal with the sequence in which foods are consumed. Thus, if a protective substance was eaten at the beginning of a meal (an "inhibitory hors d’oeuvre") and a carcinogenic compound, i.e., an initiator or promoter, is consumed later in the meal, the likelihood of protection would be greater than if the reverse sequence of consumptions occurred. Likewise, for considerations of deliberate intervention, rapidly acting inhibitors could protect against constituents of the diet that might be involved in the causation of neoplasia. In Table 3 are listed compounds that inhibit full carcinogens when administered shortly before the carcinogen. In addition, there are a number of compounds that inhibit tumor promoters when administered shortly before the promoter. These include all-trans-retinoic acid, 13-cis-retinoic acid, ethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-trans-2,4,6-nonatenalate, dexamethasone, fluocinolone acetonide, fluclorocone acetone, nordihydroguaiaretic acid, p-bromoacetyl bromide, copper(II) 3,5-diisopropylsalicylic acid, p-methoxyphenol, 2-tert-butylhydroxyanisole, 3-tert-butylhydroxyanisole, cyclic AMP, and 3-isobutylmethylxanthine (20, 36, 42, 47, 49, 50, 62-64).

Discussion

There are a large number of compounds that can prevent the occurrence of cancer. The number of experiments that have been performed that show this end result is of the order of several hundred. The chemical diversity of the inhibitors indicates that inhibition of carcinogenesis is not a highly selective phenomenon and that multiple strategies exist for bringing about this desired effect. It also makes it probable that additional compounds with chemopreventive properties will be identified in the future.
future, again adding to the choices that will be available. These
data enhance the likelihood that chemoprevention of neoplasia
will prove of value as a method of cancer control in the human.
Given this favorable outlook, where are we now and how do we
proceed most effectively?

In terms of application of existing information to prevention of
cancer in the human, there has been a focus on 2 types of
efforts. One of these has been to select compounds that have
very little toxicity and to use these in an attempt to prevent
neoplasia in selected populations. Three such compounds fall
into this category. These are ascorbic acid, α-tocopherol and β-
carotene. The hope has been that these compounds could be
administered with very little risk to human subjects and that they
would produce a significant preventive effect. In experimental
systems for evaluating inhibition of carcinogenesis, these com-
ounds have not been shown to have broad inhibitory capacities.
Ascorbic acid is effective in preventing the formation of nitroso
carcinogens from precursor compounds but in most instances is
not effective in inhibiting carcinogenesis resulting from admin-
istration of preformed carcinogens (31, 32). There is only a small
amount of published evidence showing inhibition of carcinogen-
esis by α-tocopherol, in spite of the fact that this compound has
been investigated for its inhibitory effects over a long period of
time (67). Only a few studies of inhibition of carcinogenesis by
β-carotene have been reported. These have shown inhibition of
mammary neoplasia in the rat and epidermal neoplasia in the
mouse (26, 45, 48). Thus, while the risk of the use of these
compounds would appear to be minimal, it is quite possible that
their administration to humans will not show positive results.
If this proves to be the case, recognition should be made of the
considerations involved in their early choice for studies in the
human. These negative results should not discourage further
endeavors to explore the use of more effective chemopreventive
compounds.

The second focus has been on the retinoids. This group of
compounds has inhibitory efficacy in experimental animals but
also can produce toxic reactions. Accordingly, they have been
selected for use in populations at increased risk to neoplasia.
Evaluation of the effectiveness of some retinoids for prevention
of neoplasia in humans is currently in progress. Substantial
efforts are being made to elucidate their mechanism(s) of inhibi-
tion and to develop more effective analogues. The retinoids,
however, are a special case. Nothing approaching the efforts
directed at the development and application of retinoids as
chemopreventive agents exists for other categories of inhibitors.

A common situation existing for many of the inhibitors identi-
cified thus far is that: (a) the inhibitors being studied experimentally
are first-generation compounds; i.e., these are the compounds
which originally were shown to be inhibitory and little work on
other analogues exists except perhaps for a few that are readily
available; (b) little is known about the mechanism of inhibition;
and (c) the number of investigators working on the compound
is small, in some instances a single individual. This combination
of events is not favorable for the development of the field. The use
of first-generation compounds means that there is not a clear
perspective on some major attributes of the particular category
of inhibitor. A number of first-generation inhibitors have noxious
properties. One does not know whether these are necessarily
associated with the inhibitory property of the compound or are
an unrelated biological characteristic that could be dissociated
from the essential inhibitory mechanism of the compound by
structural modification. In a number of instances, high concen-
trations of a compound are required for inhibitory effects. Again,
working with a first-generation compound, one does not know
whether this is a characteristic of the particular inhibitor or
whether structural modification would result in a significantly
more potent compound. Thus, with first-generation inhibitors,
we lack knowledge of maximum efficacy and minimal toxicity of
the particular type of compound. An additional critical deficiency
in our knowledge about inhibitors of carcinogenesis is the paucity
of the data on their mechanisms of action. Information of this
nature is an essential ingredient of an effective program.

The field of chemoprevention of cancer requires considerable
further expansion. The leadership of the National Cancer Institute
and the American Cancer Society have made major commit-
ments, intellectual and resource, to this field. One would hope
that these will be continued and perhaps enlarged. There is one
further way in which the information base can be expanded
effectively. It entails a conceptual commitment by investigators.
When an investigator works on a mechanistic problem related to
the causation of cancer, whether this be the metabolism and
targeting of a chemical carcinogen, the consequences of an
oncogene expression, or any of the numerous other investiga-
tions of mechanism, the question should be asked “How can
this process be inhibited or suppressed so as to prevent the
occurrence of cancer?” If this question were asked and followed
by appropriate experimentation when feasible, it would convert
a large group of experimental oncologists into major contributors
to developing means for cancer prevention.

The essence of the present Perspective can be summarized
quite briefly. Chemoprevention can readily protect experimental
animals against the occurrence of neoplasia. We now must learn
how to bring this protection about effectively for the human.

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