Chemoprophylaxis of Carcinogenesis: A Review

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Summary

A group of experiments is presented in which inhibition of chemical carcinogenesis in experimental animals has been achieved by administration of 1 of a variety of chemical compounds. The inhibitory compounds can be divided into 4 groups. The 1st group is composed of compounds which induce an increased activity of carcinogen-detoxifying systems; the 2nd, compounds with similar structures to carcinogens and which have been postulated to cause inhibition by a competitive mechanism; the 3rd, compounds which inhibit the initiation phase of carcinogenesis; and the 4th, a large number of compounds whose means of action is not clearly understood.

A major purpose of this review is to stimulate further work on the chemical inhibition of chemical carcinogenesis since this area of research appears to have considerable potential for yielding information of fundamental importance and conceivably might eventually have some applied aspects.

Introduction

A scattered group of animal experiments exists in which chemical carcinogenesis has been inhibited by administration of 1 of a variety of chemical compounds. The compounds bringing about this inhibition can be divided into 4 groups. In the 1st, the compound is administered for the purpose of increasing the capacity of the organism to detoxify chemical carcinogens. In the 2nd, the compounds administered are structurally related to the carcinogen being employed and it has been postulated that they inhibit by a competitive mechanism. In the 3rd, the compounds act on the initiation phase of carcinogenesis (9) possibly by inhibiting DNA-dependent RNA synthesis. The 4th group is quite heterogeneous and consists of a large number of compounds whose repeated administration is capable of delaying or preventing the appearance of neoplasms by some mechanism or mechanisms which are not clearly understood. Since in all 4 groups administration of chemicals results in inhibition of carcinogenesis, they are brought together under the term “chemoprophylaxis.”

In this review an effort has been made to present primarily major experimental contributions illustrating the various categories of inhibitory effects. Specifically excluded from consideration are compounds with known hormonal or immunologic action and dietary alterations.

PROTECTION AGAINST CHEMICAL CARCINOGENS BY INCREASING THE ACTIVITY OF DETOXIFICATION SYSTEMS. There exists in a wide variety of animal species a group of closely related microsomal detoxification systems which have the capacity to detoxify a broad range of compounds not normally present in the organism. These systems have been studied extensively by pharmacologists because of their effects on many drugs, and a considerable literature concerning their properties has been published (12, 16-18, 57). In addition to their ability to detoxify drugs these enzymes are also capable of detoxifying a variety of carcinogens to less active or inactive compounds. These include polycyclic hydrocarbons (10, 15, 20), azo dyes (19), and aromatic amines (11, 28). In the case of the latter group a complication exists which will be discussed subsequently. An important property of the microsomal detoxification systems is that an increase in their activity can be induced by the administration of appropriate compounds (1, 12, 10-19, 57). The response to an inducer can be quite nonspecific in that an increase in detoxification activity for a wide variety of compounds may result. For example, if MC (1) which is a potent inducer, is administered, an increase in detoxification of polycyclic hydrocarbons, aromatic amines, and azo dyes will occur (15, 19, 28). Evidence exists for this not only in vitro but also in vivo. It has been shown by a number of workers that the administration of polycyclic hydrocarbon inducers markedly reduces the incidence of hepatic cancer which results from feeding 3'-methyl-DAB to the rat (50, 51, 58). Other studies have demonstrated that polycyclic hydrocarbon inducers can markedly reduce the incidence of tumors of the liver, mammary gland, ear duct, and small intestine in rats fed AAF or 7-fluoro-2-acetylaminofluorene (51). In addition, administration of these inducers reduces markedly the incidence of mammary tumors which follows i.v. administration of DMBA to Sprague-Dawley rats (39). Likewise we have observed that phenothiazine inducers are also capable of inhibiting mammary tumor formation caused by DMBA (unpublished). An additional method of studying DMBA detoxification in vivo is to utilize the observation that a single large dose of DMBA will cause adrenal necrosis in unprotected rats (29, 38, 40). A close correlation has been found between the capacity of phenothiazines to induce an increased polycyclic hydrocarbon hydroxylase activity and the capacity of the compound to prevent adrenal necrosis resulting from DMBA administration (68).

Until recently the only group of compounds which were known to have the capacity to induce a marked increase in activity of systems detoxifying polycyclic hydrocarbon carcinogens as well

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1520 CANCER RESEARCH VOL. 26
Chemoprophylaxis of Chemical Carcinogenesis

as carcinogens having other chemical structures were the polycyclic hydrocarbons themselves. Recent studies have shown that several other types of potent inducers exist. These include phenothiazine and a large number of its derivatives, 2,5-bis-(4-pyridyl)-1,3,4-thiadiazole and several similar 5-membered heterocyclic compounds into which aromatic rings are substituted, flavone, benzoflavone, and 2-phenyl benzothiazole (67, 68). These studies are encouraging in that they indicate that a wider range of effective chemical structures with inducing capacity exists than previously anticipated. This diversity increases the possibility of obtaining inducers with optimal properties, including the lack of side reactions and toxicity.

A phenomenon which can occur along with the induction of an increase in a carcinogen-detoxifying reaction is a concurrent increase in activity of a 2nd reaction which enhances the carcinogenicity of the same compound. The reality of this situation has been brought into focus by the observations that polycyclic hydrocarbon inducers whose administration results in a decreased carcinogenicity of AAF by ring hydroxylation also cause an increase in N-hydroxylation of the same compound (52). A considerable amount of evidence has shown that N-hydroxylation is a step in the formation of a proximate carcinogen from the parent compound (53). In the rat the increase in ring hydroxylation is the predominant effect in vivo so that administration of a polycyclic hydrocarbon inducer such as MC results in an over-all protective effect against AAF. In the hamster, studies limited to i.p. administration of a single dose of MC have shown an increase in N-hydroxylation in the liver without increasing ring hydroxylation (52). Since the chemical nature of the inducer, the route of administration, and the dosage schedule can be critical, it remains to be determined whether this finding is unique or characteristic in this species. If it is characteristic, it will then be of great interest to observe whether chronic administration of MC and other inducers of increased microsomal enzyme activity increase the susceptibility of this species to the carcinogenic effects of AAF or if in this species protective systems other than ring hydroxylation come into play.

While under some conditions it might be desirable to make efforts to protect against carcinogens of highly diverse chemical composition which come in contact with the organism via any of the routes of entry, under others it might be preferable to consider a more selective approach involving both of these factors. For example, a more limited objective would be to try to find an effective means of inducing an increase in monoaromatic and polycyclic aromatic ring hydroxylation activity in the lung. Basic to this type of approach would be finding inducers which are selective in terms of the type of detoxification reaction stimulated. In addition, they would also have to be compounds which would have some characteristics preventing a generalized distribution throughout the body at least in their original chemical form. A degree of selectivity in the induction of increased activity of detoxification reactions has been shown to exist for some inducers. For example, Conney et al. have studied the effects of 6 inducers on 6 detoxification systems and have found that a considerable variation exists in the pattern of responses. They observed that BP had no effect in inducing increased detoxification of hexobarbital but was very effective in inducing an increased activity of the system resulting in the demethylation of 3-methyl-4-monomethylaminoazobenzene and also the hydroxylation of BP. In contrast, orphenadrine is highly effective as an inducer of hexobarbital detoxification, moderately effective with regard to the demethylation system, and only slightly effective for BP hydroxylation (17). These observations offer encouragement to further work aimed at obtaining induction of specific detoxification systems.

The 2nd problem, namely that of obtaining an inducer which acts on the tissues of a specific portal of entry without affecting other tissues, has received very little study. Most of the work on microsomal detoxification systems has been done on liver although these detoxification systems are found in many other tissues including those of the major portals of entry, i.e., gastrointestinal tract, lung, and skin (66-69). In work with phenothiazine inducers, the comparative effects of a number of these compounds on the BP hydroxylase activity of liver and the mucosa of the small intestine have been studied. The range of variation is quite appreciable. In untreated rats the BP hydroxylase activity in these 2 tissues is the same. Following administration of phenothiazine the activity in the liver will be increased about 20-fold, whereas that of the small intestine will increase slightly more than 3-fold. In contrast, administration of 2-methylmercapto-10-(2-(N-methyl-2-piperidyl)ethyl)phenothiazine-HCl (thioridazine-HCl) induces approximately a 3-fold increase in activity in the liver and a 5-fold increase in the small intestine. Other phenothiazines have been found which give intermediate results between these 2 extremes (68). The nature of the relationship between structure and relative effectiveness as an inducer for various tissues has not been worked out. It is possible that chemical modification of an inducer at its initial site of tissue contact could give it an element of specificity in that the tissues of the portal of entry would be presented with the parent compound and the other tissues of the body with a metabolic derivative or derivatives less active or entirely inactive in inducing capacity.

PROTECTION AGAINST CHEMICAL CARCINOGENS BY STRUCTURALLY RELATED COMPOUNDS. A 2nd type of experiment in which inhibition of chemical carcinogenesis has been achieved has been one in which a compound chemically related to the carcinogen was administered. Most of this work has been done with polycyclic hydrocarbon carcinogens applied to mouse epidermis. It has been shown that 1,2,5,6-dibenzofluorene and chrysene can reduce the carcinogenicity of MC, and 1,2,5,6-dibenzacridine that of DBA (47, 59). Inhibition of DBA-induced epidermal carcinogenesis has also been shown to occur owing to application of partially hydrogenated derivatives of this carcinogen (48). In extensive studies employing DMBA as the carcinogen a number of polycyclic hydrocarbons have been found to be inhibitory. The average time for skin tumor induction was doubled by administration of 1,2,5,6-dibenzofluorene or 8-methyl-1,2-benzanthracene, 1,2-Benzanthracene, 2'-methyl-1,2-benzanthracene, 7-methyl-1,2-benzanthracene, and 6,8-dimethyl-1,2-benzanthracene had slightly less inhibitory activity. Compounds less closely related to DMBA structurally, such as naphthalene, anthracene, and fluorene, did not cause inhibition (37). In addition to epidermal carcinogenesis, studies have been carried out on inhibition of subcutaneous sarcoma formation. In early work it was shown that s.c. injection of a combination of 1,2-benzanthracene and DBA resulted in a tumor yield of approximately 0.5 the sum of their individual tumor yields (64). In later work
with this type of experimental system it was found that the occurrence of sarcoma due to injection of DBA or MC can be inhibited by partially hydrogenated derivatives of these carcinogens (31, 45, 46). Fully hydrogenated derivatives of the 2 carcinogens were inactive. It is of interest that this inhibition occurs not only when the carcinogen and the partially hydrogenated derivative are injected at the same time but also when the inhibitors were injected after the carcinogen, the longest interval being 4 days.

In both the epidermal and subcutaneous carcinogenesis experiments with the polycyclic hydrocarbons, many of the investigators had set out to bring about a competitive inhibition. However, while the chemical relationships between carcinogen and inhibitors suggest this possibility, rigorous proof of this mechanism of inhibition has not been furnished. A number of possible alternative explanations of the results obtained exist. These include the possibilities that the inhibitor causes changes in distribution and absorption of the carcinogen, changes in cell population, or systemic effects. In addition a further complication to interpretation of these experiments is the fact that some of the inhibitors employed are also inducers of increased activity of microsomal detoxification systems. Since the activity of the detoxification systems is exceedingly low in the skin, it would appear unlikely that the inhibitory effects on carcinogenesis are due to an increase in activity of these systems. Nevertheless, this illustrates how factors quite distinct from competitive ones could conceivably be exceedingly important.

**INHIBITION OF THE INITIATION PHASE OF CARCINOGENESIS.**

Recently, several studies have been published which were specifically designed to inhibit the initiation phase of carcinogenesis. In the 1st of these, actinomycin D, an inhibitor of DNA-dependent RNA synthesis (56), was applied to the mouse skin 3 times during the 8-hr interval prior to the application of a single dose of DMBA and then again 3 times during the 8-hr interval subsequent to application of the carcinogen. For the promotion phase of carcinogenesis, croton oil was employed. At 14 weeks following carcinogen application the number of mice treated with actinomycin D who had skin tumors was less than 0.5 that of the untreated group and the total number of tumors was less than 0.2 of that of the untreated group (32). In further work, inhibition with actinomycin D was observed in experiments in which a single application of DMBA was employed without subsequent croton oil applications and also in experiments in which skin carcinogenesis was initiated by urethane followed by promotion with croton oil (2, 33). The authors interpret their results as supporting the hypothesis that alterations in gene action systems are early biochemical events in carcinogenesis. A critical question in the interpretation of this work and other studies of a similar nature is whether the inhibition brought about is due to a specific effect on DNA-dependent RNA synthesis or some less specific events due to the irritant or perhaps some other action of the inhibitor. In defense of the specificity of the effect, the following 3 points can be made: (a) The inhibitory effect of actinomycin D has been shown to be equally effective when this compound was administered 1 day after the application of DMBA as when it was administered on the same day. An inhibitory effect was obtained for administrations made up to 4 days following carcinogen treatment but had disappeared at 7 days. Thus it is highly unlikely that the inhibitory effects obtained are due to alterations in absorption or distribution of carcinogen. (b) The inhibitory effects were not obtained when high concentrations of actinomycin D, which result in skin ulceration, were applied 1 week after DMBA applications. (c) Inhibition has been observed with low concentrations of actinomycin D which were reported as producing "relatively little skin damage" (33). This last point is a critical one. What appears on morphologic evidence to be relatively little may involve disruption of a number of biochemical and physiologic systems. Accordingly the possibility has not been eliminated that actinomycin D is exerting some action other than that on DNA-dependent RNA synthesis.

In other studies, the initiation phase of epidermal carcinogenesis has been inhibited by 4-nitroquinoline-N-oxide. It has been shown that a single dose of this compound will inhibit BP-induced epidermal carcinogenesis when applied 1, 3, or 7 days before, or 1 day after, application of a single dose of BP. The inhibitory effect was most pronounced when the 4-nitroquinoline-N-oxide was applied 3 days prior to the BP. Under these conditions the time required for 50% of the mice to show tumors was prolonged from 10 weeks to 18 weeks (62). Maleic anhydride has also been shown to have a similar action. In these experiments multiple applications of the inhibitor were employed. Maleic anhydride was applied to the skin twice weekly for 10 weeks and this was followed by DMBA alone or DMBA and then croton oil. Under both conditions maleic anhydride exerted an inhibitory effect as manifested by a prolonged latent period and decreased tumor yield (44). It has also been shown that epidermal carcinogenesis resulting from initiation with DMBA followed 3 weeks later by application of croton oil as a promoter could be inhibited by the application to the mouse skin of phenanthrene simultaneously with the DMBA (41).

In addition to inhibition of carcinogenesis induced by polycyclic hydrocarbons, a study has recently been reported in which a different type of carcinogen, cadmium chloride, was employed. The s.c. injection of a single dose of cadmium chloride in the interscapular region of the rat resulted in the formation of sarcomas at the site of injection and also in interstitial cell tumors of the testis. In the experiment reported the inhibitor used was zinc acetate which was administered s.c. in 3 divided doses: the 1st, 6 hr prior to the cadmium injection; the 2nd, simultaneously with the cadmium injection; and the 3rd, 19 hr following the cadmium injection. All 3 administrations were at different sites from one another and from that of the cadmium. The incidence of subcutaneous sarcomas and also interstitial cell tumors was markedly diminished in the animals receiving the zinc acetate. Throughout the experiment there were no signs of systemic damage from the zinc acetate. The body weights of the different experimental groups were almost identical (35). Further work with this experimental system should prove very interesting.

Studies of the inhibition of the initiation phase of carcinogenesis have demonstrated that a variety of compounds can bring about this effect. In many respects this represents an excellent experimental system to work with. A single application of inhibitor or multiple applications during a short time interval can be employed and likewise a single application of the carcinogen can be used so that well-defined time relationships are available. Potential complications such as alteration of the nutritional state of the animal, which can be a problem under experimental conditions in which prolonged administrations of inhibi-
tors are used, can be avoided (65). The implications of the work with actinomycin D are exceedingly important. If it is proven that initiation does in fact involve an altered pattern of DNA-dependent RNA synthesis which can be specifically blocked, this would represent an advance in the knowledge of carcinogenesis of considerable magnitude.

INHIBITION OF THE EARLY STAGES OF CARCINOGENESIS. In 1929 Berenblum began a series of studies in which he showed that epidermal neoplasia induced by tar painting could be inhibited by painting the exposed area with a dilute solution of dichlorodihethylsulfide (mustard gas) (4). For example, in a typical experiment 33 of 47 mice painted with tar only showed skin tumors by 27 weeks, whereas in those painted alternately with tar and mustard gas, only 3 of 46 developed skin tumors in the same interval. Mustard gas is a highly reactive and irritating compound. Accordingly, further work was carried out in an attempt to determine the means by which it caused inhibition. In particular, 3 possibilities were considered: (a) that inhibition was the result of an effect or effects on the animal as a whole, (b) that inhibition was caused by nonspecific local irritant properties of the compound, and (c) that the inhibition was due to a specific effect on the epidermis related to neoplasia. The possibility that tumor inhibition was the result of some systemic effect was investigated in experiments in which the mustard gas was applied at a site different from that of the tar painting. Under these conditions no inhibition was observed (5). The evaluation of the role of local irritation is more difficult to deal with and was investigated by determining the effects of a series of irritants on epidermal carcinogenesis (6, 7). The results of this experiment showed that many compounds which have a very strong irritant action do not have an inhibitory effect. Examples of such irritants are turpentine, croton oil, xylene, acetic acid, trichloroacetic acid, and iodoacetic acid. In this same series of investigations and a later one, several other compounds were found to have inhibitory effects (6, 8). All of these have irritant properties. The compounds included a group which is chemically related to mustard gas and in addition, cantharidin and podophyllotoxin. Thus, while an irritant action per se was not inhibitory, the studies reported suggest that an irritant action was associated with compounds having an inhibitory effect. While it is clearly possible that highly specific local effects resulted in tumor inhibition in the work reported by Berenblum, the role of the irritant properties of the compounds employed remains to be determined.

Subsequently, a group of similar studies of inhibition of epidermal carcinogenesis was begun by Crabtree employing other compounds (21-27). Four main classes of compounds were found to delay or prevent epidermal neoplasia resulting from painting the skin of the mouse with carcinogenic polycyclic hydrocarbons. These are hydrolyzing halogen compounds such as valeryl chloride or benzene sulfochloride (22); compounds which are metabolized to mercapturates such as bromobenzene (23); the anhydrides of α,β-unsaturated dicarboxylic acids such as maleic anhydride and citraconic anhydride (24); and several low molecular weight aromatic hydrocarbons such as phenanthrene (25). In experiments with these compounds it was possible to retard and in some instances prevent the appearance of neoplastic lesions. In a typical experiment the carcinogen was applied to mouse skin twice weekly and the inhibitor on 4 other days. Under these conditions, if 0.1% BP was employed as the carcinogen and 15% bromobenzene in ether the inhibitor, the average induction time was prolonged from 16 weeks in the unprotected animals to 24 weeks in those protected with bromobenzene. If the concentration of BP was reduced to 0.05%, the average induction time was 20 weeks in the unprotected animals and greater than 40 weeks in those protected by bromobenzene applications. In the work with bromobenzene a control experiment was performed to rule out the possibility that the inhibition was due to a systemic effect. For this purpose bromobenzene and BP were applied at different sites. Under these conditions inhibition did not occur.

One of the criticisms that can be made of experiments in which an inhibitory action is brought about by a compound which is painted on the skin on alternate days to the carcinogen or at the same time is that factors such as changes in distribution or retention of the carcinogen are primarily involved rather than some specific inhibitory mechanism. Crabtree carried out an interesting experiment in which these factors would not play a role. In this experiment 0.3% BP was painted on the skin of 2 batches of 30 mice for 11 weeks and then discontinued. From this point on, 1 group of mice was painted 4 times a week with 20% bromobenzene in ether and the other group kept as a control. Between the 11th and 26th weeks, 14 of the unprotected group developed skin tumors, whereas only 5 of those treated with bromobenzene showed tumors. Thus, after all exposure to the carcinogen was completed, it was possible to inhibit the manifestations of the neoplastic process (23). Unfortunately, in this experiment the possibility that the inhibition was due to a generalized effect on the animals was not controlled, nor were weight data given. Extensive studies have shown that an impaired nutritional state can inhibit epidermal carcinogenesis. These include work which has demonstrated that a decreased caloric intake following completion of all carcinogen paintings can have an inhibitory effect (65). Thus the question of the specificity of the inhibitory effect of bromobenzene when applied subsequent to the course of carcinogen paintings cannot be determined.

As a result of the extensive studies carried out by Crabtree, it is apparent that a wide variety of compounds can inhibit epidermal carcinogenesis and a basis for wider investigations has been provided. Further work is required to establish the specificity of the inhibitory effects obtained as well as the mechanism or mechanisms involved. With regard to the latter, Crabtree postulated that the factor common to the various inhibitors of carcinogenesis which he employed was their property of combining with sulfhydryl groups by either addition, condensation, or oxidative coupling with a resultant interference with sulfur metabolism (24).

In further studies carried out by other investigators, a diverse group of other compounds has been reported to inhibit polycyclic hydrocarbon-induced epidermal carcinogenesis in the mouse. These include 4-nitroquinoline-N-oxide (63), cyclic terpenes (3), heptaldehyde (14), 2,3-dimercapto-1-propanol (27, 49), and a phenolic fraction from cresote oil (13). In the work with 4-nitroquinoline-N-oxide, it was found that this compound retards the appearance of papillomas of the skin of mice treated with BP when the 2 were applied simultaneously in the same solution or if the 4-nitroquinoline-N-oxide was applied 3 days before each BP application. In order to evaluate the possibility that a sys-
In the inhibitor studies with cyclical terpenes, a complex mixture of compounds which is not fully described was employed. This mixture was found to cause an inhibition of BP-induced epidermal carcinogenesis under conditions in which the BP was dissolved in the terpene mixture or when the BP and the terpene mixture were applied to the same site on alternate days. In an attempt to control the possibility of a systemic effect having caused the inhibition, the investigators set up a control group in which the mice were fed the terpene mixture. This resulted in a mortality of 86%. In the 6 animals surviving, no inhibition of carcinogenesis was observed (3). In the studies of 2,3-dimercapto-1-propanol, heptaldehyde and a phenolic fraction from creosote oil inhibition of epidermal carcinogenesis was found, but the work is difficult to evaluate because controls for determining the possibility of a systemic effect of the inhibitor employed are lacking, and weight data are not included in these reports.

In studies of a somewhat different nature, the biweekly i.p. injection of sodium cobaltinitrite has been reported to cause a significant reduction in the incidence of skin tumors in mice painted with MC. Weight data which were obtained in these investigations showed no difference between mice who had received the sodium cobaltinitrite and those which had not (54). The possibility that the inhibition was due to methemoglobinemia was investigated by administering sodium nitrite and p-aminopropiothenone in doses which caused an equivalent amount of methemoglobinemia to that cause by sodium cobaltinitrite. Neither of these 2 compounds inhibited carcinogenesis (55). In further studies it has been shown that cobaltous chloride has similar inhibitory effects to that of sodium cobaltinitrite (42). In other investigations in which an inhibitor was administered by injection, it has been reported that BP-induced s.c. sarcoma formation in mice is inhibited by glyceraldehyde. In these studies BP was injected s.c., and from 11 to 26 weeks after this injection biweekly s.c. administrations of glyceraldehyde, glucose, or Ringer-Locke solutions were carried out in different groups of mice. In those animals receiving glyceraldehyde a delay in the appearance of the sarcomas was found. The authors state that, in general, the appearance and weight of the various experimental groups of animals were comparable, but specific weight data are not included (60). In a previous study by the same workers, it was reported that propionaldehyde exerted an inhibitory effect on s.c. sarcoma formation under similar experimental conditions. However, a high mortality in all groups of mice involved in this experiment makes the study difficult to interpret (61). The experiments which have been carried out on inhibition of the early stages of carcinogenesis have demonstrated that it is possible to obtain highly suggestive results and form a basis for further work. Considerable additional knowledge about the mechanism or mechanisms by which the inhibition is brought about is critical. In order to obtain this information it would be desirable to have experimental data in which factors such as possible differences in distribution or retention of the carcinogen, changes in cell population due to irritation, generalized toxic effects, and nutritional disturbances can be eliminated from consideration. Experiments in which the inhibitor is applied after completion of the entire course of carcinogen application would seem particularly useful if they can be employed.

Since cancer research is primarily directed toward man, it is worth speculating on the possible implications for the human of the experimental material which has been presented in this review. In considering the total picture of the application of procedures for the prevention and cure of cancer in man it is apparent that very little is done in the interval between exposure to carcinogens and the initial morphologic evidences of neoplasia. In other words, once our capabilities for preventing exposure to carcinogens have been exhausted, our next line of defense becomes early diagnosis. Perhaps we have neglected the possibility that some effective action could be taken during this interval. Most of the human exposure to environmental chemical carcinogens appears to be of a chronic, low dosage type. The interval from the initial exposure to the development of clinically recognized malignancies is frequently of a very long duration (30, 34, 36, 43, 70). Thus it would appear that even partial additional protection by virtue of an increased carcinogen detoxification capacity or some subsequent procedure which results in a prolongation of the latent period might have the effect of preventing or minimizing significant manifestations of a malignant process during a normal life-span. Although studies presented in this review have shown that under certain experimental conditions it is possible to inhibit carcinogenesis in animals by a number of means, the data currently available are certainly not adequate for any serious consideration of application to man. Further work along these lines appears desirable for this purpose and also because of the basic implications of a number of exceedingly interesting observations which have been made during the course of these investigations.

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