INTRODUCTION

The gastrointestinal tract is the most important of the regions through which the toxic chemical agents can gain entry into the interior of the body. Apart from the frequent entry of various xenobiotic agents in the ingested foods, there are several toxic compounds generated within the gastrointestinal tract largely by the action of microorganisms on the food. Nature has provided a remarkable organ—the liver—in a strategic position in the body, so that the material absorbed from the intestine must pass through it for detoxification of the dangerous chemicals and for their conversion into forms which can be readily eliminated from the body, through the excretory organs. It is unfortunate that during the process of detoxification, some chemicals which have no or relatively a low toxicity may pass through intermediate products which are much more toxic than the original chemicals. Why this should be so, is not known, but one can speculate on two possibilities. It may be that at the time of the development of liver in the process of evolution, the environment did not have the type of agents with which we are concerned today and hence nature did not design the liver to cater for these agents. Alternatively, the liver may have been originally designed to deal with all kinds of chemical agents, but the adverse
environment together with the change in the dietary pattern may have been responsible for curtailing the degree of resiliency of the liver.

The environment and life styles of today are such that the liver is frequently subjected to insult. This can have two consequences. If trauma due to a chemical is severe, it may cause permanent damage to it resulting in chronic ill health including the development of a hepatic cancer and early death. If the damage due to a chemical is slight, it may nevertheless impair the functioning of the liver sufficiently to prevent it from dealing with a chemical stress which is within the capacity of a normal healthy liver to tolerate.

Since we have to live in this new environment we must discover ways and means which will help the liver to safely handle the xenobiotic agents and to recover from their ill effects. This is only possible if we have a thorough understanding of the metabolic processes through which these agents are processed in the liver and the manner in which the damage to the liver is caused. Although much information is available, through decades of work on the various physiological, morphological, biochemical and enzymatic changes produced by toxic chemical agents, the sequence of events has not yet been fully
elucidated. The latter is necessary as it would help to predict as to what effect a particular treatment would have on the degree of damage caused to the liver.

One of the ways to elucidate this is to study the role of selected treatments in the modification of the effects of the chemical agents. This can be explained by an illustration. Let us suppose that a chemical N produces effects A and B in the liver. The possible sequence of events could be one of the following:

\[(i) N \xrightarrow{a} A \xleftarrow{b} B \quad (ii) N \xrightarrow{d} A \xleftarrow{e} B \quad (iii) N \xrightarrow{f} B \xrightarrow{g} A\]

Different treatments may modify one of the effects, both the effects or none of these. If some treatment produces a response represented by \(A^+ B^+\), viz the response is either aggravated or mitigated in both the effects, then either of these sequences is possible and the site of action is accordingly at a, d or f. If different agents produce only the response \(A^0 B^+\), and \(B^0 A^+\) is not obtained by any treatment, then the sequence is as at (ii) and the site of action is e. If the different treatments produce the response \(B^0 A^+\) and \(A^0 B^+\) is never produced, then the sequence is as at (iii) and the site of action is at g.

If on the other hand, some treatments give the response \(A^o B^+\) and others, \(A^+ B^0\); then the sequence must be as at (i)
and the site of action of the treatment is at c or b respectively. We can consider higher chains of sequence of events as by extending B at (ii) or A at (iii) to c. In that case the different treatments will give the responses $A^0B^+C^+$ or $A^0B^0C^+$ in case of (ii) and $B^0A^+C^+$ or $B^0A^0C^+$ in case of (iii).

Another illustration of the utility of studies on the effects of modifiers of chemical toxicity is provided by the following model of sequence of events, based on such studies.

This sequence of events may well emerge from the results of the studies on effects of modifiers on parameter a, b, 1, 2 and 3 as explained below:

a) If one or more modifiers change the value of a and b in the same direction, but have no effect on the values of 1, 2 and 3, then N effects two processes A and B along separate channels.

b) If one or more modifiers change the values of 1 and 2 in the same direction, but have no effect on 3, then the B channel must be considered to lead to processes which proceed on two different sub-channels C and D.

c) If modifiers produce exclusive actions on a or b, or on 1 or 2, then the latter must be caused by independent processes.
Some examples of the useful information obtained through observations on differential response to modifiers of the various manifestations of CCl₄ toxicity are as follows. Prevention of necrogenic effect of CCl₄ but not the lipid accumulation by antihistamines observed by Rees et al. (1961) and protection against hepatic lipid accumulation but not against necrosis in adrenalectomized rats by Brody et al. (1961) are indications of separate processes involved in lipid accumulation and necrosis. Potentiation of SGPT response to CCl₄ but no potentiation of accumulation of triglycerides in liver by epinephrine and norepinephrine reported by Schwetz and Plaa (1969) suggest separate processes involved in lipid infiltration and rise in serum enzymes.

The present study was undertaken to investigate the effect of different treatments on the modification of some manifestations of CCl₄ toxicity. The various treatments given to the animals were administration of vitamin A, vitamin E, vitamin C, vitamin D plus E, garlic, BHT, glucose, thyroxine, cortisone, streptozotocin, adrenalectomy, adrenal medullectomy, acute thermal stress, acute hypoxic stress and acclimation to cold and heat. The manifestations of CCl₄ toxicity investigated were mortality, blood glucose and serum transaminases 1 hr
after 3.5 ml/Kg bw of CCl₄. Other manifestations included blood glucose, serum transaminase and tolerance to acute hypoxic and thermal stresses with 1 ml/Kg bw of CCl₄, 24 hr earlier. In addition, pathological changes in the liver were investigated by light microscopic studies. It was hoped that these studies would throw additional light on the nature of the processes involved in CCl₄ toxicity and permit an examination of the current beliefs regarding the sequence of events leading to different manifestations of hepatotoxicity. Information on the modification of CCl₄ toxicity by various treatments would also have practical value not only for CCl₄ but also perhaps for many other hepatotoxic agents.

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