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LIVING WITH ALCOHOL: DYING WITHOUT IT

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Alcohol drinking is associated with premature death because of road and other accidents, fetotoxicity and liver cirrhosis. These topics will be addressed by other papers. This paper will examine certain aspects of the relationship between drinking and cancer.

Many aspects of alcohol engender emotions and stark contrasts in opinions. Humans tend to distinguish between the "work" and the "play parts of their lives and, for most people, alcohol is much more associated with the "play" part than the "work" part. Humans also have a wont to distinguish between "righteousness" and "sin". Thus, for religious reasons, or because they have suffered in one way or another from their own or other people's over indulgence in alcohol, some people equate alcohol with "sin". By contrast, many religious and other rituals actively involve the imbibing of alcohol and even within the Christian Church the required total abstinence of some sects is paralleled by orders of monks which actively make and supply alcoholic liquor. Some of the biggest problems, however, stem from the fact that both the risks and the benefits of alcohol may be either "medical" or "social" and it is never easy to balance social benefits against medical risks or medical benefits against social risks. In the end, individuals whether they be scientists, members of religious sects of just simply members of the general public, have to determine their own attitudes in the light of their own circumstances.

Potentially Confounding Variables

The basis of long-term toxicity studies is that one compares the incidence of diseases and other effects in groups of humans or animals that are similar in all respects except exposure to the test substance. Table 1 lists some of the variables that need to be avoided, and the possibilities of such avoidance by epidemiologists and toxicologists.

It is theoretically possible to study the effects of alcohol *per se* in laboratory animals under conditions in which virtually all other important variables are controlled. Thus, one could expose comparable groups of rats or mice of inbred strains to different daily doses of ethanol while they are being fed the same amount of the same standard diet and all other circumstances are the same. Even in this case, however, there is one way in which the alcohol exposed and control groups differ. Ethanol itself has calorific value so that the caloric intake of the exposed group will be higher than that of the control group. Hence, in this respect, one would not be comparing "like" with "like". Nor could one correct this by giving the alcohol-exposed group proportionately less to eat because although this would equalise the calorie intake it would introduce a difference in intake of various nutrients.

In fact, virtually no high quality experiments of modern design which carefully exclude the possible influence of confounding variables and which examine the effects of

ethanol *per se* for toxicity have been undertaken. Such experiments as have been reported, however, have revealed neither any clear evidence of carcinogenicity or other forms of toxicity nor any clear evidence of health benefits (IARC, 1988). Cirrhosis is not produced in laboratory animals following exposure to ethanol only (Schinella and Becker, 1975).

Table 1 **Needs of Epidemiologists and Toxicologists**

	Possible Fulfilment	
	Man	Animals
Accurate long-term exposure data	-	+
Genetic homogeneity	-	+
Lack of confounding		
- calorie intake	-	+
- relevant nutrients	-	+
- drugs	-	+
- smoking	-	+*
- exercise	-	+
- occupation etc.	-	+
Reliable assessment of		
- social		
- benefits	+	-
- risks	+	-
- medical benefits/risks		
- in life	+	+
- cause of death	+**	+
- diseases of man	+	+***

* No model for human smoker
** Low autopsy rates - seriously inaccurate data
*** No animal model for Coronary Heart Disease etc.

The human situation is far more complex. For a study of ethanol toxicity in humans to be fully interpretable, one would need to be able to compare the effects of different levels of alcohol intake over many years in genetically similar populations under conditions in which total calorie intake and the types of food eaten are similar and there are no differences in life-style including smoking habits, exercise, use of medicines, occupation, social status, etc. Needless to say such circumstances are never available to epidemiologists. In particular, data on what and how much people eat and on life-style factors generally, including how much alcohol they drink, tend to be wildly inaccurate.

In animal studies health effects which give rise to physical signs as distinct from only symptoms can be assessed both during life and in the course of a histopathological examination of tissues. In humans data for in-life signs and symptoms are readily obtained but autopsy rates are generally low and death certificate data based solely on clinical assessment without autopsy are seriously inaccurate and unreliable. (Joint Royal Colleges Report, 1991).

For the many reasons listed above, epidemiologists are faced with serious difficulties when they attempt to assess alcohol for chronic toxicity and carcinogenicity in humans. By contrast the main handicap for the toxicologist is the fact that for the study of diseases such as coronary heart disease there is no usable animal model. Notwithstanding the difficulties, many authorities conclude that alcohol drinking is associated with increased risks of the developments of cancers of the oral cavity, pharynx, larynx, oesophagus and liver and with protection from coronary heart disease. According to the 1988 IARC Monograph (IARC, 1988) on alcohol drinking there was evidence of a positive dose response for all the four cancer sites listed above. It is questionable, however, that this evidence is convincing for moderate or low levels of alcohol consumption.

Also, according to the 1988 IARC Monograph, smoking interacts with alcohol drinking in relation to cancers of the oral cavity, larynx, pharynx and oesophagus and hepatitis B virus infection does so in relation to cancer of the liver. The question now is how reliable is the evidence that, in the absence of exposure to these interacting factors, moderate or light alcohol drinking is a risk factor at all?

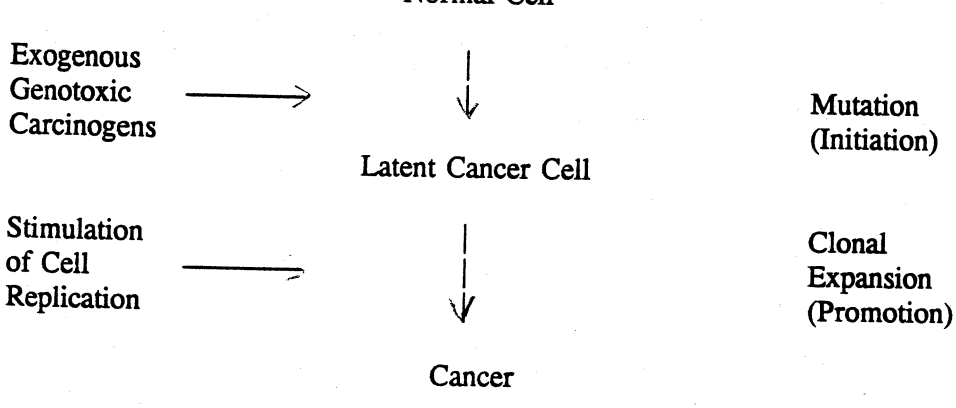
With the possible exception of the liver, experiments in laboratory animals have revealed no evidence of increased cancer incidence at any site, while the protective effect of moderate alcohol consumption on heart disease has not been studied in any species of animal that spontaneously develops the same kind of heart disease as man.

Changing Concepts in Carcinogenesis

For more than 40 years the two-stage carcinogenesis paradigm has dominated laboratory research aimed at identifying factors which cause cancer in man.

According to this paradigm, shown in its simplest form in figure 1, carcinogenesis begins with the mutation of a normal cell to a latent cancer cell and continues either with the latent cancer cell progressing to cancer under its own steam or with the enhancement of the risk that this will happen by factors which stimulate replication of mutant cells to the point at which clones of them constitute cancers.

Figure 1 **Carcinogenesis: The Paradigm Which Has Dominated Laboratory Research for 40+ Years**



Recognition that there exist substances which are not themselves mutagens but which can be metabolized to mutagens within the body constituted a major step forward in carcinogenesis research; nevertheless this was considered simply to make the first stage of the process more sophisticated while the dominance of the two-stage paradigm persisted.

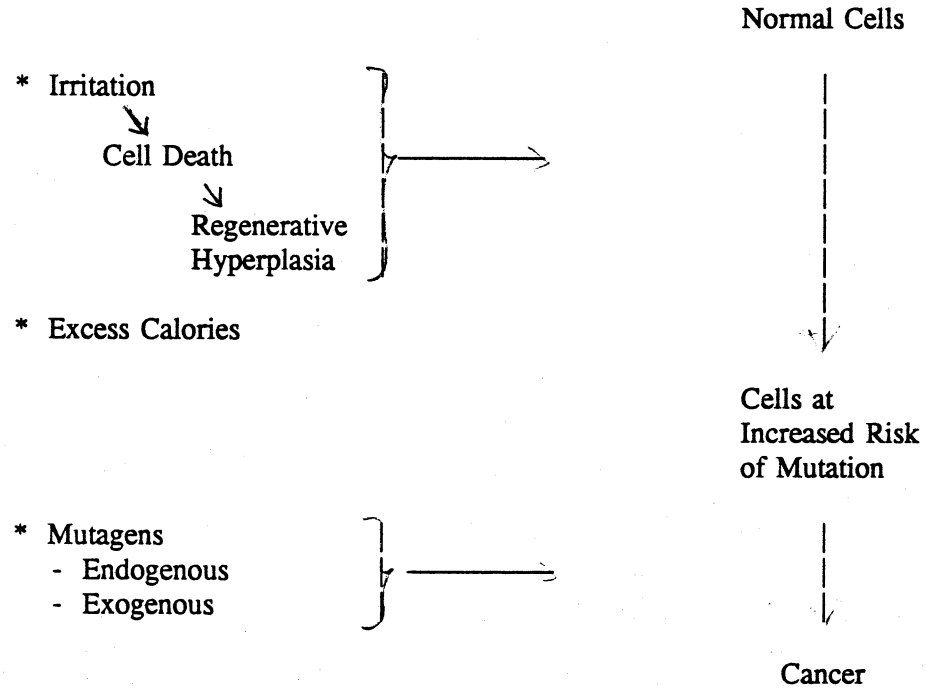
Further sophistication relating to the putative first stage of the process occurred when it was shown that metabolic pathways for the conversion of pro-mutagens to mutagens might only come into operation under conditions of high exposure dose or following the induction of the enzymes involved in metabolic activation by prior exposure to other substances.

Against this background of increasing sophistication, recent years have witnessed the recognition of a burgeoning number of substances which are neither mutagens nor pro-mutagens but which enhance cancer risk in long-term rodent studies. The term "non-genotoxic carcinogen" has been introduced to describe such substances. However rather than accept this new term a number of bone-headed researchers continue to allow themselves to be dominated by the old paradigm and accordingly choose to believe that such non-genotoxic carcinogens are simply tumour-promoters acting after exposure to background mutagens.

Recent years, however, have seen the birth of an alternative paradigm, which is shown in figure 2. This takes into account important new knowledge. Instead of mutation being seen as a rare and avoidable event, it is now recognised that the DNA of each body cell is damaged many thousands of times each day by genotoxins, many of which are endogenous in origin. Fortunately, evolution has seen to it that DNA repair systems exist. Consequently virtually all this continually-occurring damage is efficiently repaired. However, during the process of cell replication there is a brief phase during which cellular DNA is in a single-stranded state. Damage occurring at this time is not amenable to repair in the same way as damage occurring when DNA is double-stranded. For this reason more DNA damage tends to persist as mutations under conditions of increased frequency of cell-turnover. Thus, irritation and cell death leading to increased cell replication increase the risk that normally-occurring DNA damage will persist as mutations.

It is the recognition of high naturally-occurring rates of DNA damage as a consequence of the endogenous production of mutagens that endow this new paradigm with more strength than the old one. During the normal processes involved in the conversion of food, particularly fats, to energy DNA-damaging oxidative radicals are unavoidably produced and this largely accounts for much of the ever-occurring DNA damage. Exposure to environmental mutagens, of course, adds to the overall rate of DNA damage and qualitatively the damage caused by exposure to some xenobiotic substances is less readily repaired than that produced by endogenous mutagens. Nevertheless, the important point is that DNA damage which, if not repaired, can lead to mutation, is a very common event. The once widely held concept that mutations are rare and entirely attributable to exposure to xenobiotic mutagens is no longer tenable.

Figure 2 **Carcinogenesis: Alternative Paradigm**



Laboratory Research in Alcohol Carcinogenesis

Table 2 lists the theoretical ways in which ethanol might increase cancer risk. Firstly it might be a carcinogen itself or be metabolized to a carcinogen. There is good evidence that the first is not true, but equally good evidence that the second is true. Acetaldehyde, a metabolite of alcohol has been shown to be genotoxic and produce irritation and neoplasms in the nose and larynx in rodents exposed to it by inhalation. However, tumours only arise if exposure is high enough to cause necrosis and cell replication in the tissues concerned, and clearly this does not happen in persons or animals exposed to alcohol by the oral route. Neither alcohol *per se* or acetaldehyde has been shown to produce liver tumours in rodents.

Most of the 28 studies involving the exposure of rats, mice or hamsters to ethanol via the oral route reviewed by IARC (1988) were seriously flawed in one or more ways. The list of flaws includes too few animals, insufficient duration, failure to include a comparable unexposed control group, failure to match calorie intake in exposed and control groups and inadequate necropsy and histopathological evaluation. Of the least flawed studies, those by Mandard *et al* (1981), Castonguay *et al* (1984) and Griciute *et al* (1986) gave negative results for tumour induction at all sites.

Secondly, alcoholic beverages may be contaminated with genotoxic carcinogens. The development of highly sensitive chemical analytical methods has led to the finding of trace levels of known carcinogens in almost everything we eat and drink. In the past, some alcoholic beverages - mainly those made in undeveloped countries or brewed at home - have been found to contain levels of carcinogens, such as dimethyl nitrosamine that rightly caused

concern. However, today branded alcoholic beverages in Western countries are no longer significantly contaminated in this way. In any case, IARC (1988) concluded that for the mouth, pharynx, larynx and oesophagus, the evidence of risk pointed to all types of alcoholic beverage and not just to one or more particular types. If this conclusion is correct and not dependent on the use of old data, then it seems unlikely that carcinogenic contaminants provide a plausible explanation of the cancer risks associated with alcohol drinking.

Table 2 **Alcohol and Cancer Risks: Possible Mechanisms**

* Alcohol per se
  - is a carcinogen
  - is metabolized to a carcinogen (i.e. acetaldehyde)
* Carcinogenic contaminants in alcoholic beverages
* Alcohol
  - ↑↑ cancer induced by environmental mutagens
  - ↑ absorption of environmental carcinogens
  - ↑ metabolic activation of pro-carcinogens to carcinogens
  - ↑ cancer risk from endogenous mutagens
    - irritation, necrosis, reparative hyperplasia

The possibility that alcohol in one way or another promotes the development of cancer in response to exposure to environmental mutagens has been extensively studied in the laboratory. However, most of such research has involved exposure of animals to quite unrealistically high doses of known potent carcinogens and has thrown no clear light on the mechanisms that may be involved in humans.

Virtually none of the laboratory research reported so far has been based on the alternative paradigm for carcinogens outlined in Figure 2 and virtually none has related to the tissues reported to be targets for carcinogenesis in man.

Conclusions in Relation to Carcinogenic Risk

The associations between alcohol drinking and cancer risk in humans remain unsupported by laboratory findings and essentially unexplained. Whether there remains any serious risk in the case of alcoholic beverages as produced in developed countries today as distinct from 20 or more years ago has yet to be investigated and whether or not there is any risk at all in relation to moderate or light alcohol drinking is not known.

In 1988 in a personal communication, Peter Lee, an eminent independent statistician/epidemiologist expressed the opinions that:-

> *"The evidence that non-smokers increase their risk of cancer of the upper aerodigestive tract by drinking is unconvincing"*
>
> *"The evidence that light drinking increases risk of cancer of the upper aerodigestive tract is also unconvincing".*

These opinions still hold good. Better epidemiological and more realistic laboratory research in which a serious attempt is made to exclude bias due to confounding variables is very much needed. Until the results of such research are available I shall continue to choose to believe that a little of what I fancy does me good!

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