Biochemical Pharmacology, Vol. 42, No. 3, pp. 457–458, 1991.
Printed in Great Britain.

0006-2952/91 $3.00 + 0.00

COMMENTARY

IS CLONAL ADAPTATION A PRODUCT OF EVOLUTION OVER THE MILLENNIA?

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In a recent interesting and stimulating review [1], Farber claimed that during the widely accepted multistep process of carcinogenesis, *one type* of cell induced by carcinogens undergoes initiation in the liver. These initiated cells, perhaps a very common type, can grow in an environment that inhibits the growth of the majority of uninitiated cells and, thus, can rapidly give rise to hepatocyte hyperplastic nodules by clonal expansion of each "rare" resistant hepatocyte. One or more of these nodules could be precursors for cancer development. The acquired "resistance phenotype" by hepatocyte nodules is manifested at three levels of organization: physiological (resistance to inhibition of cell proliferation), cellular (resistance to visible cytologic responses to cytotoxic agents), and biochemical-molecular (presence of enzymatic patterns that reduce or counteract possible deleterious effects of chemicals). Such a phenotype is interpreted as an example of adaptation with survival value not only *per se* but for the whole organism. The intrinsic resistance of hepatocytes in nodules towards toxicants, including initiators and promoters, is an adaptative phenomenon occurring in living organisms (human and animals) because they have been exposed continuously for millions of years to carcinogens: this phenomenon has evolved to permit survival in a hostile environment. Farber has expressed the view that neoplasia may be a manifestation of the "imperfection" of this adaptative process and cancer, thus, a deviant of adaptation [1, 2].

We would like to discuss briefly some of the abovementioned statements that could, in our opinion, be misinterpreted.

The selective pressure exercised by Nature over time selects the best in a population where part of the diversity between single individuals of any species is due to a "casual" mutation. However, only mutations in germinal cells can be transmitted to the progeny. Considering the relatively low number of anthropogenic carcinogens present in the environment millions of years ago (which thus exhibited a low selective pressure) and the fact that nodules are located mainly in somatic cells, it is very difficult to understand how evolution mechanisms may have contributed to the context of differentiation towards neoplasia (physiological adaptation). In addition, taking into account also the large number of synthetic cancer initiators and promoters present in the actual biosphere today, the livers and genital apparatus of living beings normally would be filled with numerous nodules! However, that is not the case.

In other words, because the majority of cancers appear relatively late in the life history of any organism, the appearance of resistant nodules (to increase survival without the drastic effect of neoplasia) should be seen as a normal and not rare phenomenon. In fact, it is still a rare phenomenon.

It seems, instead, more reasonable to consider the resistance of hepatocyte nodules as an "internal response" of differentiated cells towards new insults.

Another problem arises from the interpretation of the unusual common biochemical pattern displayed by the focal proliferative lesions. It had been reported by Farber and coworkers that a marked decrease in activation associated with the large decrement of phase I drug-metabolizing enzymes, including total cytochrome P450 and several mixed-function monooxygenase activities, coupled with the increase in many phase II systems (i.e. more efficient conjugation and excretion of the active moieties generated) can readily account for the resistance of the nodules to xenobiotics [1, 3]. However, it should be noted that the decrease of total P450 in the course of hepatocarcinogenesis seems to be a heterogeneous process [4–6]. Direct evidence for this statement has come from the observation of Buchmann *et al.* [4], who reported a differential expression of P450 isozymes during diethylnitrosamine-induced carcinogenesis in the rat: the P450 forms namely PB1 increased during the process. More recently, in spontaneous or chemically induced hepatomas in female XVII nc/z mice, several P450-dependent steroid hydroxylases, such as progesterone 6β-hydroxylase activity [7], progesterone and testosterone 15α-hydroxylase activities, and minor testosterone 2- and 15β-hydroxylase activities, have been shown to increase up to eight times with regard to total P450 [8]. The newly observed tumoral pattern of steroid metabolism, with the elevated expression of particular P450-like monooxygenases, may even offer

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an opportunity to devise new classes of tumoral markers for early stages in liver tumorigenesis [8].

Finally, we are surprised to hear again the belief expressed in a review that post-oxidative reactions are only detoxifying [9]. It is in fact now well-established that several phase II enzymes, such as epoxide hydrolases [10], UDP-glucuronosyl transferases [11], and glutathione *S*-transferases [12, 13], are responsible for the bioactivation of many environmental pollutants. Therefore, each phase II enzyme system may be considered as an "activating system" toward specific chemical classes, such as halogenated hydrocarbons in the case of glutathione *S*-transferases or aromatic polycyclic hydrocarbons in the case of epoxide hydrolases.

On the basis of these considerations there is no doubt that the magnification of phase II enzyme activities, as they appear during chemical hepatocarcinogenesis, may have, simultaneously, a dual effect.

If on the one hand, it is possible to have an increase in detoxification and excretion for some chemicals, then on the other hand the large number of activated compounds points out the importance of this aspect for human health. In general, each drug-metabolizing component should be considered as a "detoxy-toxicant" depending on the chemicals involved. From this point of view, taking into account that humans are exposed to a myriad of substances, attempts to modulate oxidative and/or post-oxidative reactions rates by dietary components, undertaken to reduce the risks of cancer and mutations (as it appears in the field of anti-mutagenesis and anti-carcinogenesis), should be reconsidered carefully [1].

Acknowledgements—We are grateful to Professor S. Grilli, Istituto di Cancerologia, Università Degli Studi di Bologna, Professor N. M. Trieff, Department of Preventive Medicine and Community Health, University of Texas, Medical Branch at Galveston TX (U.S.A.), and Professor K. Hemminki, Institute of Occupational Health, Helsinki, Finland, for critical comment on the manuscript.

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