Dr. Kadlubar also discussed some host factors in bladder carcinogenesis. Urinary pH can be expected on theoretical grounds to influence bladder cancer risk from certain aromatic amines. Data were presented indicating that the urinary pH level is indeed an important human risk factor for exposed workers.

A. Haugen (Institute of Occupational Health, Oslo, Norway) presented details of a study on the exposure of coke oven workers to polycyclic aromatic hydrocarbons (PAH). Total, volatile and particulate-bound PAH determined at the breathing zone were compared with urinary excretion. Data on 38 single PAHs shows similar distributions of the compounds between particulates and gas phase. Benzo (a)pyrene DNA-adducts, detected in the lymphocytes of coke-oven workers, as already described by K. Vähäkangas, did not compare well with exposure levels, as measured in urinary samples, indicating that wide interindividual variation in benzo(a)pyrene activation may exist.

In summary, the development of short-term tests and the analysis of test data has reached a level where prediction of a potential human risk from an environmental exposure may be calculated at an early stage of testing. Such predictions may be used to provide a decision point for further testing. However, more accurate methods for determination of the biologically active dose have to be developed if monitoring of individual exposures is to be made.

This may be achieved by measuring directly the genotoxic exposures in humans. Although such methods are now available for studies of exposures to a few well known model carcinogens, the methodology is still at a very early stage for other applications. A large body of knowledge on distribution and metabolism, activation mechanisms, etc. must be at hand for calibration of detection methods for the single carcinogens. Careful animal experimentation is needed at several stages in methods development in order to achieve useful and interpretable results. On the other hand, advances in the techniques for analysis of DNA-adducts lends promising support to this approach in cancer prevention. Hopefully, in the near future combination of cancer epidemiology and new approaches in detection of genotoxic exposures will make possible a reliable identification of the most important risk factors in human cancer.

Sequential Changes During Neoplastic Cell Transformation

Reported by: M. ROBERFROID
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Chemically induced liver cancers are the end point of a multiphasic and progressive process which leads initiated cells (or initiated tissues) to morphologically defined malignant tumours. For operational reasons that process has been divided in phases, the so called initiation (I) selection (S) and promotion(P).

Initiation is the necessary but not always sufficient event. When that event is by itself sufficient (as reported for mice by H.J. Hacker and his colleagues from Heidelberg, FRG), the results of cytochemical analysis of putative preneoplastic foci and preneoplastic lesions support the concept developed for other studies on hepatocarcinogenesis in rats. Indeed, among other changes, a basic shift in carbohydrate metabolism shows a particularly close linkage to neoplastic transformation. Single dose initiation may thus by itself induce in liver cells all the potentialities for carcinogenesis.

Selection (S) and/or promotion (P) which usually require chronic administration of a chemical are neither necessary nor sufficient to complete the malignant transformation. When they are applied, after initiation (I) they speed up the process. Within certain limits of time, these effects remain reversible. Among the early effects of the so called promoters of hepatocarcinogenesis, expression of gene programme(s) that provide(s) growth advantages for putative preneoplastic cells could be a key event. Various classes of promoters may induce the expression of various gene programmes leading to the same growth advantage (R. Schulte Hermann from Marburg, FRG). As evaluated in term of malignancy, selection (S) or promotion (P) of chemically initiated hepatocarcinogenesis reduces the lag period for the appearance of the first malignant tumour. They also increase the number of rats with tumour(s) (tumour incidence) and the number of tumours/liver (tumour yield). The triphasic protocol which sequentially combines initiation (I), selection (S) and promotion (P) appears to reconstitute closely the sequence of processes which appear during the chronic treatment of rats with a so called complete carcinogen (J. de Gerlache et al., Brussels, Belgium).

Genetic events are also associated with the early stages of rat hepatocarcinogenesis as induced by the triphasic protocol. Applied after initiation (I), selection and early promotion increase nucleolar activity in hepatocytes. This stimulation of rRNA synthesis is not due to polyploidisation since the ratio of diploid to tetraploid nuclei increases in those early stages. A population of diploid cells may thus appear after selection and during the early stages of promotion of initiated cells (or initiated liver!) (M. Kirsch-Volders et al., Brussels, Belgium). From initiation to malignant transformation, whichever way is followed (initiation, initiation-selection, initiation-promotion or initiation-selection-promotion), the liver (mouse or rat) follows a pathway which can be characterized by the appearance of phenotypically altered foci, putative preneoplastic and neoplastic lesions. Even though some arguments may support such a correlation, there is still no definitive proof for an obligatory relationship between such lesions and malignant tumours. Clearly there seems to be no correlation between the phenotypical nature, the number and/or the size of the preneoplastic lesions and the morphological nature, the incidence and/or the yield of malignant tumours.

Selection (S) and/or promotion (P) of chemically initiated hepatocarcinogenesis accelerate an already ongoing process. Selection and promotion could be additive or synergistic as evidenced by the analysis of the kinetics of appearance of malignant tumours in the triphasic protocol. Selection (S) and promotion (P) could, at least partly, imply genetic events leading to changes in gene expression, ploidy and possibly chromosome structure that provide growth advantages to some cell populations. It remains however to be demonstrated that such cells are the "initiated cells" which by clonal proliferation constitute the "preneoplastic lesions" from which the malignant tumour(s) arise.

The Application of Monoclonal Antibodies

Reported by: M.I. COLNAGHI
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The topic of research in this seminar devoted to monoclonal antibodies (MoAbs) attracted a large number of presentations indicating widespread interest in this subject. In fact, following Professor R.W. Baldwin's masterly Mühlbock Memorial Lecture, there were many interesting presentations dealing with this topic on various occasions throughout the 3-day meeting and concluding with this seminar on the application of MoAbs. Overall, this provided an up-to-date assessment of the status of the art of a wide spectrum of applications of MoAbs in oncology.

The results presented in this field of research appeared to arouse a general feeling of optimism which can be justified as follows: a) the ability of several MoAbs to define differentiation markers is no longer questionnable and this will certainly contribute towards increasing our understanding of malignancy; b) it has been demonstrated that some of these MoAbs are capable of predicting tumour progression and therefore special attention is now being devoted to improving and developing them as valuable prognostic tools; c) there is also no doubt as to the usefulness of several MoAbs in diagnostic procedures where they have allowed improvement of conventional methodologies in areas such as histopathology, cytology, in vivo tumour localization and detection of micrometastases in vitro.

As far as therapeutic approaches are concerned, a more cautious attitude is required, mainly due to two particular problems: a)the available monoclonal reagents are apparently never strictly tumour specific, and b) the expression of the relevant epitopes on tumour cells is often heterogeneous. Although in diagnostic and prognostic approaches the difficulties these factors present are not so limiting, in therapeutic applications (particularly those in which in vivo manipulations are concerned) there are much more serious limitations. For example, in the case of in vitro therapeutic applications, such as bone marrow purging in the context of autologous bone marrow transplantation, these limitations can be overcome by using an operationally tumour-specific pool composed of a cocktail of several different MoAbs with complementary reactivities, as opposed to the use of a single reagent. So far this alternative has been giving promising results. The same type of approach could also be adopted for in vivo therapeutic applications, but in this case it is much more difficult to attain operational specificity. Furthermore, the antigenic nature of murine MoAbs, which at present represent the majority of reagents available, imposes yet another limitation. The use of human MoAbs would definitely help to resolve this problem, but their production still involves a number of difficulties. A possible solution could be offered by application of genetic engineering techniques for the generation of what are now called 'chimeric' antibodies: reagents composed of an appropriate antigenic binding site of murine origin, whereas the rest of the antibody molecule is human. These 'chimeric' molecules should theoretically be less immunogenic than their murine counterparts.

It therefore seems that the optimistic feeling referred to above can be justified by the fact that we are now conscious of the difficulties involved in using MoAbs and, in addition, methodologies are available to surmount the problems presented in their diverse applications in cancer diagnosis and therapy.

Leukocyte Adherence Inhibition Techniques in Cancer Detection

Reported by: T. SANNER
(Laboratory for Environmental and Occupational Cancer NHIK, The Norwegian Radium Hospital, Oslo, Norway)

The leukocyte adherence inhibition (LAI) assay was developed by Dr. W. Halliday about a decade ago. The test is based on the finding that sensitized peripheral leukocytes from patients with cancer exhibit a reduced ability to adhere to a glass surface when incubated in vitro with extract from a tumour of the same type. The test provides an assessment of cellular immunity and has primarily been used in relation to cancer. At an International Workshop on LAI in Buffalo, N.Y. in 1978, coded samples were analyzed and a successful demonstration of an in vitro assay of specific antitumour immunity in humans was achieved for the first time.

Although the experimental procedure of the LAI test is simple, there are a number of unknown factors which may influence the results, and the test in its present form is not suitable for use in routine laboratories. However, in specialized laboratories the test may be a useful diagnostic tool. With the use of LAI techniques several important findings which may throw light on tumour immunology in general, and lead to the development of a simpler test system, have been made during recent years. It was therefore considered timely at this meeting to attempt to summarize the present