CHEMICAL CARCINOGENS

Mutagenic Potential

from our Cell Biology Correspondent

MALIGNANT transformation induced by chemical carcinogens is stable; once a cell has been transformed its progeny are transformed. The most obvious way to account for chemical carcinogenesis is to suggest that it results from chemically induced mutations, in which case potent carcinogens should be potent mutagens. When, however, carcinogens such as the polycyclic hydrocarbons were tested for mutagenic activity in conventional assay systems, involving the use of bacteria or phage as target organisms, they were found not to be strongly mutagenic. Such observations cast something of a shadow over the somatic mutation theory of chemical carcinogenesis. Chiefly as a result of the recent work of Heidelberger and his associates, however, it is now clear that polycyclic hydrocarbons *per se* are neither potent mutagens nor potent carcinogens, but epoxides produced during the intracellular metabolism of the parental hydrocarbons are. The failure to detect mutagenic activity of classical carcinogens in microbial assay systems apparently stemmed from the failure of these organisms to metabolize the carcinogens and so activate them.

As long ago as 1950 Boyland postulated that epoxides are produced during the metabolism of polycyclic hydrocarbons. In the past 18 months Heidelberger's group and others have detected epoxides as intermediates of the metabolism of these compounds in microsomes. Heidelberger's group have also established that these epoxides react with DNA and protein and that they are more potent carcinogens than the parental hydrocarbons. Huberman, Aspiras, Heidelberger, Grover and Sims (*Proc. US Nat. Acad. Sci.*, **68**, 3195; 1971) can now report that the epoxides produced during the metabolism of methylcholanthrenes and benzanthracenes are mutagenic as well as cytotoxic for Chinese hamster cells in culture; the epoxides of 7-methylbenz(a)anthracene, for example, produced 5 per cent 8-azaguanine resistant mutations among cells which survived exposure to the epoxide. Some phenols derived from polycyclic hydrocarbons are also more mutagenic and more cytotoxic than the parental compounds.

In spite of differences in the response of different sorts of cells to the various epoxides and phenols, Huberman *et al.* confidently conclude that the polycyclic hydrocarbons, which themselves are of low chemical activity, require to be metabolically activated before they become potent mutagens and carcinogens; moreover, the epoxides are most probably the ultimate carcinogenic and mutagenic metabolic derivatives of these compounds. It is noteworthy that Cookson, Sims and Grover reported in December (*Nature New Biology*, **234**, 186; 1971) that several epoxides of the methylcholanthrenes and dibenzanthracenes are mutagenic for phage T2, the mutagenic potential of these epoxides correlating positively with their carcinogenic potential. All in all, therefore, it seems that at least some chemical carcinogens are carcinogenic because they are able to mutate their target cells.

Of course, if transformation by the polycyclic hydrocarbons depends on the metabolic activation of the parental compounds, cells pretreated in such a way as to increase the activity of the microsomal enzymes involved in this metabolism might be expected to be more sensitive to transformation by a hydrocarbon and perhaps less susceptible to its cytotoxic effect. Dipaulo, Donovan and Nelson (*Proc. US Nat. Acad. Sci.*, **68**, 2958; 1971) report examples of just such an enhancement of transformation and protection from cytotoxicity. For example, Syrian hamster cells pretreated with the weak carcinogen benz(a)anthracene are subsequently more susceptible to transformation by the potent carcinogens benzo(a)pyrene or 3-methylcholanthrene and are less susceptible to their cytotoxicity than are cells not pretreated. Such findings indicate not only that the carcinogenic and cytotoxic properties of these carcinogens can be dissociated but also that the former property depends on metabolic activation.

MEDICAL RESEARCH

Dialogue on Cancer

from a Correspondent

THERE has been much argument recently among the cancer research fraternities as to the correct balance between applied, clinically orientated studies, and those more fundamental operations which seek answers to relevant basic biological problems. As a contribution to the discussions, Dr H. E. M. Kay, dean of the Institute of Cancer Research in London, thought it would be useful to continue and enlarge upon previous teaching at the institute by a course in the principles of clinical and experimental oncology. The idea was to ask distinguished protagonists of both the clinical and experimental views to discourse, perhaps appropriately in the British Museum (Natural History), on specific topics, discussion of which might be fruitful both for the institute and for those other members of the scientific community who could afford to come along (£2 per head per meeting for non-institute members). It was agreed that these occasions should be on Monday evenings at 5 pm and should last two or more hours. Vigorous discussion was envisaged. The attempt to create a dialogue was at least praiseworthy and accords well with the dictum *Medice, cura te-ipsum.*

The series of twelve meetings began on January 10, and in the unenviable starting position Dr R. J. C. Harris (Microbiological Research Establishment) enacted his brief which was to survey significant aspects of cancer research. He pointed out that the viewpoint of the experimentalist was often restricted in relation to the variability of malignancies. The clinician, on the other hand, relied essentially on histopathological diagnoses for the formation of his attitudes. Various characteristics of malignant cells such as loss of contact inhibition, neoantigens, alteration of glycolytic pattern, cell surface changes (which affect agglutinability by various plant lectins) and enzyme peculiarities have been adduced but it was usually difficult to decide which, if any, of these phenomena were relevant to the malignant change *per se* and which were consequent upon it. Dr Harris pointed out that poor understanding of normal differentiational processes put some limit on the interpretation of the sort of changes which can occur at the onset of malignant conditions.

Many of the salient features of cancer research such as carcinogenesis by azo-dyes, soot and viruses had been discovered many years ago but perhaps much of the early work, particularly on experimental animals, had been restricted by the failure to use inbred animals, first, to transplant tumours with success and, second, to obtain reproducible results.

Dr Harris felt that the study of tumours in domestic animals was particularly important because these animals share the human environment to a considerable degree. He quoted various of the relevant statistics and some of their pitfalls. For example, the incidence of testicular tumours was higher in dogs than cats, but this may reflect the lower incidence of testes in man's feline friends rather than anything else.

It has been established that most if not all carcinogens are mutagenic but this did not necessarily mean that all mutagens are carcinogens. With these and other examples Harris briskly breathed on and polished anew some of the well loved chestnuts of cancer research workers.

Sir Richard Doll (University of Oxford) tackled the problem of the age dependency of cancer. By urging the audience at speed over the various slopes and peaks of graphs relating tumour incidence to time, Sir Richard