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Experimental Carcinogenesis: Achievements and Objectives in Relation to Human Bladder Cancer

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Experimental research over the last thirty to forty years has contributed significantly to understanding some of the causes of human bladder cancer. It has played a complementary role with epidemiology in the identification of contributary environmental factors, and has enabled some industrial chemicals to be positively identified as bladder carcinogens and directed suspicion towards others, thus preventing many unnecessary deaths.

Since methods have been developed for reliably inducing a high incidence of bladder cancer in experimental animals, the biogenesis and development of the disease has been studied extensively at both the subcellular and the histological level. This in turn has led to a better understanding of the long, clinically silent, pre-neoplastic phase of the disease. Most experimenters and clinicians are now agreed that there is no such phenomenon as a benign bladder tumour, and that low grade, exophytic papillary growths as well as carcinoma in situ are pre-neoplastic lesions which progress inevitably to invasive malignant growth with time.

Experimental research has confirmed that bladder cancer is truly a disease of multifocal primaries, although local implantations can be seeded from neighbouring tumours in the lower urinary tract. It is now largely accepted that the single papillary tumour which may be detected on cystoscopy is the relatively innocent forerunner of a host of malignancies to come, which will arise from the multiple foci of neoplastically transformed cells throughout the epithelium. The awareness of this silent threat has altered the clinician's approach to his patient, for he is now acutely aware that removal of the visible tumour does not constitute a "cure" even for the local disease, but only temporarily halts the lethal cascade of further neoplasms. In addition, experimental studies have made and are still making important contributions to improved methods of early detection and diagnosis of human bladder cancer. These are all major achievements for experimental research in bladder cancer and it is relevant to assess what impact they have made on the control of this disease in man.

It is popularly assumed that early detection, and consequent early treatment of neoplasms can be equated with an improved prognosis for the cancer patient. Thus, it would seem reasonable to hope that advances in knowledge achieved by the experimental approach coupled with improved therapeutic techniques, would be reflected in improved survival and reduced morbidity and mortality. Regrettably, this is not the case. In an article entitled "The curability of vesical cancer: greater now or then?", Marshall and McCarron (2), demonstrated only a marginal improvement in the mean survival of a series of bladder cancer patients between 1960 and 1971, by comparison with a similar series between 1932 and 1955. This can be interpreted as a discouraging reflection not only on the inadequacy of current therapeutic techniques to contain the disease once it has reached a clinically detectable stage but also on the failure of experimental bladder cancer research to affect patients' survival. The reasons for continuing poor survival rates, however, are numerous and complex, and involve not only clinical problems but also public attitudes to cancer. The identification of environmental carcinogens can contribute very little to cancer prevention if individuals are not prepared to modify their habits to avoid risk. Both individuals and governments are remarkably hypocritical; a society which sanctions a total ban on the sale of a food additive on no more than suspicion, but neglects to restrict cigarette smoking which is known to be the major cause not only of lung cancer but also of bladder cancer, bronchitis, emphysema and a host of cardiovascular problems, may be held to get not only the politicians but also the disease it deserves. Because of such attitudes, detection of carcinogens may make little impact on the disease. Equally well, early detection and diagnosis of the disease is of only limited value when, with a few exceptions

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(7, 8), bladder cancer is ultimately uncontrollable by current surgical techniques, radiotherapy and/or chemotherapy.

The poor prognosis for the bladder cancer patient thus presents a major challenge to both clinicians and experimenters. There are a number of obvious areas in which experimentally induced cancers in animals can be used as models for the disease in man. At least these methods are now available for the relatively rapid chemical induction of a 100% tumour incidence in the rodent bladder (1). By comparison with many other organ sites, where reliable methods for producing a high tumour incidence in animals are not yet available, this is a promising situation. Experimentally induced bladder cancer is an ideal model with which to investigate the efficacy of chemotherapeutic drugs, singly or in combination. It is time that the kinetics of cytotoxic drug action were studied in properly controlled conditions in experimental animals where sequential sampling and the use of objective biological markers for assessing cytotoxicity are possible. The potential value of combination chemotherapy with different cytotoxic compounds is very high, but the side effects can be at best distressing and at worst intolerable. It is neither practical nor ethical to use clinical trials to investigate all the possible permutations and complexities of combination drug therapy when the welfare of individual patients must come before the acquisition of new information, even if that information is potentially useful for the modification or design of subsequent treatments. Some experimental research on these lines is under way (5) but there is need for many more in depth studies of chemotherapy in experimental animal models.

Another potentially rewarding area for experimental research in bladder cancer is the development of control measures to be applied during the long, clinically silent, pre-neoplastic phase of the disease. It is in this area that knowledge already obtained by basic biological research and experimental carcinogenesis studies over the past few decades should prove to be of greatest value. Already studies have shown that cancer is not necessarily an irreversible biological phenomenon (3). Both clinical and experimental studies indicate that carcinogenesis is a multi-stage process (evidence reviewed by Peto, (4)) and this raises the possibility that the rate of progression of neoplastic growth may be open to manipulation. If the length of the latent period between induction and proliferative neoplastic growth could be increased, this would offer a useful additional method of controlling bladder cancer in identified "at risk" populations, for in this site, cancer mainly develops towards the end of mans' normal life span. One such approach is currently being investigated in a number of laboratories where the potential is being tested of synthetic vitamin A analogues, or retinoids, to control not only bladder cancer but neoplastic disease in other organ sites (6).

Until now, the clinical control of cancer has been directed towards extirpation of the tumour and its metastases and advances in treatment have reflected improved efficiency in our ability to remove or selectively kill the cancer cells in the presence of normal dividing host cells. While this ablative approach is, and will continue to be, of prime value for the rescue of the cancer patient, the real advances in cancer control in the next twenty years will probably come from a more biological approach to the problem, possibly based on measures designed to redifferentiate neoplastically transformed cells so that they will once again be responsive to the host mechanisms which control organogenesis, reversible reparative hyperplasia and normal cell growth. These are theoretically attainable objectives, but progress will depend on continued support for both basic biological research and applied experimental carcinogenesis studies.

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