Experimental Aspects of Environmental Carcinogens

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Purposes of laboratory studies

THE question 'Does substance X cause cancer in man?' cannot be answered directly by animal experiments. One purpose of laboratory studies is to test agents suspected, on chemical or epidemiological grounds, of causing cancer in man. Sometimes events occur in the reverse sequence. The experimentalist, in the course of an empirical survey of environmental factors, discovers an agent that induces cancer in animals, and this suggests the need for an epidemiological study on man. Another most important purpose of laboratory studies is to elucidate mechanisms of cancer induction. The pinpointing of the active ingredient in a mixture, and studying the effect of different doses and different conditions of exposure are exercises that are difficult or impossible to carry out in man. The underlying aim of all laboratory studies is the same as for studies in the epidemiology of cancer, namely, the prevention of the disease. The two disciplines are interdependent in their progress towards this end.

Requirements and pitfalls of laboratory tests

Common sense as much as special knowledge dictates the design of laboratory tests for carcinogenicity. The material used for the test should be chemically pure, or, at least, of the same degree of purity as that to which man is exposed, the animals should as far as possible be free from other disease and the conditions under which the experiment is conducted should be closely controlled. Since it is not possible to exclude all carcinogens from the environment of laboratory animals, and since they are as susceptible as man to the seemingly 'spontaneous' development of cancer, untreated animals must be observed in parallel with animals under test. Clearly the results of an experiment in which animals are exposed in the same way as man are likely to be more directly applicable to the human situation, but for some purposes it is justifiable to make use of model test systems which bear little relation to the circumstances of human exposure. The unrealistic nature of such tests must be taken into account in judging how the results should be applied to man.

Because untreated animals develop cancers, the terms in which the results of laboratory tests may be stated are not simply 'positive' or 'negative', but depend on a comparison of tumour incidence in treated and control groups. It follows that sufficient animals must be studied and must survive until the time tumours appear.

The long latent interval between exposure to a carcinogen and the manifestation of its effect is a feature that distinguishes tests for carcinogenicity from tests for other forms of toxicity. Even when animals are maximally exposed to a potent carcinogen, cancers may not appear until a quarter or a third of the natural life-span of the species has elapsed. With less exposure this time may be much longer. For these reasons prolonged observation of test animals (e.g. at least 18 months for mice and two years for rats) is a normal requirement for the acceptance of a negative result. Wherever the effects of potent carcinogens have been studied over an appropriate dose range, a direct relationship between tumour development and dose has been demonstrated.

The validity of the results of tests for carcinogenicity depends on the quality of the pathological evaluation. Small animals decompose rapidly after death, so they must be killed as soon as they become sick—which entails their frequent careful examination by trained observers—or after a predetermined period of observation. A world shortage of suitably trained pathologists has made the establishment of good standards difficult.

The significance for man of studies on experimental animals

There are numerous examples of materials that have been shown to be carcinogenic both in man and in laboratory animals—coal tar, cigarette smoke, asbestos, mineral oils, various radioactive substances, and certain aromatic amines, to mention but a few. In all these instances, carcinogenicity for man has been suspected or demonstrated *before* tests in animals have been initiated. We shall never know how much human cancer has been prevented because substances first shown to be carcinogenic in the laboratory did not come into general use. The most potent carcinogens can usually be shown to induce cancer in almost any animal species in which adequate tests are made, some of them are active following administration by a variety of routes. The significance for man increases as the number of species found to react positively increases, as the minimum dose found necessary for cancer-induction falls, and as clear-cut relationships between exposure dose and cancer incidence come to light.

A fundamental problem in interpretation stems from the impossibility, in a single test, of distinguishing between a carcinogen and a co-carcinogen—i.e. an agent that is not carcinogenic itself but

which enhances the activity of a carcinogen. Except in the case of hormones, the risk of this mistake being made probably recedes as the number of species tested and found to give positive results increases. Lack of clear-cut dose-response relationship suggests co-carcinogenic rather than carcinogenic activity.

Need for short-term tests

Life-span studies on animals are tedious and expensive but so far no satisfactory substitute for them has become available. Newborn animals are sometimes more sensitive than older animals and their use makes available more of the natural life-span for purposes of observation. At present *in vitro* test systems pose more questions than they answer.

Action

The results of animal studies, unless supported by parallel epidemiological evidence, can do no more than suggest that man will be at risk of developing cancer if he is exposed to a particular agent. The desirability and possibility of taking active steps to prevent human exposure to the agent depend on a wide variety of circumstances. Mere suspicion of risk for man could justify banning the use of a food colour that had no nutritive or preservative value, but it might be entirely unjustifiable to stop the use of a life-saving drug even though some risk of the subsequent development of cancer, possibly after a long latent interval, is entailed. Nobody doubts that certain lubricating oils and asbestos dust are relatively potent carcinogens for man, but the use of both are basic to life and work in an industrial society. Unless and until safer alternatives are available, the approach here must be to try to reduce exposure to a point where the risk of cancer development is negligible.

No room for complacency

Committees at both national and international levels periodically review the possibilities of carcinogenic hazard from drugs, food additives, and food contaminants such as herbicides and pesticides. The recognition of a cancer hazard in industry leads—sometimes, alas, all too slowly—to the drawing up of regulations and the adoption of appropriate safety precautions. There is no room for complacency about the efficiency of these systems of protection, nevertheless, they are probably more stringent and more effective than most members of the public realize. The greatest deficiencies are the unevenness with which precautionary measures are applied, and the lack of machinery for instigating investigations of the safety of entirely new processes. It is equally difficult to initiate studies on factors that have been present in the environment for centuries, the safety of which is presumed rather than known.

Industrialization certainly increases the risk of exposure to particular carcinogens, but it should not be forgotten that some potent ones are of natural origin. Man has opted for a mode of life in which he attempts to control his environment whilst, at the same time, contaminating it. One may marvel at his achievements, or deplore them, but there is little possibility of reversing his decision. The sophistication of test methods is making it easier to obtain a positive result in a carcinogenicity test and the list of carcinogens and supposed carcinogens is getting rapidly longer. To brand a substance as 'carcinogenic' on inadequate evidence may in the long run be as dangerous to man's progress and survival as leaving him on occasions at risk of exposure to a weak carcinogen.

Cancer Epidemiology

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Introduction

ELSEWHERE in this issue Professor Boyland suggests that most human cancer is due to external avoidable agents; such cancer is therefore preventable. Because rational preventive measures must be firmly based on sound epidemiological knowledge, I have chosen to write about what epidemiology is rather than about what it has already achieved in the cancer field. Other contributors to this series of articles, for example Professor Clayson and Dr. Harris, have discussed some specific examples of epidemiological studies.

One reason why every medical man should be familiar with present-day concepts of epidemiology is that the accuracy of his observations and the completeness of his records are one of the indispensable bases of the discipline and so, in contrast to the laboratory sciences, we are all involved whether we like it or not.

Just as the familiar concept of natural history included a detailed description of fauna and flora and of the environment in which they flourished or declined, so does epidemiology imply a study of a disease, of the person who suffers from the disease, and of the circumstances in which that person spent his life.

That epidemiology is now an acceptable term when applied to chronic disease and to slowly-acting causes shows how our ideas have changed with the passage of time. The old division into epidemic and endemic diseases originally implied a fatalistic acceptance of the endemic ones as an unalterable part of the scheme of things, whereas epidemic diseases, although at times regarded as manifestations of divine displeasure, were recognized at an early date as preventable or controllable.