Influences of Hormones in Tumor Development

Volume I

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PREFACE

The increasing awareness in recent years that our environment directly or indirectly influences carcinogenesis has focused much of our attention on external factors. What is being held as general deterioration in the quality of the environment has been widely reported on and has become an important area of social and scientific concern. This has come to outweigh our concern for the part played by the internal milieu and by genetic susceptibility. No critical assessment of the complex interplay of modifiers that finally lead to malignant growth should ignore this triad. There is no doubt that in some cancers, the influence of one or more factors seem of overwhelming importance. However, it appears reasonable that, whatever theory of primary cancerogenesis* one may adhere to, internal modulation of the exposed tissue is a necessary prerequisite for tumor induction and growth.

Hormones have traditionally been assigned an important role as modifiers of the neoplastic process. Their key role in metabolism makes them a logical target for speculation of this kind. The exquisite balance between the hormones in response to physiological needs, the minute amounts of active substances acting at the molecular level, and the continuing elucidation of the amplifying systems which translate their messages, all offer potential controls where the observed changes might be affected. Hormones are not necessarily components of mitotic mechanisms; cells can divide in their absence, but the overall regulation of cell division seems to be under their control. Hormones are also capable of affecting the genetic regulatory system by modifying gene expression.

It is accepted that hormones modify cancer risk, the response of the body to carcinogens and the biological behavior of established tumors. Some hormones seem to produce tumors directly, albeit at heroic levels. Experiments involving the removal of glands that secrete substances which stimulate or support tumor growth have destroyed the idea that all cancers were independent growths. At least some tumors, like many endocrine target tissues, can be shown to be dependent on normal control mechanisms. Our knowledge on therapeutic effects of hormones has been beneficial to innumerable patients.

Tumors of endocrine organs and of organs controlled by hormones cause some 90,000 deaths out of an estimated total number of 350,000 cancer deaths in the U.S. per year. Hormone-induced tumors, ectopic hormone production, and efforts to influence the natural history of tumors by administration of hormones in experimental animals represent a considerable share of basic research. The last decade has brought about a major qualitative step in our armamentarium with the discovery of hormone receptors which already has an increasing impact on clinical thinking.

The successful attrition of billions of malignant cells in a clinically apparent tumor — a cancer "cure" — evokes much scepticism. On the other hand, step-by-step modulation of such cells towards redifferentiation by endocrine therapy does not seem to be impossible to achieve.

We have tried to present an assessment of these uncertainties and challenges in basic research with clinical implications. We have divided the information on current views and results into sections by hormones. In these, the much appreciated work of our coauthors may be seen. It is next to impossible to cover this dynamic and wide-ranging topic comprehensively, but we hope that an updated review of relevant experimental and clinical research will contribute to the development of this promising field of enquiry.

* For a note on the distinction between cancerogens and carcinogens, the reader is referred to *Nature* (London), 267, 306, May 26, 1977.

The relationship of hormones to neoplasia is complex and multifaceted; it is conceivable that better understanding and manipulation of this relationship will pave the way for more rational and effective treatment of many cancers.

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Chapter 1

ANIMAL MODELS FOR CANCER RESEARCH

J. A. Kellen

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I. INTRODUCTION

Ethical considerations and restrictions severely limit human experimentation in cancer. Epidemiological studies in man are fallacious in our constantly changing environment; genetic analyses of heterogeneous material with so many variables such as relatively low numbers of progeny and a high rate of illegitimacy produce dubious results at best. Because of these variations and uncertainties, retrospective and prospective studies are difficult to design, to evaluate, and to compare.

The nature and exact timing of the primary neoplastic event in man has been impossible to determine — the variable latency of neoplastic growth obscures any valid picture of the natural history of human cancer. The successful emergence of neoplastic clones is a process which cannot be studied in vivo. Two extreme views are current as to how this occurs. One is that malignant transformation is a rare event which produces a cell fully capable of continued growth and escape from regulatory mechanisms; host resistance is of little or no importance. The other school of thought is that malignant transformations are frequent. The majority of transformed cells are unable to produce a tumor, because they succumb to various defense mechanisms of the host.

All these are but an oversimplified and incomplete enumeration of the obstacles encountered in efforts to put the study of human oncology on a scientific basis. With problems such as these, the need for biological models in cancer research is evident. However, the ultimate goal is to apply the information gained to the human counterpart of the disease.[1]

Those concerned with the quality of the environment have become increasingly plaintive. There has been mounting pressure from both the public and the legislature to conduct extensive tests for oncogenicity, a formidable task when one considers the time necessary to test for tumor induction through several generations and in statistically significant numbers of models at a variety of levels. It is clear that there are more new substances being introduced in our environment than can be assessed with any certainty. Controversies are sure to arise, especially when there are serious economic consequences. There is the wide-open question of the innumerable substances which have been in use for many years and are historically thought to be innocuous.[2] The demand for testing for cancerogenicity* is growing, and at present, animal models are needed to evaluate this effect. The truly enormous numbers of laboratory animals demanded by these tests limit a laboratory's resources and raise violent emotional protests from the public. This has become a perfect example of the wish to have our cake and eat it. On one side, experimentation on animals is a popular anti-scientist topic and may curb badly needed financial support for research; on the other side, researchers must yield to the legitimate worry about environmental cancerogenesis.

If deductions are made from observations of tumors in large numbers of uniform animal hosts and these deductions are extrapolated for use in human oncology, there are grave risks. Although enormous efforts have been made by clinicians to derive valid statistics from human data, no two patients of any series are alike; none is "repeatable." The time elapsed between the initial oncogenetic event and the clinical appearance of the neoplasm is unknown, as is the initial growth rate of the tumor; postmortem examinations are not performed in all cases; and treatment of patients is highly individualized. This latter may be the result of the influence of a local strong personality, serendipity in the choice of cases with favorable prognosis, reluctance to accept or enthusiasm for new treatment modalities and many other, very subjective, factors. All this creates great difficulties in setting up a valid, reproducible protocol. Only in the last decade have comparable studies in significant series of human patients been obtained. There is no need to emphasize that the above problems are minor in animal experimentation if the research design is soundly conceived. An appropriate design with extensive and correct data collection and registration offers unquestionable advantages. Generalizations from observations made in impeccable animal experiments and their projection to closely similar human counterparts are a snare and a delusion, and into this trap many enthusiastic researchers seem to have fallen. To stress similarities without critical assessment of the many differences often generates unwarranted scepticism and a general negative attitude towards extrapolation from results obtained with animals.

II. THE VALIDITY OF ANIMAL MODELS

Tumors are generally classified in animals used as models thus:

1. Spontaneous
2. Transplantable
3. Induced by cancerogens

* In this chapter, carcinogens will refer to agents which induce carcinomas only; cancerogens, to agents which cause all types of tumors. For this distinction, see *Nature* (London), 267, 306, May 26, 1977.

Necessarily, there is an overlap in the categories. Rodent strains with a high incidence of spontaneous tumors are suspected of having vertically transmitted virus infections which might be the primary cause of or adjuvant to tumor growth. Transplantable tumors, although obtained by a most unphysiological approach (if such a term can be used in tumorigenesis), allow experiments to be combined with changing environmental factors, external and internal.

The evaluation of drugs and their combinations is a particularly complex problem, ranging from unwanted general toxicity to specific cytotoxic effects on the neoplastic population. Extrapolation from relatively small models with large tumor masses and weight-correlated drug levels can be erroneous.[3] Immunotherapy is presently being tested in animal hosts, and it appears that there are several suitable models available. Optimal conditions for immunological protocols, assessment of humoral and cellular responses, and exact definition of the maximal initial tumor size (or number of tumor cells) can be determined and easily reproduced in animals.[4]

Animal models allow for extensive experimental manipulations of the tumor growth itself, which quite obviously cannot be achieved in human oncology. The following list presents an incomplete enumeration of the major fields of interest:

1. Diaplacental transport of cancerogenesis, administered at different periods of gestation
2. Nursing of litters from mothers exposed to a cancerogenic factor
3. Follow-up studies for several generations on the effect of the above
4. Combination of tumor growth and treatment with drugs, including toxicity studies
5. Tumor transplantation, from single-cell to multiple sites; partial ablation, contralateral re-transplantation
6. Spontaneous rejection, regression, or enhancement of the above
7. Manipulations of the immune mechanism, specific and nonspecific, including prophylactic administration of tumor or fetal material; testing of drugs which enhance or suppress the immune response
8. Genetic susceptibility of species, strains, and their hybrids, under defined conditions
9. Virus infections and tumorigenesis
10. Endocrine ablation and tumorigenesis

The necessity, scientific and ethical, to study animal models in cancer research, gave rise to comparative oncology as a discipline. The purposeful foundation of this approach is said to have been laid by the Medical Committee of the Edinburgh Society for Investigating the Nature and Cure of Cancer in 1802.[5] Since then, innumerable animals, large and small, have been sacrificed in a continuous and persistent effort to solve the enigma of cancer. Experimentally induced tumors in laboratory animals have become valuable models, readily available and reproducible. The natural history and histological features of these growths have been studied and recorded. There is a growing awareness among scientists that basic differences exist between tumors in models and in man.

The nomenclature of animal tumors, based largely on that of human tumors, is confusing and often misleading. Indiscriminant use of routine terminology may indicate certainty where none exists; thus the exact stratification of experimental tumors according to their histopathology is frequently the only assessment of reproducibility of the study. The basic criteria of malignancy in man, spread and metastasis, may be completely missing in some models, although the histological characteristics closely resemble the human counterpart, and the growth itself is lethal for the host.[6]

The ultimate proof of the validity of any experiments performed on animal models must be their practical and successful application to human disease. Acceptance of

analogies and parallelisms without testing in man cannot be justified. Of course, it is sometimes difficult, for ethical and technical reasons, to take the ultimate step and extend new principles to the patient. Early rejection of apparently unsuitable models because of discrepancies in the natural history of disease is equally undesirable.[7]

One of the most frequently encountered pitfalls of the extrapolation of results from animal models is the simplicity of the models themselves. Cancer induction by extreme levels of substances or transplants of millions of tumor cells into highly inbred animals, maintained under well-controlled and uniform conditions, does not reflect the intricate and complex situation in man.[8]

To determine the appropriateness of a chosen model is a demanding task in itself. Although there now exist a well-catalogued spectrum of animal species and strains which host particular tumors and tumor banks with stored tumor cells of a wide variety, researchers still lack models which truly parallel human conditions such as histopathology, invasiveness, metastasis, and hormone response, to name only a few. Some models do resemble a particular human condition closely, but it is almost impossible to find models similar to the human counterpart in most of its aspects.

III. LIFE SPAN AND BODY SIZE

Any deductions and extrapolations based on animal tumor models are limited by two important differences of scale: life span and body size. Both parameters will be considered.

A. Life Span

Data obtained in tumor hosts from different species support the view that the average tumor volume doubling time is positively correlated with the life span of the particular model. For practical reasons, experiments with relatively long-lived animals are seldom tried. The widely used rodents combine the advantages of early puberty, multiple parity, and short life span; tumor latencies in spontaneous neoplasia are short; chemical cancerogenesis is usually successful in weeks, and transplants take in days. On the other hand, the importance of intrinsic factors is illustrated by the fact that site, histopathology, and growth rate of tumors induced by a particular method vary greatly, even in inbred strains, with genotype, age at exposure, feeding, and mating.

Comparisons of time scales have been attempted, and with calculations correcting for life span of the species used as the model, approximations can be achieved. For example, one day's progression of cancer in the mouse is equivalent to about one month in man; the evaluation of the natural history of pulmonary cancer established the ratio of 3:65 days for mouse and man. Even in careful assessments of this kind, it is often impossible to deduce comparable data.[9]

Tumors in experimental animals develop after latent periods, which are dependent not only on the cancerogen itself, its level, the extent of exposure, and the route of administration, but also frequently on the species and strain studied. The scientific merit of such studies often necessitates observation periods spread over the animal's average life span. For this reason, dogs and primates are generally unsuitable and impractical.

Apart from the choice of the appropriate and responsive model species and strain for testing cancerogenesis a variety of factors come into consideration. Age has been shown to influence results greatly. In general, neonatal animals or those immediately postweaning give uniform and useful information about food additives and other environmental chemicals. However, some cancerogens need to be metabolized, and only mature enzyme systems in the host bring about the necessary breakdown products. The interplay of hormones is sometimes of utmost importance; thus, only sexually mature animals (or even pregnant hosts) may be suitable. Experiments requiring a

lowered immune response or other phenomena related to advanced age will be based on senescent animals, such as retired breeders.

B. Body Size

The wide variations of body mass between the animal species studied as tumor models are as obvious as they are frequently ignored in an oversimplified extrapolation. The implications of differences in size may render invalid data from an animal system which is otherwise an acceptable model. In the earliest stages of the neoplastic process, the mass of the host would appear to be of little importance in the tumor-host relationship. At later stages, however, just the volume of the tumor in animals may give rise to symptoms and cause death. Considerations of tumor mass/body mass are rarely discussed, but they certainly affect the relevance of animal models to clinical cancer. Most of the research findings thus can be applied to humans only by analogy.

IV. TESTING FOR CANCEROGENICITY

In view of the complexity of environmental cancerogenesis, it is insufficient to define the effect of an agent or agents as the direct cause, in a dose-related manner, of tumors. The problem has many facets: the increase in the number of tumor-bearing individuals in an exposed population, the increase in the number of tumors in each individual, the reduction of the latent period of tumor induction, or any combination of these. In addition, the site of action of the cancerogen complicates conclusions: local contact, selective organ accumulation, site of metabolism, and excretion must be taken into consideration. There may even be multiple sites. When all these factors are duly weighed, it is clear that proper testing and decision-making are difficult and the use of animal models unavoidable.

Skin-painting, force-feeding, or injection are the usual techniques of introducing the suspected cancerogen into the model. Local and general susceptibility strongly influence the outcome. To design an experiment which would mimic a typical "natural" situation in man is not feasible. Inhalation of minimal amounts of the material is very rarely applied in testing, although a large proportion of substances in the environment reach us through the air. Caging under constant conditions and feeding a precisely defined laboratory chow is hardly comparable to our modern, mobile life and the individual variability in food preferences.

As has been mentioned, even in a well-defined laboratory environment, genetic and species- or strain-specific factors may play havoc with statistical evaluations. The internal milieu, levels of hormones fluctuating with ovulation, circadian rhythms, stresses from manipulation or tumor growth, and many other unknown influences are to be blamed for frustrating attempts to reproduce experiments.

It is next to impossible, based on animal experiments (or on mutagenicity in submammalian cells or microorganisms), to pass a verdict that a given substance is "non-cancerogenic," even if extensive and prolonged testing does not show any increase in tumor incidence in a particular organ or an overall increase in one or more species. If no detectable effect is observed at high levels of the tested compound in appropriate models, exposure of man to much lower doses is assumed to be an acceptable risk. Although the following viewpoint is abhorred by dedicated environmentalists, a reasonable "risk-benefit ratio" should always be evaluated. Pesticides, which have contributed enormously to our well-being by eradicating parasites and improving crops, are a typical example. Their role in human cancerogenesis is practically negligible and certainly unproved for the majority of compounds used; still, their very existence in measurable levels in the adipose tissue of birds and mammals gives rise to a storm of protest and intense pressure to discontinue their use. It seems that no member of the particularly vociferous lay public realizes that modern analytic methods are able to

determine amounts so minuscule it is difficult to comprehend them in relation to the environment.

The argument that environmental cancerogens are the principal cause of human cancer and that, once recognized, their effect is ultimately preventable, is simplistic and fallacious. Cooperative efforts of a variety of researchers have indeed identified a steadily increasing number of cancerogens.[10] The direct and specific nature of these has often been found by experiments in animals using extreme dosages. The rationale for massive exposure is the necessity to compensate for relatively small numbers of tested animals. Evaluations of potential cancerogens are presented and interpreted with different conclusions by epidemiologists, oncologists, biochemists, and endocrinologists. The saccharin issue is a good example: a potential cancerogen has been increasingly consumed by humans during the last decade, yet target organs, identified in animal models, have not been affected in continuously exposed human populations, such as diabetics and weight-conscious persons. Of course, the induction period of human tumors may well stretch out for several decades, so that negative epidemiological findings may not yet reflect the impact of those substances more recently introduced to the environment.

Cancerogenicity testing reveals surprising differences among species and even strains. For example, some rat strains do not respond to 7,12-dimethylbenzanthracene, while others show a 100% inducibility of mammary tumors. Thus, susceptibility of the model to a particular substance must be considered in the research design; for reasons mentioned elsewhere, the rat, mouse, and hamster have proved the most useful. Extensive registries of experimental cancers are available, and a recent publication mentions 21,500 accessions to the NCI (National Cancer Institute, Washington D.C.) Registry alone.[11]

In practice, government and industry apply "safety factors" regulating permissible human exposure to a wide variety of substances. Extrapolation from animal experiments has been the playpen of biomathematicians and theoreticians, with numerous untenable generalizations. Although establishing a maximal safe level for substances without proven cancerogenic effect is relatively simple, it appears that a "no-effect" level for a recognized cancerogen is philosophically difficult to defend. For practical purposes and because of the ubiquitous character of a multitude of potentially hazardous compounds, it will be impossible to completely remove certain cancerogens from our life most of the time.

A. Screening

Screening of chemicals with cancerogenic potential is conducted mainly in small rodents. In order to unify the design of studies and achieve comparable and valid data, exact guidelines have been worked out. The abbreviated criteria presented in the list below have been suggested by the NCI Carcinogenesis Bioassay Program.

I. Husbandry: Define source of animals, caging, species/strain selection, genetic stability, feeding and bedding, weight - space relations.
II. Randomization: Consider equal age, sex, and weight distribution.
III. Toxicology: Acute, prechronic, subchronic, and chronic repeated-dose studies; include appropriate control groups, untreated and vehicle-treated.
IV. Carcinogen treatment: Establish sufficient levels to produce detectable and statistically significant numbers of tumors and adequate numbers of survivors.
V. Information and data recording: Standardize accuracy, completeness, and coding according to SNOP (Systematized Nomenclature of Pathology). Define the end point: mortality, survival for certain time periods, tumor incidence and frequency, growth rate, weight curves, etc. Route and site of administration: In-

clude details such as force-feeding, distribution of dosage during the day, age at exposure, incorporation into food or drinking water.

How reliable are animal or in vitro tests in predicting cancer and other health hazards in man? The question remains open. Competent opinion usually tends to consider only epidemiologic studies as conclusive, but because of the time and costs involved, the difficulties in interpretation, and their relative insensitivity, the only realistic alternatives are still in vivo and in vitro tests. At best, judiciously designed studies may prove that a suspicious substance is oncogenic for one or another of the species tested. It is impossible to prove that a substance is not cancerogenic; nor can it be proven conclusively that the oncogenic agent identified in animal models causes tumors in man.

B. Research Objectives

The study of cancerogenesis is continuously expanding and necessitates the design of a variety of experimental situations which in turn require the use of animal models. The main objectives of these studies are presented on Table 1.

The majority of compounds known to be cancerogenic in man are also cancerogenic in one or more animal species; tumor characteristics and localization may be completely different. Cancerogenesis in animal models does not necessarily imply induction of tumors in man, under routine environmental conditions. Animal studies also tend to predict toxicities which are not subsequently observed in man; on the other hand, adverse reactions with different symptoms and in different organs have been observed in patients at a greater or lesser dose than in the animal model.

V. HORMONES AND ANIMAL MODELS

Hormones are known to have a profound influence on cell growth, although there is no hard evidence that they are able to push normal cells into uncontrolled proliferation and thus cause the transformation to malignancy. Hormones are, with a few doubtful exceptions, not considered oncogenic, but prolonged exposure to large doses is related to the increased frequency of some cancers.

TABLE I

Research Objectives using Animal Models

Objective to clarify	Factors studied
Mechanisms of cancerogenesis	Metabolism; interaction with cellular macromolecules; viral activation; identification of target tissues; role of sex, age, dosage, timing
Biological characteristics of tumors	Karyotype; hormonal control and response; antigenicity and transplantability; natural history of growth, spread, metastasis, and regression
Tumor therapy	Hormonal; chemotherapy; immunotherapy; combinations of the above; immunoprophylaxis
Prenatal exposure (diaplacental cancerogenesis)	Tissue specificity; timing and levels; combination with chronic postnatal exposure; fetal metabolism