efficient, and the morphology of large-scale jets argues strongly for nonrelativistic motion of the jets. If these jets are only mildly supersonic and dominated by nonrelativistic plasma, then the turbulent boundary layer that surrounds the jet may provide the required particle acceleration, magnetic-field amplification, and transport of metal-enriched gas far from the interstellar medium. Slow jets increase the total energy requirements for the source, but not beyond the limits of credibility.

Compact jets are also inefficient, and arguments can be made for their relativistic or nonrelativistic motion. At present there is no clear-cut resolution of this issue, but it is fair to say that a consistent picture could be constructed wherein all jets are nonrelativistic. Observations of jet phenomena in extragalactic radio sources seem to require modifications of earlier models for the central energy source, and, although these have yet to be done in detail, models of the interaction of jets with their environment supply encouraging agreement with observations.

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Criteria for Evidence of Chemical Carcinogenicity

Interdisciplinary Panel on Carcinogenicity

Criteria for assessing the evidence for the carcinogenicity of chemicals have been described in several documents including a 1977 report of the Subcommittee on Environmental Carcinogenesis of the National Cancer Advisory Board (NCAB) (*1*) and the preambles to the monograph series of the International Agency for Research on Cancer on the evaluation of the carcinogenic risk of chemicals to humans (*2*). The report of the subcommittee of the NCAB recommended that "The general criteria should be reviewed on a continuing basis and revised in the light of new knowledge."

The Interdisciplinary Panel on Chemical Carcinogenicity was convened by Philippe Shubik at the request of the American Industrial Health Council to reevaluate the criteria for assessing the evidence for the carcinogenicity of chemicals as a result of recent increases in the quantity of data and research in carcinogenesis (*3*). The panel met on 31 October and 1 November 1983 and 24 and 25 February 1984 in Washington, D.C. The report that follows is particularly concerned with those areas that have been most affected by advances in knowledge.

The panel expresses its concurrence with the philosophy that was well expressed by the NCAB subcommittee (*1*):

> The criteria that are described are general guidelines and not rigid, universal criteria. The complexity of the problem dictates that the evaluation of potential human hazards of a given agent must be individualized in terms of the chemical and metabolic aspects of that agent, its intended use(s), the data available at the time the decision must be made, and other factors pertinent to the case under consideration. Each case must be considered on its own and the criteria appropriate for one agent may not necessarily apply to another.

The panel also agreed that the generalized definitions and significance of benign and malignant neoplasm presented in the NCAB subcommittee's report were adequate for present purposes without modification (*4*).

Since 1977 numerous bioassays of chemicals have been reported from in vivo studies; many in vitro tests have been undertaken and new in vitro tests have been devised. As a result much new research on the mechanisms of action of chemical carcinogens has been reported and suggestions put forward for classifying carcinogens; the influence of biometrics has been prominent in the development of a variety of mathematical models for risk assessment; and there have been controversies about the overall quantification of risk from chemical carcinogens to the human population. These factors have been influential in determining the priorities for the present deliberations.

Evidence Derived from Human Studies

Clusters of cases of a specific type of cancer associated with a particular exposure suggest that certain chemicals or combinations of chemicals may be carcinogenic to man. This has been the basis for much of our current knowledge of occupational cancer occurrence. The problems that confront the epidemiologist in such situations include the reality of the excess cancer incidence, the difficulty of estimating exposure, and

The members of the panel were: Philippe Shubik, Green College, Oxford University, chairman; Arnold Brown, University of Wisconsin–Madison; Charles Brown, National Cancer Institute, Bethesda, Maryland; J. R. P. Cabral, International Agency for Research on Cancer; David Clayson, Bureau of Chemical Safety, Health Protection Branch, Health, and Welfare, Canada; Ian Higgins, University of Michigan; Wayne Levin, Hoffmann–La Roche, Inc.; Peter Magee, Fels Research Institute, Temple University, School of Medicine; Mortimer L. Mendelsohn, Lawrence Livermore National Laboratory; Robert A. Squire, Johns Hopkins University, School of Medicine; Bruce K. Bernard, Scientific Research Associates, Inc., rapporteur. Requests for reprints should be addressed to Dr. Philippe Shubik, Green College, Radcliffe Observatory, Oxford OX2 6HG, England.

the exclusion of confounding factors (*5*).

Potential carcinogenicity may be suggested by descriptive (hypothesis generating) epidemiological studies that explore the relationship between exposure to some factor or factors and the development of cancer in general or cancer at specific sites.

Descriptive studies are usually classified as exploring relationships with respect to time, place, or personal characteristics. Observations relate incidence of, or mortality from, cancer in general or cancer at specific sites to the introduction, increasing use, and removal of potentially carcinogenic exposures; to differences between geographical locations; and to personal exposures at work, from hobbies, leisure activities, food, water, and behavior. A primary problem is posed by difficulty in excluding confounding factors.

Analytical studies (hypothesis testing), in contrast, are carefully designed to explore hypothesized relationships and again two types are recognized: (i) case comparison studies in which the past history of exposure and personal characteristics of persons with cancer are contrasted with the same characteristics of those who do not have cancer and (ii) cohort studies in which the personal histories and exposures of a sample of the population are documented and the sample is followed over the years to determine the rate of occurrence of cancer. This rate is then related to the categories of exposure determined at the outset. The latency of cancer introduces difficulties into both types of study.

A helpful type of study is often possible in industries where good occupational hygiene records have been kept. Here it may be possible to define a group of employees whose exposures can be estimated at some time in the past. By relating categories of past exposure to subsequent mortality the waiting period needed in current cohort studies can be eliminated. Such studies are usually referred to as historical mortality studies.

An important factor in assessing carcinogenicity in man is the demonstration of dose response. Whenever possible, the dose estimated from level and duration of exposure should be related to cancer incidence or mortality.

One of the main problems of epidemiologic studies has been the difficulty of measuring exposure and estimating dose. Often studies of occupational exposure have been based on qualitative assessments such as high, medium, or low. Major improvements could be realized through better documentation of human exposure to potential carcinogens. Personal sampling has been used increasingly. For substances where portable sampling instruments are available, this provides a more relevant approach to individual exposure. We look forward to the time when such personal sampling can be coupled effectively to health outcomes.

Human data provide the only direct evidence that a chemical produces cancer in man. Negative epidemiologic results cannot ensure complete absence of carcinogenic hazard from a chemical or a process. Negative epidemiological results may indicate that the duration from the first exposure was too short, the sample size was too small, the dose was too low, or the substance to which people were exposed was not a carcinogen. In epidemiology, as in other disciplines, it is impossible to prove a negative. The lowest degree of risk that is likely to be directly detected by epidemiological means can be estimated, but risks below this can only be inferred by extrapolation from data obtained at higher exposures. Negative results thus indicate the limits within which a specific type of exposure will not affect the incidence of cancer in man.

Because of their central role in the identification of human risk, epidemiological studies are indispensable and require substantial expansion. Strengths and weaknesses of such studies, as is the case with experimental data, should be evaluated individually for robustness and weight.

Summary. The Interdisciplinary Panel on Carcinogenicity reviewed and reevaluated criteria for assessing evidence of carcinogenicity of chemical substances. The panel reviewed criteria applicable to data derived from human epidemiological studies and from both in vivo and in vitro laboratory studies. A critical appraisal of all these sources of information led to the conclusion that the characterization of human risk always requires interdisciplinary evaluation of the entire array of data on a case-by-case basis. Animal studies, whenever possible, should be augmented by studies of mechanisms, metabolism, and pharmacodynamics. Such studies may assist in assessing risk to man. Recognizing the utility of such data should point the way for better assessment in the future.

Evidence from Long-Term Bioassays

The carcinogenicity of a substance in animals is established when administration in adequately designed and conducted experiments results in an increase in the incidence of one or more types of malignant (or, where appropriate, a combination of benign and malignant) neoplasms in treated animals as compared to untreated animals maintained under identical conditions except for exposure to the test compound. Determination that the incidence of neoplasms increases as the result of exposure to the test compound requires a full biological, pathological, and statistical evaluation. Statistics assist in evaluating the biological conclusion, but a biological conclusion is not determined by the statistical results (*6*).

Certain data derived from animal studies, although suggestive of carcinogenic risk, may require additional study before extrapolation to conditions of human exposure can be made. For example, there are different tumor end points in bioassays conducted in vivo, some of which are enhancements of the background incidence of neoplasms seen in the untreated control animals. It is not uncommon for some of the control rodents in such studies to develop incidences of even 100 percent of neoplasms of a particular kind. If control animals develop, say, 50 percent of a certain kind of neoplasm, and this incidence is significantly increased in treated animals, or if there is a decreased latency period for the occurrence of such tumors, this is usually classified as an example of carcinogenesis. In other studies the end point may be represented by the occurrence of neoplasms that are not seen at all or only rarely seen in the controls. Instances of decreased latency or increased incidence of neoplasms in animals with a high incidence in controls requires full evaluation using a high level of statistical significance and, if possible, an analysis of the incidence in historical controls. The potentially large variation in the incidence of these neoplasms adds to the uncertainty in the evaluation of their significance.

The interpretation of these different patterns of tumor development in test animals should recognize the likelihood that they represent different mechanisms and may have different significance to human risk. Each experiment must be assessed according to the nature of the end points in the test animals, and different weights of evidence may be accorded

for purposes of extrapolation to humans.

Instances in which the only manifestation of carcinogenesis is a decreased latent period or an increased number of neoplasms with a high incidence in controls may require validation in further experiments before being extrapolated to humans. Some of these enhancements may be a result of relatively nonspecific effects such as changed caloric intake, the use of high doses leading to excessive cytotoxicity and cell proliferation, or other experimental conditions, which may not be relevant to human exposure.

Special bioassays of chemicals are sometimes undertaken to demonstrate effects such as cocarcinogenesis and promotion (*7*). These terms were originally meant to describe specific experimental conditions but are now widely used to describe modifications of the effects of a variety of carcinogens. There is no doubt that when the mechanisms of carcinogenesis are fully understood the role of certain modifying factors will prove to be of considerable practical importance. Presently, the relevance of these factors in human carcinogenesis cannot be determined, and for the moment such bioassays can only be used as ancillary evidence in assessing data for potential human hazard.

The statistical evaluation of carcinogenesis results makes use of experimental variables. These may include the time for observation of neoplasm (latent period), incidences of neoplasms, and time to death from neoplasms and other causes. The determination of time to neoplasm often requires an experimental design in which subgroups of animals are killed and examined at frequent intervals during the experiment in order to identify the onset of neoplasia. The exceptions to this added requirement are the instances in which neoplasms, such as those in the skin, can be diagnosed clinically from the time of their first appearance. However, most experimentally induced or enhanced animal neoplasms are not rapidly fatal, and clinical observations or terminal autopsies do not generally provide a valid basis for estimating time to onset of neoplasia.

In most cases, neoplasms of different cellular origin appear to originate independently. Consequently, it is reasonable for purposes of statistical analysis to evaluate tumors of different cellular origins separately.

In all instances the robustness of the data must be ensured. This may vary not only with the particular model chosen for the study, but also with practical conditions such as experience and training of personnel, adequacy of facilities, and avoidance of confounding factors. The strength of the data depends in part upon its robustness. Robustness in turn is a function of scientific design, execution, analyses, and interpretation of the study. An important element is the rigorous adherence to codes of good laboratory practices (*8*) and suitable quality assurance procedures.

Evidence from Short-Term Tests

Early markers of neoplasia. Many investigators have long hoped to find early tissue changes that would predict carcinogenicity, but this has so far eluded discovery. A recent approach is the effort to correlate enzyme-altered foci in the liver with eventual hepatoma occurrence. So far, the correlation has been too inconstant for this test alone to be a satisfactory basis for classifying compounds as carcinogens. A variety of other short-term tests for identification of preneoplastic lesions or markers of neoplastic transformations have been suggested, but they are still at the research stage; the panel expects that this area will receive increasing attention (*9*).

Tests for genetic alterations. Beginning over a decade ago, in vitro tests for genetic changes were developed and rapidly applied to the practical problem of carcinogen identification. This approach was spurred on by the belief that genetic alteration in somatic cells is closely linked to one or more of the stages of carcinogenesis, and by the early results which showed that the coupling of metabolic activation to relatively simple bacterial assays for mutation gave results highly correlated with the carcinogenicity of certain groups of chemicals.

Approximately 100 of these tests are now available. They involve many organisms ranging from prokaryotes to human cells and can be performed under various conditions ranging from studies of isolated DNA to observation of cells in vitro and in vivo. The tests can be grouped into three general categories based upon their end point:

1) Tests for DNA damage including adduct formation, strand breakage, prophage induction, and DNA repair.

2) Tests for mutagenicity, including forward and reverse mutation as evidenced by alterations of DNA, gene products, or cellular behavior.

3) Tests of chromosomal effects including aneuploidy, structural aberrations, micronuclei, and sister chromatid exchange.

In the main these tests are effective at measuring their intended genetic end points and, when used in batteries, are effective for identifying genetic effects of chemical toxins. It is less clear how well these tests identify chemical carcinogens or how they should be used in the absence of corroborative data on carcinogenicity.

The initially high correlation observed between genetic change and carcinogenicity has decreased with the enlargement of the set of chemicals tested and with the separation of test development from test deployment. Estimates of correlations between findings in such tests and determination of carcinogenicity in vivo varies, depending on the chemical class, test type, and laboratory. At present, the overall performance of short-term tests, as judged by the proportion of correct results for chemicals classified by carcinogenesis bioassay, is in the range of 50 to 70 percent. Although often significantly better than chance, these results are not adequate to allow reliance on short-term tests alone in the determination of carcinogenicity. However, thousands of chemicals have yielded positive results in short-term tests and require further analysis. This has created a gnawing problem for scientists, regulators, industrialists, and the public. Pending developments that may clarify these issues are: (i) continued improvements in the assays, particularly in regard to standardization and metabolic activation; (ii) expanding the chemical classes to which such assays respond; (iii) analyses of large data bases of results from short-term tests with carcinogens and noncarcinogens so that patterns of response and validation of performance can be established; (iv) extensions of assay methods to easily obtained human samples for coupling to epidemiological studies; and (v) clarification of those mechanisms of carcinogenesis that these tests are intended to simulate.

Tests for transformation in vitro. Changes in growth, colony formation, and colony morphology in culture have been related to exposure to carcinogens and to tumorgenicity when the affected cells are transplanted to animals. The use of cell transformation has become a major research tool for those studying mechanisms of carcinogens by viral, chemical, and physical agents. The methods have also been applied to the identification of chemical carcinogens but with less success and reportedly poor predictivity. However, in view of the potential inherent in these methods to elucidate some aspects of cancer causation, continued research and validation of these methods is to be encouraged.

Metabolism and Pharmacokinetics

Administration of a chemical to an animal is usually followed by its absorption and distribution throughout the animal's body. In some cases the physical properties of the chemical, such as lack of solubility or the presence of an ionized form at normal physiological *p*H, may lead either to the substance not being absorbed from the gastrointestinal tract or to its localization at the site of administration. Once in the body, the chemical will usually be metabolized by a number of enzymes that are present in different tissues. Overall, the beneficial effect of metabolism is to solubilize the chemical and thus facilitate its excretion from the body (*10*).

The pharmacokinetics of chemical carcinogens is of special importance because at elevated doses the body may be unable to clear the chemical as rapidly as it is administered so that, after a lag, the chemical may attain toxic concentrations. Pharmacokinetic studies are also important because they may determine the concentration of a carcinogen or its metabolites at particular sites. As in other enzyme systems, metabolic enzymes become saturated as the amount of substrate increases. In such a situation, enzymes with a low affinity for the substrate may become more involved in the metabolic process. Overall, such an effect will appear as a discontinuity in a plot of the percentage of an agent converted to a specific metabolite versus the administered dose of the agent. Such a discontinuity has been called a metabolic threshold and is important in assessing the effects of the high doses given in animal studies relative to the lower doses to which humans are normally exposed.

With many carcinogens, metabolism leads to the formation of reactive species as well as more readily excreted metabolic products. Reactive metabolites are formed from most major classes of chemical carcinogens, such as *N*-nitroso compounds, aromatic amines, polycyclic aromatic hydrocarbons, and aflatoxins. In each case the reactive metabolite is capable of reacting with macromolecules, including DNA, the target that is assumed to be critical for initiating carcinogenesis. The chemical structures of the DNA adducts derived from these interactions have been established in many cases and lend support to the suspected structure of the metabolite.

The activities of metabolic enzymes may be markedly affected by the physiological and pathological condition of the host and by environmental factors. Enzyme induction has been the most investigated method for modifying enzyme activity. It can either enhance the formation rate of the active metabolite or stimulate other pathways that produce inactive metabolites. The magnitude of induction varies with the inducing agent, the substrate used to assay the activity of the enzymes and the species, strain, and sex of animal. The biological consequences of enzyme induction on the carcinogenic response depend not only on rates and pathways of metabolism but also on disposition and clearance rates of active metabolites.

The situation becomes more complicated when you consider the complex nature of the mixed function oxidase system involved in the transformation of many chemical carcinogens to active metabolites. For example, multiple isozymes of cytochrome P-450, that is, forms with different amino acid sequences, exist in a given tissue, each with different, but overlapping, substrate capacities. Many are regulated independently, so various factors lead to selective increases or decreases in specific isozymes. The amount of each isozyme present in different individuals is an important factor to consider in the variability of human response to chemical carcinogens.

These parameters limit extrapolation of metabolic data from test species to the human situation. Comprehensive metabolic studies in different species can, however, provide valuable data for comparison with that data obtained from human studies. Once the metabolic profile of a particular carcinogen is established from animal studies, human tissues can be tested in vitro to determine if the same metabolites are formed.

In most in vitro tests the activation system determines the outcome. Numerous factors influence the metabolism of foreign chemicals in vivo, and results from short-term tests are often influenced by the selection and preparation of the metabolizing systems. Consequently, no single system in vitro can be totally satisfactory or can exactly mimic pharmacokinetic parameters that influence the fate and disposition of the test chemical in vivo. Nevertheless, when used appropriately, in vitro metabolic activation systems can provide valuable insight about the generation of potentially carcinogenic intermediates.

The Mechanism of Carcinogenesis

The classification of carcinogens on the basis of their mechanisms of action would greatly accelerate carcinogen identification and provide logical approaches to methods of cancer prevention. A working group from the International Agency for Research on Cancer (IARC) (*11*) concluded that, at present, no classification of carcinogens according to mechanisms could be exhaustive or definitive. However, elucidation of mechanisms has value in the identification and evaluation of specific carcinogens (*12*).

Our panel concurs with the IARC's conclusion: in certain situations, the particular mechanisms of action of some carcinogens provide guidelines for preventive measures. These situations include carcinogenic effects directly related to the hormonal changes caused by certain compounds and carcinogenic effects in the bladder caused by compounds that induce bladder calculi. These carcinogenic effects can be dealt with differently from those of compounds that induce cancer without the apparent intervention of other physiological or pathological factors.

In spite of the inability to derive a generic classification of carcinogens, case-by-case scientific evaluations may be reached for individual substances. Chemical carcinogens can, in principle, be divided into two categories. One category gives nonthreshold dose responses, is stochastic in mechanism, and may have some probability of producing carcinogenic effects at any dose. The second category gives threshold dose responses and, theoretically, has a no-effect level. A few chemicals can be placed, provisionally, in one category or the other; but for the bulk of chemical carcinogens, we are currently unable to discern in which compartment they fall. By dealing with chemicals case-by-case and by studying mechanism, we can look forward to doing better than this.

Extrapolation from Experimental Data

Animal experiments are commonly conducted with higher exposure levels than those normally encountered by humans. Therefore, the first step in a quantitative evaluation is to extrapolate the results from high doses to effects from doses corresponding to human exposure. The second step is to extrapolate across species from animal experimentation to the human situation. Both steps entail large uncertainties (*13*).

The first step, extrapolation from high to low doses, depends upon the presumed dose-response relationship. A number of mathematical models have been proposed for this extrapolation,

each being necessarily simplistic. These dose-response models are quantitatively similar to one another in the range of experimentally observable response rates, that is, 10 to 100 percent, yet they may yield substantially different estimates at lower, unobservable response rates. Estimates for low-dose responses that differ by three to four orders of magnitude are not uncommon. This uncertainty is the single most important limitation of the models. Current knowledge does not yet allow the selection of one particular model, and experimental data from animal bioassays are not sufficient to discriminate among the competing models.

Cancer can occur through means other than exposure to a specific chemical. The manner in which this "spontaneous" response is incorporated into a dose-response model is another major source of uncertainty in extrapolating from high to low doses. Two methods have been proposed: one method assumes that the process leading to spontaneous cancer is independent of the process induced by exposure to the suspect agent; the other, that the two processes are identical. As with the different mathematical models for dose response, these two methods yield dose-response curves that are statistically indistinguishable in the observable response range but yield substantially different extrapolations. Other sources of uncertainty in extrapolating from high to low doses include the possible existence of thresholds, determination of the effective dose at the site of action (compared to the administered dose), and the mechanism of carcinogenic action.

The second step in extrapolation, from the laboratory to the outside world, involves additional sources of uncertainty. The route of exposure for the laboratory animal is often different from that for exposed humans, and the responses of the two species to the carcinogenic insult may be substantially different. Experimental animals are often genetically homogeneous and share nearly identical environmental conditions; however, they do not always agree, qualitatively and quantitatively, in their carcinogenic response. In addition, they may differ in the site of their carcinogenic response. Humans are a genetically outbred species living under widely diverse environments; they are exposed to a large variety of carcinogens and noncarcinogenic modifying factors that may enhance or even inhibit the agent in question. There are unknown biases involved in extrapolating dose response obtained under homogeneous experimental conditions to heterogeneous environmental conditions.

Different age-related patterns of exposure may have a substantial effect on risk. Experimental animals are usually exposed to a near-constant level for most of their lifetime, whereas human exposure patterns may vary widely from day to day. The results of extrapolating from one exposure pattern to another are dependent upon assumptions about the mechanism of carcinogenic action, thus providing another degree of uncertainty to extrapolation.

Further development of biometric models should be encouraged in order to provide statistical analyses for evaluation along with all relevant scientific data. Pending elucidation of the mechanisms of cancer, statistical estimations of the relation between exposure and response will be most helpful when the models incorporate pharmacokinetic data and the time between exposure and tumor development, distinguish between the administered doses and target doses, and correct for the duration of exposure and competing risks. The most probable estimates should always be presented together with the confidence limits of the estimates. Enough data should be presented to show how well the estimates fit the experimental data; and assumptions incorporated in the model, together with any uncertainties, should be clearly stated.

The Overall Assessment Process

Chemical carcinogenesis is a rapidly moving field, and great quantities of data have been accumulated during the past decade. Even though an individual experiment may yield only suggestive information, this information may be of considerable importance when considered together with other data (*14*).

Clearly, when the primary source of data comes from epidemiological studies in man, it may be possible to evaluate a chemical and institute scientifically based preventive measures. However, even in the instances where data are available from humans, the data must be supplemented with information from other sources before a conclusion can be reached.

For example, toxicological evaluation of carcinogenicity has classically relied upon long-term in vivo studies as the primary source of data. Such studies have been performed in a routine manner, and evaluations have followed predetermined formulas. This rote method is rapidly giving way to evaluations that take into account findings from in vitro tests, metabolism studies, and biometric analyses as well as any other available information. One of these methods alone cannot produce a reliable estimate of a chemical's risk to man, but taken together they provide an estimate with a high level of confidence.

Carcinogens act via different mechanisms, which results in their having different magnitudes of risk to man. Even though there is no basis for the exact extrapolation of risk from experimental animal to man, current advances, if exploited to the fullest, can provide a basis for distinguishing the degrees of risk from different carcinogens. The scientific criteria should be reviewed often, and scientific advances should be fully adopted.

The scientific characterization of human risks from carcinogens involves the evaluation and integration of data from many disciplines. It requires scientific impartiality to review all appropriate data, both negative and positive, including statistical estimations of low-dose response. Quantitative characterization of human risk requires scientific experience and judgment in order to weigh the evidence. Because of the strengths and weaknesses of the data to be evaluated in the assessment of human risk and the complexity of the problem, case-by-case analysis is most appropriate (*15*).

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3. The panel acknowledges support of the workshop by the American Industrial Health Council.
4. In (*1*), p. 461, column 2: "This subcommittee has found it useful to state generalized definitions of malignant and benign neoplasms, recognizing that in practice the diagnosis of a particular neoplasm is an operational one based on convention, experience, and experimental data.

"A malignant neoplasm is composed of a population of cells displaying progressive growth and varying degrees of autonomy and cellular atypia. It displays, or it has the capacity for, invasion of normal tissues, metastasis, and causing death to the host. Benign neoplasms are a less autonomous population of cells, exhibit little or no cellular atypia or invasion of normal tissues, and do not metastasize. In particular cases, however, benign neoplasms may endanger the life of the host by a variety of mechanisms, including hemorrhage, encroachment on a vital organ, or unregulated hormone production. The cytologic and histologic criteria utilized in determining whether a lesion is benign or malignant differ depending upon the tissue in which the neoplasm arises. Evaluation of whether a specific lesion is benign or malignant should, therefore, follow standard criteria used by experimental oncologists and pathologists with emphasis on correlation of the histopathologic pattern with the biologic behavior of the lesion or type of lesion. In equivocal cases, the diagnosis of a specific lesion may require a panel of experts, recognizing that they may not always agree.

"Depending upon the particular case, benign

neoplasms may represent a stage in the evolution of a malignant neoplasm and in other cases they may be 'end points' which do not readily undergo transition to malignant neoplasms."

In this report, we have used the term "neoplasm" freely to describe both benign and malignant neoplasms.

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15. In today's phraseology, this report has been concerned with scientific risk assessment and not with risk management. The process of risk management, by definition, begins after risk assessment has determined that a risk to a human population exists. Whereas "assessment" deals with biological significance, "management" deals with the possible alternative regulatory actions. Included in risk management may be evaluations of costs, feasibilities, risk-benefit ratios, availability of replacement substances or processes, and the level of risk that is acceptable to the society in question. Management of risks is a political, social, and economic issue. Scientists acting as scientists have a role in this phase, but it is limited to ensuring that the biological meaning of the risk is understood throughout the process.

RESEARCH ARTICLE

Antibodies to Human c-*myc* Oncogene Product: Evidence of an Evolutionarily Conserved Protein Induced During Cell Proliferation

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The viral oncogene v-*myc*, which is harbored by avian myelocytomatosis viruses, is derived from a cellular gene (c-*myc*) found in all vertebrates (*1*). The cellular *myc* gene contains three exon sequences transcribed from two promoters located either just 5′ of or just within the first exon (*2–4*). Considerable interest has been shown in the c-*myc* gene since Burkitt lymphoma cells show translocations that have brought the c-*myc* gene in close proximity to the immunoglobulin heavy chain locus, t(8;14), or the immunoglobulin light chain loci, t(2;8) and t(8;22) (*5*). The molecular mechanism by which c-*myc* oncogenicity can occur, however, remains obscure although several mechanisms regarding its activation have been proposed. These include a transcriptional activation of the c-*myc* gene resulting from the chromosomal translocation (*6*), a deregulation of the c-*myc* gene allowing constitutively high levels of expression (*7*), a removal of an untranslated 5′ exon, thus facilitating c-*myc* gene expression at the translational level (*8*), release of a transcriptional repressor (*9*), a differential usage of promoters in normal and malignant cells or somatic mutations occurring at a high level as a result of its proximity to the immunoglobulin locus (*10*).

The protein product of the c-*myc* gene is, most likely, responsible for c-*myc* oncogenicity, and some information on potential properties of the c-myc protein has been obtained from studies with the myelocytomatosis viruses. The transformation specific protein from MC29-type viruses is synthesized as part of a polyprotein with a molecular weight of 110,000 (110K), in which v-myc protein is fused to the gag protein (*11*). The p110K$^{gag\text{-}myc}$ polyprotein is found largely in the cell nucleus, binds to double-stranded DNA, and at least a fraction of the protein is associated with chromatin (*11*). Two other members of the myelo-

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