WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

GREEN COLLEGE, OXFORD

INTERPRETATION OF NEGATIVE EPIDEMIOLOGICAL EVIDENCE FOR CARCINOGENICITY

EDITORS
N. J. WALD R. DOLL

IARC SCIENTIFIC PUBLICATIONS No. 65

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Proceedings of a Symposium held in Oxford, 4–6 July 1983

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The International Agency for Research on Cancer (IARC) was established in 1965 by the World Health Assembly as an independently financed organization within the framework of the World Health Organization. The headquarters of the Agency are at Lyon, France.

The Agency conducts a programme of research concentrating particularly on the epidemiology of cancer and the study of potential carcinogens in the human environment. Its field studies are supplemented by biological and chemical research carried out in the Agency's laboratories in Lyon and, through collaborative research agreements, in national research institutions in many countries. The Agency also conducts a programme for the education and training of personnel for cancer research.

The publications of the Agency are intended to contribute to the dissemination of authoritative information on different aspects of cancer research.

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EDITORS' NOTE

The Editors were aware that since the time of the meeting, new studies had been reported on a number of the compounds considered, but since these could not be discussed by all the members of the Symposium, they have not been included in these Proceedings.

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FOREWORD

The role of the International Agency for Research on Cancer, as a research institution committed to public health, is to generate and disseminate information useful for the prevention of human cancer. Following a request received in 1968 to provide information on environmental chemical carcinogens, the Agency has devoted one of its most important programmes to identification of environmental carcinogens and to evaluation of the probability that exposure to them may lead to cancer in humans. Through this programme, which is centred on the production of a series of *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans,* over 700 chemicals, groups of chemicals or mixed exposures have been evaluated. More than 12 years after the first request to prepare a list of human carcinogens, the Agency extracted from its *Monographs* series a group of chemicals and occupational exposures that are evaluated as being causally associated with cancer in humans, and another group of chemicals and industrial processes that are evaluated as being probably carcinogenic to humans.

The Agency welcomes any input that could better the criteria for evaluating data on carcinogenicity, as this will help to upgrade its contribution to cancer prevention. The Agency therefore supported the initiative taken by Sir Richard Doll and Dr P. Shubik to call a symposium to discuss one of the most difficult and controversial issues in cancer epidemiology—the interpretation of negative epidemiological results. The Agency is glad to be able to publish these proceedings, which constitute an important contribution to the evaluation of epidemiological data. It should be stressed, however, that the resulting publication is completely separate from the *IARC Monographs* series. For instance, each volume of the *IARC Monographs* is the responsibility of a large working group of experts in many fields of research related to the evaluation of carcinogenic risk; in the present publication, each article is individually authored and is therefore the sole responsibility of the authors and the editors. The categorization of evidence proposed in the introduction to this volume as a working tool for the participants of the Symposium is in no way connected with the categories used in the *IARC Monographs.*

The chemicals chosen for consideration in this Symposium had all, except for nitrates, been evaluated within the *IARC Monographs* series, and all may be seen as 'problem compounds', in the sense that the available epidemiological data did not reveal a causal relationship between exposure and human cancer, nor did they provide clear evidence for the absence of such an effect. In particular, the evidence provided by data from long-term tests in experimental animals was sometimes at variance with the epidemiological evidence.

Our presently limited knowledge of the mechanisms of carcinogenesis does not allow a direct extrapolation from experimental data to the human situation, as this would be scientifically unjustifiable. For this reason, the Agency has adopted a prudent attitude (supported by the advice of many experts), which is to consider that in the absence of adequate human data, and for practical purposes, chemicals for which experimental results provided sufficient evidence of carcinogenicity (i.e., evidence of a causal association), should be regarded as if they presented a carcinogenic risk for humans.

By definition, and by the nature of the facts, data obtained from studies in animals, strong as they may be in demonstrating the absence of carcinogenic effect, will never invalidate a positive epidemiological study. By the same nature of facts, the reverse should be true—that is, an epidemiological study or series of studies showing that an exposure did not cause an increased risk of developing cancer should overwhelm any experimental evidence of carcinogenicity. In reality, the conditional in the preceding sentence indicates that it could do so, if and when the negative evidence provided by epidemiological studies is adequate and convincing, an ideal situation that is very rarely reached. The participants in the present Symposium have considered, on a case-by-case basis, what might constitute 'adequate and convincing' evidence.

What remains to be seen, therefore, is the extent to which epidemiological studies can be used to conclude that a compound does not represent a carcinogenic risk to humans, even if there is clear evidence of carcinogenicity in experimental studies. As Sir Richard remarks, 'No hard and fast criteria can be laid down that will automatically lead to an appropriate conclusion in all circumstances'. In the pages that follow, an attempt has been made to distinguish between the different degrees of evidence that may be provided by epidemiological data. The presentations in this volume may not provide elements that would justify a change in the attitude of the Agency, but they contribute to the clarification of several aspects of the evaluation of carcinogenicity data and point to the necessity of obtaining better information covering, in particular, individual exposure levels.

I should like to congratulate the initiators of this Symposium as well as all the participants for their contributions, which have undoubtedly helped to deepen the discussion on the validity and the limits of the data on which a qualitative, and ideally also a quantitative, assessment of human risks has to be based.

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PURPOSE OF SYMPOSIUM

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PREFACE

The opening session was devoted to discussion of the purpose of the Symposium and the way in which subsequent sessions could be made most fruitful. A number of suggestions were made for improvement of the paper that had been prepared for discussion at this session, and these have been taken into account in the text that follows. The exact wording remains the responsibility of the author (RD), but the general tenor of the paper, as it now appears, was acceptable to the participants in the Symposium as a whole.

INTRODUCTION

The progressive reduction in mortality rates that has taken place over the last 50 years and the growth of our ability to control the spread of infectious diseases and to treat them effectively have, in many countries, concentrated the attention of those concerned with public health on the main killing diseases of middle life and early old age and, in particular, on cancer and ischaemic heart disease. These, between them, are now frequently responsible for more than half the loss of all expectation of life under 85 years of age—the former being responsible, in England and Wales, for slightly more than the latter (Doll, 1983).

So far as cancer is concerned, it is now common ground, for all who have been engaged in its study, that the great majority of cases are in principle preventable, in the sense that it should be possible to reduce the risk of developing the disease at a given age by some 80 or 90% (or, rather, reduce by this amount the risk of developing the sum of the many disparate diseases that are grouped together under this generic head). There is, however, less unanimity about how this objective can be reached. With one strategy we seek to understand the mechanism by which cancer is caused, to identify by laboratory experiments those agents that might be expected, on the basis of that knowledge, to cause cancer in man, and then to eliminate them from the

environment or, at least, to minimize the extent to which man comes into contact with them. With another, we look at the variation in the incidence of cancer in different groups of people, seek to characterize the conditions that give rise to exceptionally high risks, and then seek to modify those conditions.

The first strategy has had so many successes to its credit in recent years that we may reasonably hope that it will not be long before we come to understand what the characteristic features of a cancer cell are, the way such features are produced, and the conditions that enable clones of cells developed from them to multiply disproportionately and to spread throughout the body. Such knowledge should eventually indicate whether the disease can be eliminated altogether or whether, as most suspect, we shall have to lower our sights and aim only at reducing its incidence. Meanwhile, this approach has provided us with a variety of tests for detecting agents that can alter DNA, cause cells in culture to behave like the cells of a malignant tumour, or produce tumours in laboratory animals.

The results of such tests correlate well with human experience, in the sense that one or more of them is nearly always positive when an agent has been found to cause cancer in man. It should be noted, however, that when such an agent is identified, efforts are made to demonstrate its carcinogenicity in the laboratory that are far more intensive than those that are normally made in the testing of agents for which no human evidence is available, and some of the agents evaluated as confirmed or potential human carcinogens would not have been detected by the normal execution of routine tests.

There is, nevertheless, good reason to hope that the use of laboratory tests will draw attention to many of the avoidable causes of human cancer that are still unknown, including both external agents and those that are synthesized *in vivo,* and their use should prevent the introduction into industry of new powerful carcinogens with the consequent production of occupational hazards. Quantitative prediction is, however, still very uncertain, and it is not possible to tell from the results of tests on cells how readily, within two or three orders of magnitude, an agent will produce cancer in laboratory animals, nor from the effect of tests on one species how readily, to the same degree of accuracy, it will produce cancer in another. Nor can it yet be presumed that qualitative prediction from one species to another is always certain, when the mechanism is not known by which a particular type of tumour is produced in the laboratory, the tumour is produced in peculiarly susceptible species, or the dose required to produce the tumour is grossly large.

The second, epidemiological, or (as Richard Peto has called it) 'black box', strategy has hitherto obtained the most important practical results, in the sense that it has first drawn attention to most of the risks that have so far been recognized as causing large numbers of cancers throughout the world. It has the great merit that when it does reveal a cause it also provides an indication of the size of the effect; but its scope is limited by the variation in human behaviour and human exposure, and we can hope to obtain useful information from it only when that variation is both large and consistent. It is of value as a complement to the first mechanistic strategy for four principal purposes:

(i) to demonstrate risks that have been overlooked or suggested only tentatively by laboratory tests,

(ii) to estimate the level of exposure that produces the highest additional risk of disease that is likely to be socially acceptable (whatever society may determine that to be),
(iii) to ensure that disproportionate resources are not devoted to problems that are likely to be minor to the neglect of others that are likely to be more important, and
(iv) to check the correctness of conclusions about the causes of cancer by monitoring the effect of their removal.

In this Symposium, we are concerned only with the second of these uses of epidemiology and then only in certain defined circumstances: that is, when the validity of extrapolating the laboratory evidence to man is open to question and when epidemiological observations exist that do not clearly demonstrate the existence of a human hazard. It should be noted, however, that the selection of agents for discussion was made in 1982 and further evidence may have accumulated since then. The fact that an agent is included in the programme should not, therefore, be regarded as evidence that the participants, nor even the members of the organizing committee, necessarily believe that it is safe for man to use. Its inclusion is evidence only that, at the time the Symposium was planned, the majority of members of the organizing committee thought that the laboratory evidence was insufficient to justify the belief that the agent necessarily caused a material human hazard in the doses that men and women had habitually received and that the human evidence of carcinogenicity was negative or open to question. It is possible, therefore, that as our discussion proceeds, individuals, or the participants as a whole, may conclude that evidence of carcinogenicity of one or other substance is now so strong that a human hazard must be presumed to occur, if indeed it is not regarded as proved. Alternatively, of course, they may not; and the interest of our Symposium rests in the type of conclusion that, for practical purposes, can then be reached.

ASSESSMENT OF LABORATORY EVIDENCE

As the programme has been arranged, we shall discuss first, for each agent, the laboratory evidence that suggests that it may present a carcinogenic hazard for man. Only very brief periods have been allowed for this part of our discussion, for two reasons: first, because it was thought that the results that had been obtained in the laboratory were reasonably clear and that, although their implications for man might be open to doubt, the facts were not; and, secondly, because most of the participants in the Symposium are epidemiologists or statisticians. It is hoped, therefore, that the laboratory evidence can be presented concisely and that it will not give rise to controversy.

Such laboratory evidence may be unequivocal or it may be complex and internally variable and it is difficult to classify it into categories with clearly different implications for extrapolation to man. The IARC has taken a lead in trying to define such categories and classified positive evidence for carcinogenicity as being either 'sufficient' or 'limited' (IARC, 1982); and this may be the best that can be done in our present state of ignorance. With the empiricism that toxicologists are accustomed

to, chemicals with 'sufficient' evidence for carcinogenicity have generally been accepted as posing a potential hazard to man, even in the absence of detailed knowledge of the mechanism by which they exert their effect, while chemicals with 'limited' evidence are thought to require further study before any such conclusion can be drawn. More recently, however, it has come to be realized that carcinogens with 'sufficient' evidence for carcinogenicity may act by different mechanisms and that even for these substances reasons may be found that make extrapolation from one species to another inappropriate.

It seems, therefore, that experimental toxicological data on carcinogenesis can forewarn us of potential hazard to man, but that our final decision must rest on a full assessment of our total knowledge, including that derived from human observations and the economic, sociological and ethical features of society.

ASSESSMENT OF EPIDEMIOLOGICAL EVIDENCE

Limits of usefulness

It is commonplace in logic that it is never possible to prove a hypothesis, only to disprove it, unless, of course, the hypothesis can be shown to be tautologous, as in mathematics. In practice, however, we are prepared to act as though biological hypotheses are true when they have been supported by experiment, and we confidently predict effects from our presumed knowledge of the mechanism by which they are produced and the way in which the agents act. We accept, too, for practical purposes, that epidemiological evidence can be strong enough, even when it is only circumstantial and no experiment has been carried out, to justify the conclusion that an agent is a cause of disease. If then, the agent is removed and the disease disappears (or, more likely, is reduced in incidence), few scientists think it worthwhile to argue whether or not a causal relationship has been established—unless, of course, some new evidence is obtained that casts doubt on the conclusion.

Whether epidemiological evidence, or any other type of evidence, can ever be said to show that an effect is *not* produced is not, I suggest, a very different matter. In theory, it cannot be done; in practice, we do it every day. Proof of absence of an effect by epidemiological means (in this practical sense) is, however, very much harder to achieve than proof that an effect *is* produced, particularly, perhaps, in the case of cancer, which has many causes and may not be produced by a particular agent in detectable amounts until several decades after exposure has occurred. Doll and Peto (1981) summarized their position as follows:

'Unless epidemiologists have studied reasonably large, well-defined groups of people who have been heavily exposed to a particular substance for two or three decades without apparent effect, they can offer no guarantee that continued exposure to moderate levels will, in the long run, be without material risk. For this reason prudent restrictions on occupational or public exposure to various substances often have to be based on indirect inference from laboratory studies of the agent being examined, without any direct evidence concerning its actual effect on humans. That is not to say that human evidence can ever be dispensed with. It is always relevant, but the weight that can be given to it varies greatly with the duration and intensity

of the exposure experienced.... Negative human evidence may mean very little, unless it relates to prolonged and heavy exposure. If, however, it does and is consistent in a variety of studies (correlation studies over time, cohort studies of exposed individuals, and case-control studies of affected patients), whereas the laboratory evidence is limited in scope to, for instance, a particular type of tumour in a few species, negative human evidence may justify the conclusion that for practical purposes the agent need not be treated as a human carcinogen. In practice it is, of course, not usual for such perfect negative evidence to be available, but even less conclusive negative human evidence may help determine priorities between different lines of action.'

Combination of data

To this I should like to add, for the purpose of this Symposium, only three comments. First, I should have thought that the statement that human evidence is always relevant and can never be dispensed with, if available, was non-controversial, were it not that the Occupational Safety and Health Administration (1980) in the USA sought to lay down criteria for the admissibility of evidence that tended to show the lack of an effect. These criteria were that the data should refer to groups of subjects who had had at least 20 years' exposure, had been followed for at least 30 years, and were numerous enough for a 50% increase in the predicted type of cancer to be statistically significant. Such data would certainly carry substantial weight, but the exclusion of all other data would be unwise. A laboratory investigator can be advised to use so many animals, to test so many species, to treat at so many levels of dose, and to observe for a minimum length of time, as all these conditions are under his personal control—subject only to the constraints of finance and the availability of personnel. It is, however, unproductive to lay down similarly rigid rules for the epidemiologist, as experiments cannot be repeated and the conditions of the experiment are not under the epidemiologist's control. In practice, we can seek to overcome the deficiencies of one set of data only by combining it with sets from other sources, and any set that would be capable of showing a positive effect is worth considering. Indeed, it *must* be considered, if one is to avoid the trap described by Gaffey (personal communication), in which a positive effect is accepted because it appears in one set of data at the 1 in 20 level of significance, while 19 similar sets are exluded because they fail to satisfy more stringent requirements for the submission of negative results.

From what we know of the induction of cancer, it would be reasonable to require all sets of data to be set out in such a way as to show separately the results of observations made more than 10 years after first exposure, irrespective of whether this showed positive or negative results; but it would be unwise to exclude automatically even the first 10 years' data. In some circumstances, these could be crucial; as, for example, when examining the safety of an immunosuppressive drug that might replace azathioprine in the treatment of patients receiving renal transplants. The only safe rule is to consider the totality of the evidence, making sure, however, that it is set out in such a way that conclusions can be drawn about the presence or absence

of effects for different durations of exposure, at different periods after exposure first began, and for different levels of dose.

Negligible risks

Secondly, I should like to echo the conclusions of a Royal Society (1983) Study Group that some induced events are 'of so low a frequency that the manager or regulator of risk can reasonably regard them as negligible in their overall impact on society, even though the consequences to the rare individual may be serious'. What this frequency should be is not easy to decide and almost certainly should be allowed to alter depending on the nature of the risk, its origin, and society's perception of it (which is, at least in part, subjective). It is, in any case, a matter for society itself to determine and not for the epidemiologist, whose job it is to calculate the risk and to explain what it means in practical terms. To help society reach a practical solution, the Study Group suggested that imposed risks can legitimately be treated as trivial at the point at which individuals, who are aware of the risks, would not commit significant resources of their own to reduce them. This, however, is a difficult point to assess, because so few people are conscious of the magnitude of small risks, and have little opportunity to demonstrate their preferences. To quote the Study Group's report again, 'There may be a wide spread of individuals' views... and decisions are likely to leave some people feeling they are exposed to risks calling for further control. There is a widely held view, though perhaps better described as speculation, that few people would commit their own resources to reduce an annual risk of death to themselves that was already as low as 10^{-5} and that even fewer would take action at an annual level of 10^{-6}... while the manufacturer of a product might for the sake of his good name seek to keep the numbers of possible deaths very low, not all the inhabitants of the country will buy his product, and so... the figure of 10^{-6} is probably still appropriate, except perhaps if clear causal links are established in the risks from certain consumer products. In such circumstances we would consider 10^{-7} to be an annual level below which further control was certainly not justified, but even then the further problem of the very salient situation... may well remain.'

Estimates of risk

Thirdly, we need to consider whether we are going to pay more attention to the best estimate of a risk or to its upper or lower confidence limits. Both types of evidence are, of course, relevant, but we should, I suggest, give different emphasis to each depending on our prior hypothesis. When our data point to an unsuspected risk, we have all been accustomed to paying the greatest attention to the lower confidence limit to see whether the absence of an effect is plausible, and we shall want to pay similar attention to the upper confidence limit in the opposite situation in which the prior evidence suggests that a risk is likely to occur and we have failed to find it. When however, the prior evidence is inconclusive and has served only to stimulate enquiry, we should, I believe, make up our minds whether to postulate a risk on the totality of the evidence and then, if we do, put the greatest emphasis on the best estimate that

we can make, modifying our confidence in it appropriately by knowledge of the width of its confidence limits.

Categories of evidence

The data that we shall be considering in the next three days will present many problems and will, I suspect, often provide exceptions to the general rules that I have tried to consider. They will not be solved by voting, but by the accumulation of experience and the conduct of experiments—if, indeed, they are ever solved at all. It would, however, help to decide what sort of evidence is needed in different situations if we were able to classify the existing human evidence (with no more than two or three dissentients) into one or other of the following five categories. They may not meet all eventualities, but they can be regarded as guides to the sort of conclusion that could be reached with respect to individual agents.

1. Evidence that supports the idea that the agent is carcinogenic to man
2. Evidence that is inadequate in quantity or quality to justify any useful conclusion
3. Evidence that is inadequate to permit a firm conclusion, but which suggests that the agent is unlikely to have produced a quantitatively large increase in risk under the conditions of exposure that have operated in the past
4. Evidence that weighs against the possibility that the agent is carcinogenic to man; but is not strong or consistent enough to outweigh laboratory evidence of carcinogenicity, even though the laboratory evidence is of doubtful generality
5. Evidence that weighs against the possibility that the agent is carcinogenic to man so strongly that one can either:
   (a) disregard, for practical purposes, laboratory evidence of doubtful generality; or
   (b) set a very low upper limit to the human risk produced by the conditions of exposure that have operated in the past if, on the basis of laboratory evidence, the agent must be presumed to be potentially carcinogenic to man.

If an agent is classed in category 3 or 4, it may be thought that the evidence is strong enough to justify waiting before any drastic action is taken, so long as arrangements can be made to obtain further human evidence that would ensure that even a small risk (should one exist) will eventually be detected.

The use of categories such as these has never been discussed by the International Agency for Research on Cancer and is not, of course, in any way a reflection of the Agency's policy. They represent a first attempt to deal with the problem of assessing the significance of 'negative' epidemiological evidence. They were found helpful by the participants in the discussion that followed, but remain the responsibility of the author.

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