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Co-carcinogens and man

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Separatum

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CO-CARCINOGENS AND MAN

There is a danger that the experimentalist, behind the barricades of impressive measuring instruments and in the habitat of a research building, will lose sight of the human problems of cancer that are the real reasons for his work. At the same time it is easy for a clinical cancer consultant to leave himself too little time to keep pace with what research workers are doing, and, because he does not understand their work, come to regard it as irrelevant. The purpose of the present discourse is to improve understanding between the clinician and the research worker in relation to cancerous disease.

The ultimate aim of most of my research work has been the prevention of cancer in man. This tends to bring me into contact, not so much with clinicians concerned with the treatment of cancer, but with manufacturers of agricultural chemicals, food additives or drugs, with government officials who draw up legislation concerned with the use of such substances, with factory doctors and occupational hygienists, and with epidemiologists. Clearly established cancer cannot be prevented: prevention can only apply to disease that is not already present. There are good reasons to believe that there is usually an interval of 15 to 50 or more years between the first exposure of man to carcinogens and the development of overt cancer. This long interval inevitably separates the cancer-preventist and the cancer-therapist in the way they think about the disease and the emphasis that they feel should apply to different aspects of cancer research.

A proper assessment of the human problem is a first requirement in any approach to the prevention of cancer. The pathologist must classify cases of the disease into meaningful sub-categories. Different pathologists must be persuaded to use a uniform classification. The epidemiologist must then calculate the incidence of each form of cancer in each sex and for each age group. Even these basic requirements are difficult to fulfil; in particular, low autopsy rates and lack of histopathological confirmation reduce the accuracy of the data available.

In the light of this basic information a search for causative factors may follow one of two courses. Epidemiological methods may be used to look for an association between exposure to genetic or environmental factors and the development of particular forms of cancer, or a search may be made by the experimentalist for agents that cause cancer in experimental animals under conditions that imitate human exposure. A suspicious or positive finding in either experimental or epidemiological studies usually prompts a parallel investigation in the other discipline.

These comments apply to the search for causes that contribute to the existing human cancer burden. Another important aspect of cancer prevention is the screening of chemical substances before they become part of the human environment in the form of pesticides, food additives, or agents associated with newly introduced industrial processes. It is with this special aspect of cancer prevention that the following remarks are primarily concerned.

Thirty years ago, Shear (1938) introduced the term "co-carcinogenesis" to refer to a fraction of coal tar which, though not carcinogenic itself, enhanced the carcinogenic activity of another fraction of the tar for the skin of experimental animals. In the 1940's Rous and his colleagues and Berenblum and Shubik, introduced the two-stage concept of cancer induction, according to which cancer might be induced by sequential exposure to a tumour-initiating agent and a tumour-promoting agent, in that order but not in the reverse order. For a while, thereafter, the terms "co-carcinogen" and "tumour-promoter" were used almost interchangeably, and there was a tendency to think that tumour-promotion was a discrete and definable process, possibly definable in terms of specific changes at the cellular or molecular level (for reviews see Salaman, 1958; Salaman and Roe, 1964). However, it is now quite clear that this is not the case: carcinogenesis may be enhanced by a wide variety of quite different mechanisms. Making the position even more complex and confusing is the fact that, under certain circumstances, potent carcinogens may act as co-carcinogens (Roe and Rowson, 1968). Potent chemical carcinogens may under certain circumstances, act with oncogenic or facultative-oncogenic viruses to induce cancer (e.g. Ahlström and Andrewes, 1938; Duran-Reynals, 1957; Rowson et al, 1961; Tanaka and Southam, 1965) but the types of cancers that arise and their time or appearance are either typical for causation by the virus or typical for causation by the chemical carcinogen, and in many cases, the role of the other factor can be fulfilled by various non-carcinogenic agents. The induction of malignant lymphoma in mice by oestrogens, X-irradiation, the administration of

chemical carcinogens, or adrenalectomy, preceded the knowledge that a group of oncogenic viruses are intimately involved in the causation of the disease. It may well be that the day will come when it is considered absurd to regard natural oestrogens as " carcinogenic ". Although at the present time no-one would refer to the effect of adrenalectomy on the incidence of malignant lymphoma in the mouse as " carcinogenic ", undoubtedly many chemical agents that do no more than adrenalectomy does in relation to lymphoma induction are widely regarded as " carcinogens ". In other words, if in an animal experiment, exposure to substance X results in tumour development, or in an increased incidence of tumours of a particular type, it is impossible without further information to know whether the observed effect is due to the direct carcinogenicity of X or to its acting co-carcinogenically with a virus, a genetic factor, or another environmental agent.

Because the list of agents that have been called " carcinogens " is so long, and their variety so diverse, legislators have, understandably, so far refused to consider the implication for man of agents referred to by experimentalists as " co-carcinogens ". In my view, however, it is because the situation is complex, and because there is the constant possibility of confusion between the two types of activity that discussion of the significance of co-carcinogenic factors in the human environment should no longer be deferred. Failure to consider co-carcinogens carries twin dangers: firstly man may be exposed to co-carcinogens, the effects of which are just as serious in terms of increased incidence of cancer, as those for exposure to a carcinogen. Secondly, unless some attempt is made to distinguish between the two types of activity in the course of animal experiments, whole groups of potentially useful agents may be banned from the human environment because, under certain, special conditions, they enhanced cancer development co-carcinogenically in a laboratory animal species. The list of chemical agents now branded as " carcinogens " is long and growing longer. In years to come the categorisation of agents (especially pesticides and food preservatives) as carcinogens on inadequate grounds — perhaps, without any knowledge of the mechanism involved — could prove to be a serious bar to human progress.

Isonicotinic acid hydrazide (INAH) has saved hundreds of thousands of tuberculosis patients from prolonged suffering and the possibility of early death from the disease. Several groups of workers, but notably Dr. Biancifiori and Professor Severi in Perugia (Juhasz

et al, 1957; Biancifiori and Severi, 1966), have shown that the administration of the drug induces tumours of the lung, liver and lymph glands in mice, and mammary tumours in rats. It would be unthinkable to withdraw this life-saving drug from the clinic because of these results, though the results are certainly worrying enough for one to advise caution in the use of INAH especially to children for purely prophylactic purposes (Roe, Boyland and Haddow, 1965). Fortunately, there is no evidence that INAH induces cancer in man (Hammond et al, 1967) though lack of evidence may reflect no more than that the minimum induction for cancer development since INAH came into widespread use has not yet elapsed. In the meantime, we urgently need to know the mechanisms involved in the induction of cancer in mice by the drug — is this an example of carcinogenicity or co-carcinogenicity? If the latter, is the manifestation of this co-carcinogenic activity dependent on conditions peculiar to the mouse and rat? The conspicuous failure so far (e.g. Peacock and Peacock, 1966), to induce tumours with INAH in species other than the mouse and rat leads one to suspect (— and to hope —) that the activity is co-carcinogenic and dependent on species-specific conditions.

Mineral oils of the types responsible for mule spinners cancer in cotton workers in Lancashire during the latter part of the 19th century and the first half of the 20th, contain both carcinogens and co-carcinogens (Roe et al, 1966, 1967; Horton et al, 1957). It has recently become a matter for concern that certain sulphur-containing additives may markedly enhance the overall carcinogenicity of the oil (Horton et al, 1965). Harington (1965) and Harington and Roe (1965) suggested that the carcinogenicity of asbestos may depend on the fact that it readily absorbs carcinogenic polycyclic hydrocarbons on to its surface. The latter may be present in oils associated naturally with asbestos, or in oils used in the manufacture of jute bags in which asbestos in stored (Roe et al, 1966, 1967). In other words, it is possible that asbestos is not itself carcinogenic but acts as a carrier of carcinogens.

Retention of asbestos fibres in the lung after inhalation is thus associated with retention of adsorbed carcinogens. In Moscow, Shabad and his colleagues (1964) have found that whereas it is not easy to induce lung cancer in rats by the intratracheal instillation of 3,4-benzopyrene alone, the same amount of BP mixed with carbon black particles on which it is adsorbed is a potent inducer of neoplasms of the lung. Saffiotti has obtained similar results in experiments with BP and haematite dust in hamsters (Saffiotti et al, 1964) and Yasuhira (1967) has done so with 20-methylcholanthrene and Freund's adjuvant in rats. The role of asbestos in relation to the induction

of bronchial carcinoma and mesothelioma in man may, therefore, be one of co-carcinogenesis. A recent report by Selikoff and his colleagues (1968) provides support for this view. In their study of 370 asbestos insulation workers in New York, they have seen 24 cases of lung cancer among 283 regular cigarette smokers, and not a single case among 87 non-smokers. It may be, therefore, that asbestos is not carcinogenic on its own but enhances carcinogenesis by cigarette smoke by providing surfaces on to which BP and other carcinogens present in tobacco smoke may be adsorbed. Alternatively, pulmonary fibrosis associated with asbestosis may prolong the retention of tobacco carcinogens in the lungs.

Basic to all I have said is the need for a new definition of carcinogenesis. Ideally one would like to be able to define carcinogenesis in terms of events at the molecular level. This is not yet possible, partly, perhaps, because little attempt has been made in the case of many seemingly weak carcinogens to study the mechanisms involved. Personally, I would be very reluctant to regard a chemical agent as carcinogenic unless it was fairly clear that it could induce changes in the nucleic acids of cells. Perhaps the day is not too far off when simple quick but reliable in vitro techniques are available for distinguishing true carcinogens by their reaction with nucleic acids. Our main preoccupation will then become with co-carcinogens and with the protean mechanisms by which they may act.

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