The Role of Experimental Research in the Study of the Prevention of Malignant Tumours

L. M. SHABAD

The author discusses the role of experimental oncological research in the prevention of malignant neoplasms, with special reference to the conclusions drawn from such research in the USSR. He points out that experimental research can contribute to cancer prevention in two ways: (a) by supplying information on the occurrence of carcinogenic substances in the human environment—in the atmosphere, in industry and in foodstuffs—and thus providing a rational basis for the introduction of measures to prevent cancer from arising; and (b) by throwing light on the series of tissue changes that may precede the development of the malignant tumour and hence making it possible, through the timely treatment and cure of known precancerous conditions, to prevent cancer from developing.

In order to prevent cancer it is essential to know its causes. There is no doubt that experimental research plays an outstanding role in the study of the etiology and pathogenesis of tumours, and experimental oncology may therefore serve the cause of cancer prophylaxis. However, it is not enough merely to assert the fact. It seems to us that it has now become both possible and necessary to outline certain definite methods of preventing malignant tumours and that in this respect experimental oncology has an absolutely determinate and important task to perform. In this paper, an attempt will be made to demonstrate this on the basis of some examples taken mainly from the work of the author and his colleagues.

In our opinion, there are two lines of approach to the prevention of malignant neoplasms:

1. Preventing cancer from arising ("hygienic" prophylaxis);
2. Preventing cancer from developing ("clinical" prophylaxis).

"CLINICAL" PROPHYLAXIS

To begin with the second of these lines of approach, clinical prophylaxis, it was noted long ago, at least in regard to cancer of the skin and lower lip and some other forms, that cancer is not of sudden occurrence but is merely the last link in a long chain of changes developing over a comparatively lengthy period. On the basis of these observed facts, the idea of pretumoral changes and of precancer took root in clinical medicine.

There is still much that is obscure in the concept of precancer. At the same time, much has become clear through experimental cancer research, which has made it possible to study, step by step, systematically and on the basis of extensive material, the course of development of malignant tumours in different organs in various animals, and to give concrete meaning to the term "precancer".

Material has been accumulated over many years in our laboratory on the experimental study of precancer in various animals. The development of cancer of the skin, lungs, stomach, pancreas, liver, kidneys, thyroid gland, mammary glands, uterus, ovaries, testes, prostate and seminal vesicles, etc. has been investigated from this point of view and changes have also been described for which, in our opinion, "presarcoma" would be a suitable name.

Firm experimental establishment of the fact that precancer possesses certain regular features is an encouragement to diligent search for precancerous conditions in human pathology and to their thorough study. Such instances are meant as the relationship of adenocarcinoma of the stomach or rectum to adenomatous polyps, or of mammary-gland cancer to proliferative fibroadenomatosis or fibrocystic disease of the breast with proliferation of the epithelium, or of cancer of the uterine cervix to non-healing pseudoerosions (changes that resemble erosion only

---

1. Member of the USSR Academy of Medical Sciences; Head, Department for the Study of Carcinogens, Institute of Experimental and Clinical Oncology, USSR Academy of Medical Sciences, Moscow.
Several stages can be distinguished in the development of cancer.

The first of them is a characteristic diffuse, uneven and irregular hyperplasia which differs from inflammatory or regenerative hyperplasia and is functionally and morphologically distorted. This can be seen from the lack of correspondence between the morphological manifestations and the functional condition. A clear example is the diffuse hyperplasia of the mammary-gland epithelium in male rats, or in virgin female rats without lactation, induced by the administration of large quantities of oestrogens. This type of epithelial change can be regarded as a pathological neoplastic variant of the process of which the physiological prototype is the hyperplasia of the mammary-gland epithelium during lactation.

The second stage in the development of malignant tumours, in our opinion, is that of focal and nodular proliferations, differing from the surrounding tissue only in that their general structure and component cells are to some degree atypical. As our research has shown, such proliferations may possess their own stroma.

The third stage in the development of cancer is that of the so-called “benign” tumours—papillomas, adenomas, etc. Experimental research has demonstrated with particular clarity that the benignancy of such tumours is only relative and that it is very often possible that they will develop into cancer. At the same time, it should not be forgotten that there is a possibility that a malignant tumour will arise from a nodular precancerous proliferation direct, that is, without passing through the third stage of development of the process.

The fourth—and final—stage in the process is cancer itself—the malignant tumour.

The stages in the development of cancer mentioned above can be discovered, as a rule, in all forms of induced cancer subjected to sufficient study. However, it is not always possible to establish exactly the boundaries between the stages since they merge into one another, being parts of a continuous process.

Numerous experiments carried out by Monastyrskaya (1952), Prokofyeva (1952) and other colleagues of ours have shown that inflammation does not promote the development of cancer and is not an obligatory stage in the phenomena leading to it; in other words, it is not of precancerous significance. Carcinogenic hydrocarbons inhibit inflammation, distort its character and destroy the interrelationships between the epithelium and the connective tissue (Vasilyev, 1959).
Cancer and inflammation are different pathological processes and this in itself is enough to indicate that inflammation is not significant as a precancerous sign. This does not mean, of course, that a combination of the two processes cannot occur in a number of cases. Recently, in our laboratory, cancer of the lungs was induced in rats by intratracheal administration of large doses of 9,10-dimethyl-1,2-benzanthracene (Pylev, 1961). In this instance, the precancerous changes developed in some cases from bronchiectases with chronic inflammation, while in other cases they had no connexion with inflammatory foci. Thus, although cancer may sometimes occur against a background of inflammation or its after-effects, this does not mean that inflammation plays a role as a precursor of cancer.

In assessing the role of inflammation in cancer it is useless to speak in general terms. It is essential to determine the exact significance that may be attached to a particular form of inflammation at particular stages in the induction, development and progression of the tumour. At the same time, account must be taken of differences in the form and site of different neoplasms. The multiplicity of neoplasms presupposes a multiplicity of possible interrelationships between cancer and inflammation.

Thus, for example, while inflammation is not an essential link in the chain of phenomena leading to cancer, its presence at the period when proliferation of the cancer cells has already begun may play an important role. In some cases, perifocal inflammation may further the growth of the tumour and the formation of its stroma, giving tumour-growth mechanical and nutritional support, as was shown, for example, in the experiments of Vasilyev (1958). In other cases, inflammation may further the breakdown and destruction of at least part of a tumour, as is often seen in clinical practice when tumour tissue suppurates and undergoes liquefactive degeneration.

From the morphological point of view the name "precancer" could be given to microscopic multicentric and often multiple foci of non-inflammatory, atypical proliferation of immature epithelium (or fibroblastic or osteoid tissue in the case of pre-sarcoma) with a tendency to infiltrative growth but without, as yet, destruction of the tissue. The name "precancer" in the narrow sense of the word should be given to these focal proliferations and so-called "benign" tumours, which particularly often and directly turn into cancer. The diffuse, uneven, irregular hyperplasia of tissue which precedes focal proliferations but is not precancer in the strict sense of the word may, nevertheless, be considered as a pretumoral change.

Thus, in our interpretation, the concept of precancer is made narrower and more concrete. In our opinion it is better to reproach for confusing the notion of precancer with the beginning of cancer than to allow the concept to be loosely used for a mass of non-specific changes, so-called "background processes", various precursive diseases, etc. In our view non-specific changes of this type, preceding or accompanying cancer, should not be considered as precancer, a term that should be reserved for defining the beginning of the onset of cancer.

The various pretumoral changes, like benign and malignant tumours themselves of course, may progress at different rates. Thus skin papillomas induced in mice by painting the skin with carcinogenic hydrocarbons usually grow considerably more slowly if the carcinogen is given in a small dose or at a low strength. The reverse is true when considerable doses of strong carcinogens are applied. Thus it is possible, to a certain extent, to regulate the rate of development of precancerous changes experimentally.

Precancerous changes may not only be halted in their development, as has just been mentioned, but may disappear altogether. The possibility of the disappearance of manifest precancerous changes can easily be demonstrated by careful observation of skin papillomas induced in mice by means of carcinogens. It is a matter of general knowledge that the number of papillomas occurring at the site of painting is considerably greater than the number of cancerous tumours that develop there. This state of affairs is due to the disappearance of individual papillomas as well as to their confluence.

Thus diffuse hyperplastic changes and even precancerous focal proliferations may disappear altogether. Pretumoral and precancerous changes may not develop into cancer. This indicates the conditional nature of the very concept of precancer. The possibility that what is known as a "spontaneous cure" of precancer may occur has very important implications for its successful rational treatment.

At the same time, it is quite clear that the prompt cure of precancer represents a very considerable step towards cancer prophylaxis. The idea of the process of tumour development as a single pathological process, passing through a number of stages
and phases, makes it possible, by eliminating one stage or phase, to interrupt the whole process. Thus we see that experimental cancer research, by giving a practical foundation to the precancer concept, has paved the way to the prevention of the development of cancer from precancerous and pretumoral changes. The concept of precancer, which arose in clinical practice and has now been checked experimentally, returns to clinical practice enriched by many facts. At the present time it is far from having merely a theoretical interest; it is of great practical importance in both the individual and the mass prophylaxis of cancer.

In ordinary clinical practice a number of such pathological phenomena as papillomas and adenomas of various kinds, various focal proliferations of the epithelium, hyperkeratoses, etc. are now regarded not merely as "benign" tumours, but also as a possible stage on the road to cancer, and are consequently subjected to radical treatment. Thus, individual clinical cancer prevention is being practised every day.

Mass clinical prophylaxis against the development of tumours has become possible as a result of the prophylactic medical examination of wide sections of the population, and particularly of special groups exposed to particular carcinogenic factors. Thus clinical cancer prophylaxis comes into contact with "hygienic" prophylaxis, the problems of which will now be discussed.

"HYGIENIC" PROPHYLAXIS

Possible methods of preventing the occurrence of any disease are evolved as a result of a thorough study of its etiology. The more that is known of the causes of a particular disease, the greater the possibility of eliminating it. At the present time the etiology and pathogenesis of tumours have not been fully elucidated, but the facts accumulated nevertheless make it possible to indicate ways of preventing the occurrence of tumours. These ways are based on the concept that blastomogenous agents exist which may act upon man, a concept that arose as a result of observations of what are known as occupational tumours.

In the workers in some occupations particular forms of tumour are encountered more frequently than in the ordinary population of their district. Thus, as long ago as 1775 the well-known English doctor, Percival Pott, described cancer of the skin in chimney-sweeps, localized in most cases in the region of the scrotum, the penis and the thighs, that is, in places subjected to the greatest contamination with the products of the distillation of coal. It will be remembered that at that time boys climbed up inside the chimneys in order to clean them.

"Consumption" of miners in the Schneeberg in Saxony and at Jachimov in Bohemia had also been known for a very long time. It has proved to be an occupational cancer of the lungs caused by radioactive substances.

At the end of the last century observations were published on the very high frequency of bladder cancer in workers in aniline-dye factories in Switzerland and Germany. Later, cases of this type of bladder cancer were described in all countries of the world where the industry existed, and it was established that its occurrence was connected with certain chemical substances—β-naphthylamine, benzidine, dianiisidine, etc.

At the beginning of the twentieth century, some years after X-rays and other forms of radiation had begun to be extensively used in medicine and industry, reports appeared of cases of occupational cancer occurring amongst radiologists as the result of excessive irradiation without proper protection. Malignant tumours of the jaws, observed in the United States of America among women painting luminous watch dials, were caused by the action of radioactive salts.

In the twenties in Great Britain, occupational cancer of the skin was reported as occurring among mule-spinners, who leaned with part of the body against machine parts abundantly lubricated with shale oils.

At the present time a considerable number of forms of occupational tumours have been described. The examples quoted are enough to show that there are forms of tumour in man whose causes are known. The elimination of those causes or even a reduction in the amount of the harmful agent will help to prevent the tumours. It should be emphasized that all known observations of occupational cancer and all the vast amount of experimental material gained from the study of carcinogens shows that the growth of tumours depends to a large extent on the dose of the blastomogenous agent. The smaller the dose, the smaller the number of people or animals in whom cancer develops and the later its onset. Therefore, not only the complete elimination but even some reduction in the quantity of blastomogenous substances to which man is exposed is a way of preventing tumours. Nowadays chimney-sweeps' cancer, radiologists' cancer and
some other forms of occupational cancer have practically disappeared as a result of changes in working conditions, the introduction of new industrial techniques, protective measures and measures of personal hygiene, which have helped to eliminate the effect on the organism of blastomogenous agents. These facts show that cancer prophylaxis is in principle a possibility.

The study of occupational tumours naturally led to extensive experimental research on the carcinogenic effect of various chemical substances that were suspected of causing various types of occupational cancer. A great deal of modern experimental oncology has developed from such research and very many facts have been discovered that can be used for cancer prophylaxis.

Thus, during the period when cancer was being induced experimentally by painting the skin of animals with coal-tar, a large number of different tars, pitches, bitumens and mineral oils obtained from various sources and produced by various methods were investigated. It was discovered that a particular product may differ in its carcinogenic effect. For example, when various Soviet shale tars were investigated by my colleagues and myself (Larionov, Soboleva & Shabad, 1934), it was found that some of them induced many more tumours than others. The same applies to some mineral oils and to the “coolants” used in the engineering industry (Prokofyeva, 1938; Verkhovskaya, 1941). The work of Bogovski (1960) showed that different shale products from Estonia had differing degrees of carcinogenic effect. On the basis of these data it is possible in a number of cases to substitute a slightly carcinogenic product for a highly carcinogenic one.

Differences in the carcinogenicity of coal-tar and other tars, and the possibility of substituting a less dangerous product for a dangerous one, are of great topical interest in many fields—for example, in evaluating various building materials from a hygienic point of view, in building roads, etc. In the USSR regulations are in force under which the bitumens used for road surfacing in inhabited places must contain a considerably smaller quantity of blastomogenous hydrocarbons than coal-tars (Malyugina, 1955).

At the present time the question is being raised of “decarcinogenizing” industrially important tars—that is, eliminating their carcinogenic properties. It can be considered as proved that this process is theoretically possible (Danetskaya, 1952; Bogovski, 1960).

Since the discovery of chemically pure carcinogenic substances, a number of facts that can be used for cancer prophylaxis have come to light as a result of experimental study. Several research schemes of this kind have been carried out in our laboratory. Thus Kleinenberg (1939) showed that while 3,4,8,9-dibenzopyrene is a strong carcinogen, its quinone, which is the basis for one of the dyes used in the textile industry, does not induce tumours. Recently, Pliss (1959), by systematic research on a number of benzidine derivatives, has demonstrated the highly carcinogenic properties of 3,3′-dichlorobenzidine. Oral administration or subcutaneous injection of this substance in rats and mice caused various malignant tumours, often multiple, in about 80% of the rats and 40% of the mice. Both at the site of the hypodermic injection (sarcoma) and at some distance from it (cancerous tumours of the mammary glands, the sebaceous glands and the liver, papillomas of the bladder, etc.). Other work by Pliss (1958) has shown the comparatively slight, but undoubted, carcinogenic activity of dicyclohexylamine and its nitrite.

It is impossible to dwell at greater length here on individual pieces of experimental research that have provided facts which can be used for tumour prophylaxis. One general proposition, however, may be stated.

In view of the fact that the chemical industry is continually producing a large number of completely new substances with which people will sometimes come to be in close and lengthy contact, both at work and in the home, and that ever-increasing quantities of new chemicals are being used in agriculture, the food industry, cosmetics production, etc., the question arises of whether the new substances may not include products with blastomogenous activity. Early testing of such new substances in animal experiments is an important task. It should be remembered that the latent period of development of a tumour, according to our data, is equal to about one-fifth of the longest life-span, thus constituting 15-18 years in man but only about 6 or at the most 12 months for the laboratory mouse or rat, which has a life-span of not more than 2½ years. Thus it is possible to detect blastomogenous properties in a particular substance experimentally long before it manifests its effect on people.

So far it is mainly questions connected with harmful occupational factors that have been dealt with. This is natural because, historically, observation of occupational tumours led to experimental
study of carcinogens. Systematic research in animal experiments on the possible carcinogenic effect of a number of new products of the chemical industry is undoubtedly of assistance in evolving measures to prevent occupational cancer. However, if somewhat more profound consideration is given to the possible results of such work, it will be realized that they range far beyond the mere control of occupational hazards. Harmful blastomogenous factors may develop from occupational factors into general environmental factors, affecting large numbers of the people and not merely a restricted group of workers in the branch of industry concerned. This may happen in the case of many products of the aniline-dye industry and many other dyes. For example, at one time a colouring agent known as "Buttergelb" or "butter yellow" was, in a number of countries, added to foodstuffs, particularly butter, margarine, flour and macaroni; this agent was none other than dimethylaminoazobenzene, a carcinogenic substance that induces liver tumours in rats and mice, as was established by Kinosita as long ago as 1937.

Among the numerous dyes and all the various preservatives used in the food industry today there may still be substances with possible blastomogenous activity. It is no accident that, as mentioned later, a number of special international conferences have been devoted to this problem.

Another example of the transformation of an occupational factor into a general environmental factor is the classic case of chimney-sweeps' cancer. There is no doubt that this form of occupational cancer was caused by the products of fuel combustion: tars, soot, and smoke. Now smoke from house and factory chimneys still enters the atmosphere. Consequently, it naturally springs to mind that the atmosphere may be polluted with carcinogens, particularly those carcinogenic hydrocarbons contained in coal-tar and similar products. The wonder is not that such pollution does actually occur, but that it has only recently been proved to occur by means of the modern, precise methods of spectral fluorescence analysis.

About ten years ago, the author and a group of co-workers began a systematic study of atmospheric pollution with the powerful carcinogen 3,4-benzpyrene, and established that it was present in the air of a number of Soviet cities (Gurinov, Zore, Ilyina & Shabad, 1953). Later, many facts were accumulated in extensive research by a number of Soviet workers concerning the quantitative distribution of 3,4-benzpyrene in various cities and various districts of the same city, and the relationship between this pollution and many sources of contamination of the human environment with 3,4-benzpyrene (Shabad & Dikun, 1959).

Details of the study of atmospheric pollution with carcinogens need not be given here; the question is now attracting the attention of many research workers and has obviously already become a recognized feature of general and municipal hygiene and experimental oncology. Only one aspect of the matter needs emphasis here—the possibility of carrying out successful campaigns against such pollution and of preventing the discharge of 3,4-benzpyrene into the air or considerably reducing the quantity so discharged. This is a matter of taking a number of technological and sanitary-engineering measures to improve the conditions of fuel combustion and to trap the fumes discharged. Rational town-planning and the large-scale use of district heating and electrification are also of great importance. A special investigation carried out by Dikun & Nikberg (1958) in the neighbourhood of a coke-and-pitch factory of an obsolete type in the city of Makeyevka showed that, after the design of the coke ovens had been improved, there was a sharp reduction in atmospheric pollution with 3,4-benzpyrene. Comparative studies of snow samples in two neighbouring cities of Siberia—Irkutsk and Angarsk—showed that in the new, properly planned town of Angarsk, where the residential quarters are separated from the factory districts by a green belt and are served by a district-heating plant, only very small quantities of 3,4-benzpyrene were found, whereas in the old city of Irkutsk the air contained quantities of the pollutant equally as large as those present in other big industrial cities (Shabad & Dikun, 1959).

The study of atmospheric pollution with 3,4-benzpyrene is of great interest in connexion with the problem of lung cancer. It is now generally recognized that the frequency of lung cancer has greatly increased. Many workers (including ourselves) consider that one of the reasons for this increase in the incidence of lung cancer is the presence of carcinogens in the air inhaled by human beings. It is well known that city dwellers contract lung cancer more often than the rural population, and that it is encountered more often in large cities than in small ones. It is characteristic that contamination of the air with 3,4-benzpyrene, as our data in particular have shown (Shabad & Dikun, 1959), is considerably more marked in large cities than in smaller cities and small towns, and is practically non-existent away
from towns and large industrial areas. Thus, campaigning for cleansing the air of carcinogens is one method of approach to the prophylaxis of lung cancer.

Carcinogenic hydrocarbons may enter the human lungs not only through atmospheric pollution but also through the smoking of tobacco. The idea that there is a possible connexion between lung cancer and smoking is based on clinical statistics and physico-chemical research.

The data obtained from clinical statistics, mainly in the United States and the United Kingdom, lead to the conclusion that cancer of the lungs is found considerably more often among cigarette smokers than among non-smokers.

Spectral fluorescence analysis techniques have been used by a number of authors to detect in tobacco smoke that same well-known carcinogen—3,4-benzpyrene. Thus, according to the data of Dikun & Chushkin (1959), which fully correspond to the findings of research workers in other countries, 1.6 γ of 3,4-benzpyrene is found in the smoke from 100 cigarettes without filter tips and 1.1 γ in the smoke from 100 Russian papirosy (cigarettes with long cardboard holders). Thus, a carcinogen is contained in the products of smoking, although in small quantities. This is also confirmed by the results of experiments on animals. According to Gritsyute & Mironova (1960), painting the skin of mice with tobacco tar led to the development of tumours only in rare instances (in 1.5-2% of cases only).

Experimental research on the part played by smoking in the causation of lung cancer should be continued along various lines: for example, a search should be made for harmful substances other than 3,4-benzpyrene in the products of smoking; and a more thorough study should be made of the relationship between the appearance of carcinogens in tobacco smoke and the combustion conditions of the tobacco and the nature of the smoking. However, the facts already accumulated provide a basis for a number of methods of prophylaxis against this carcinogenic factor: on the one hand, obviously, a reduction in smoking or the giving-up of smoking altogether; on the other hand, improvements in the production of smokers' requisites, such as the design of special filters to trap the carcinogens, special treatment of the cigarette paper, etc.

It is of great importance for solving the problem of lung cancer prophylaxis to devise an experimental model as close as possible to bronchogenic cancer of the human lung. Without dwelling here in detail on this problem, on which a number of researches have been carried out in our laboratory at various times, it should be recalled that many research workers over a period of some forty years have tried to induce experimental lung cancer by introducing carcinogens into lung tissue, but without success. Apparently, the most important factor in the induction of lung cancer is the deposition of the carcinogen over a sufficiently long period. Very recently, in our laboratory (Pylev, 1961) success was achieved in regularly inducing lung cancer in 30% of rats by means of intrabronchial administration, by intubation, of 6-10 mg of 9,10-dimethyl-1,2-benzanthracene, incorporated in Indian ink to improve its adsorption.

Above, a great deal has been said about the content of carcinogens, particularly 3,4-benzpyrene, in various types of smoke. It was natural to consider also the possibility of carcinogens being present in smoke-cured foodstuffs, which are sometimes subjected to lengthy smoke treatment. The components of the smoke may not only affect the surface of the foodstuff but also penetrate into the inside.

In 1954, the Czech research worker Šula and his colleagues detected 3,4-benzpyrene in smoked meat (Dobeš, Hopp & Šula, 1954). Gorelova & Dikun (1958) carried out systematic quantitative determinations of 3,4-benzpyrene in several forms of smoked fish, and in smoked sausages. Spectral fluorescence analysis showed that 1 kg of fish smoked by the ordinary hot process may contain between 1.7 γ and 7.5 γ of 3,4-benzpyrene. At the same time, it was found that as much as 38% of the total amount of 3,4-benzpyrene detected in smoked fish may penetrate inside the fish when it is smoked whole, and as much as 87% when it is smoked in fillets.

In various varieties of sausage, Gorelova & Dikun detected between 1.9 γ and 10.5 γ of 3,4-benzpyrene per kg; 65% of the amount of substance found penetrated inside the sausage.

The above data show that carcinogens are actually present in smoked foodstuffs. What is their pathogenic importance? It must be emphasized that the quantities of 3,4-benzpyrene found are extremely small, but cannot be neglected, especially in cases when, for some reason or other, smoked products make up a particularly large proportion of the diet. This proposition can be illustrated in the following way.

Voitelovich, Dikun, Dymarski & Shabad (1957) studied the frequency of malignant tumours in the Tukum District of the Latvian SSR. The data for the fishing population in two places on the coast were
compared with data for the population in six agricultural areas well inland, but in the same district. It was found that the mean annual morbidity from malignant tumours, in terms of cases per 100,000 inhabitants, was 318 in the places on the coast, whereas in the inland areas it was only 149. This difference is due to the considerably higher frequency of malignant tumours of the digestive tract among the population in the coastal places; such tumours are three or four times as common among the fishing population as among the agricultural population of the inland areas. It is interesting to note that the frequency of mammary-gland tumours and tumours of the uterus and ovaries is identical in the two population groups.

Another example which suggests that extensive consumption of smoked products possibly plays a part in the causation of cancer, and particularly cancer of the digestive organs, in man is the study by Kaufman, Mironova & Shabad (1959) of the causes of death among workers in sausage and fish-curing factories, who in the nature of things eat large quantities of smoked food. It was found that these workers do indeed contract cancer with particular frequency, especially cancer of the gastrointestinal tract.

Thus, the observed facts suggest that smoked foods, if consumed in large quantities, may be of importance as a carcinogenic agent for man. This makes it necessary to look for ways and means of reducing the quantity of such known carcinogens as 3,4-benzpyrene in food products, or of completely eliminating them.

Present food-curing techniques are based on very ancient principles—the same principles, in fact, that were applied by primitive man when he hung pieces of meat over the smoke of his camp fire. Naturally it is essential now to devise new curing techniques, based on the latest discoveries of physics and chemistry. In doing so, it must be remembered that it is essential to prevent carcinogenic admixtures in foodstuffs. It is difficult to imagine any way of reducing the quantity of 3,4-benzpyrene or, even more, any way of ensuring its complete absence, in smoke, which consists of a very complex mixture of substances, difficult to control. For that reason, our attention has been concentrated recently on methods of curing in which either smoke is not used at all or the period of action of the smoke is reduced to a minimum. What is aimed at is, so to speak, "smokeless" curing or curing with little smoke. There is a possibility of doing this by treating foodstuffs with curing fluids by the so-called "wet-curing" method.

Recently, Gorelova, Dikun & Lapshin (1959) reported that fish treated with curing fluids contains far less 3,4-benzpyrene than fish smoke-cured in the usual way. The use of new methods of curing, and particularly of curing fluids, which can be analysed to ensure that they contain only a very small quantity of 3,4-benzpyrene (or none at all), is one of the ways of preventing exposure of the human organism to carcinogens.

Further improvements in curing methods require still more experimental work. The effect of various curing fluids or other means of preparing smoked products can be investigated in animal experiments. There is no doubt that in this case also the results of experimental research will promote tumour prophylaxis among human beings.

As stated above, the problem of preventing human exposure to carcinogens is in the forefront of the problems of occupational, municipal and food hygiene. Special attention is being paid to the possibility of the presence of carcinogenic additives in foodstuffs and to measures directed towards eliminating such additives.

The interests of food hygiene in regard to blastomogenic substances are by no means only concerned with the problem of food curing. At the present time, the food industry uses large quantities of colouring agents, preservatives, flavourings and other substances needed in the production of certain foodstuffs. Naturally, any colouring agents that may arouse even a mere suspicion of having blastomogenic properties should be withdrawn from the food industry. The colouring agent "butter yellow" (dimethylaminobenzene), which, as mentioned above, has been shown experimentally to induce liver tumours, is now prohibited in all countries (it has never been used in the food industry of the USSR). Systematic efforts are now being made to find substitutes even for those food colours which, although experimentally they have not induced tumours, are closely similar to blastomogenic substances in their chemical structure. Thus, measures have been taken to find substitutes for napthol yellow, various forms of Sudan, etc.

Special interest is being aroused by the problem of insecticides, herbicides, substances to inhibit germination in stored vegetables, and many other chemicals that may enter human food together with agricultural products. Without going into detail on this subject, it may be mentioned that many compounds
allied to urethane, which is known to induce certain tumours under experimental conditions, have been suggested for preventing germination in stored vegetables. Systematic preliminary experimental research on a number of substances to prevent germination will make it possible to reject dangerous substances and substitute harmless ones. 

The problem of the possible presence of carcinogenic additives in food has attracted the attention of a number of international organizations, particularly FAO and WHO. The Joint FAO/WHO Expert Committee on Food Additives (1961) adopted a number of general basic principles, including the following:

"... Food additives should be used for the benefit of the consumer; they should not be permitted for any deceptive or misleading purpose.

"... Food materials and all chemicals and processes at present in use for the preparation and distribution of food should be subjected to adequate examination to ensure minimum risk in use, if this has not already been done, or unless previous knowledge indicates that this is unnecessary.

"... All chemicals and processes proposed in the future should be subjected to adequate examination to minimize risk before being accepted for use.

"... The presence of carcinogenic substances in food might be a significant factor in the occurrence of what is considered to be spontaneous cancer in man and animals.

"... Since dose-response relationships have been demonstrated in the case of carcinogenic agents, the reduction of carcinogenic substances in food to the lowest practicable level may be one of the effective measures towards cancer prevention.

"... Many factors may influence dose-response in carcinogenesis. Their complexities are such that it is agreed that no assuredly safe level for carcinogens in human food can be determined from experimental findings at the present time."

These quotations show the very great importance of the campaign against carcinogenic food additives. It is clear that experimental research may play a very significant role in furthering the cause of cancer prophylaxis. In the planning of such research, the purpose of the experiments and, more important, their range, need to be clearly defined. For example, in order to evaluate the carcinogenic effect of a particular food additive, it is not enough to set up experiments based on administering the substance subcutaneously to animals or painting it on their skins; it is essential to introduce the additive into their digestive tract. The fact that sarcomas are obtained at the site of subcutaneous injection does not mean that the same product will have a carcinogenic effect if given by mouth. To illustrate this statement, it is enough to refer to the well-known results of experiments involving the subcutaneous insertion in rats of polymer plates. The fact that sarcomas developed around the plates would never lead anybody to suspect plastic tableware of having a carcinogenic effect.

A very important but also very difficult problem, particularly in relation to carcinogenic food additives, is that of the possibility of setting hygienic standards for carcinogens. This problem has been discussed on many occasions at a number of national and international conferences, and the general conclusion is that it is impossible to lay down maximum permissible doses of carcinogens. This is not only because it is extremely difficult or even impossible to make quantitative determinations of many carcinogens. The important point is the fact that the information at present available on the mechanism of action of carcinogens suggests that it is impossible to determine what would be permissible doses. For instance, it has been proved that carcinogenic aminoazo compounds and hydrocarbons combine with proteins. Factors which must not be forgotten are the accumulation of carcinogens in the organism and the possibility of co-carcinogenesis, that is, the potentiation of the effect of carcinogens by non-specific factors.

The impossibility of establishing maximum permissible doses for carcinogens in no way means that it is impossible to devise prophylactic measures. Cancer prophylaxis is served by reducing to the greatest possible extent the doses of carcinogens to which man may be exposed. This has been soundly demonstrated in many thousands of animal experiments, and in the case of human beings, in regard to occupational neoplasms and tumours among smokers. The lower the dose of the carcinogen, the smaller the number of people who contract the disease and the later its onset. It should be borne in mind that if only very small doses of carcinogens are ingested, they may induce cancer so late that it will practically fall outside the normal human life-span.

It has naturally not been possible in this review to outline all the aspects of experimental oncology that may be put to use for cancer prophylaxis. Thus, no mention has been made of radiation-induced tumours: attention has been concentrated on chemical carcinogens alone. However, the material quoted seems to us sufficient to throw light on the
principles of the problem. Experimental research
does, indeed, contribute to the prevention of tu-
mours, since it discovers carcinogenic agents, and,
once a substance is known to be a carcinogen,
various measures can be taken against it. For ex-
ample, it may be eliminated altogether from the
human environment by the prohibition of its use
in industry or in the home; its effect on human beings
may be minimized by such means as sealing off
production processes and thus reducing human
exposure to contact with it; it may be rendered
harmless ("decarcinogenized"); it may be replaced
by some less harmful or entirely harmless product;
the dose or length of time to which people are
exposed to it may be reduced. All such prophylactic
measures should be based on the corresponding
experimental findings. It is in this way that experi-
mental oncology, which grew up as a result of the
practical observations of occupational tumours in
man, is now repaying its debt to practical medicine.

RÉSUMÉ

D’après les travaux de l’auteur et de ses collaborateurs,
la prophylaxie des tumeurs, considérée du point de vue
du pathologiste et de l’expérimentateur, revêt deux
aspects: d’une part l’hygiène anticancéreuse, destinée à
prévenir l’apparition du cancer; d’autre part, la prophy-
laxie clinique, dont le but est d’enrayer le développement
du cancer.

La prophylaxie clinique consiste à déceler et à traiter
temps les manifestations précancéreuses, car tout cancer
a son «précancer». Les altérations précancéreuses des
divers organes présentent un tableau morphologique
derfèrent, mais comportent des traits communs. On peut
distinguer quatre phases principales dans le dévelop-
pement des tumeurs malignes: 1. hyperplasie diffuse,
irrégulière; 2. proliférations nodulaires; 3. tumeurs
relativement bénignes; 4. tumeurs malignes. Il importe
distinguer les processus précancéreux des altérations
inflammatoires et régénératrices. L’inflammation n’est pas
nécessairement l’un des maillons qui conduisent au cancer.

Les mesures d’hygiène anticancéreuse tentent de pré-
venir l’apparition du cancer en empêchant les agents
cancérogènes, en particulier ceux du milieu ambiant,
d’agir sur l’organisme humain. L’idée de l’action cancé-
rogène de telles substances se fonde sur de nombreuses
observations de cancers professionnels. Il suffit en effet
de supprimer les agents en cause, ou de réduire leur
action, pour voir diminuer la fréquence de ces cancers
professionnels. C’est ce qui permet de parler d’une
hygiène anticancéreuse.

Le nombre croissant de nouveaux produits chimiques
avec lesquels l’homme entre en contact à l’heure actuelle,
impose l’étude de l’éventuel pouvoir cancérigène de ces
substances, sur l’animal d’expérience. Les additifs alimen-
taires sont l’une des premières classes de produits à sur-
veiller. L’auteur insiste notamment sur la présence de
benzo-3,4 pyrène dans les poissons et les saucisses
fumées. On a constaté que le cancer de l’appareil digestif
est plus fréquent chez les personnes qui consomment des
aliments fumés en grande quantité (pêcheurs, ouvriers
des entreprises de fumage), que dans la population envi-
ronnante. On met actuellement au point des techniques
de fumage qui permettent de réduire les hydrocarbures
cancérogènes dans les aliments fumés.

Le pouvoir cancérigène des polluants de l’atmosphère
est l’objet de vastes recherches. L’auteur et ses collabo-
rateurs ont cherché l’origine de plusieurs de ces substan-
ces; ils ont procédé à une étude comparative de la situa-
tion d’un grand nombre de villes et ont démontré que,
dans certains cas, un aménagement plus rationnel des
villes et la combustion plus complète des combustibles
permettraient de diminuer la quantité des polluants
cancérogènes. On a également étudié les substances can-
cérogènes que l’on risque d’absorber en fumant le tabac,
et les mesures prophylactiques qu’il y aurait lieu de
prendre. On est parvenu à provoquer des tumeurs expé-
rimentales chez le rat, par injection d’hydrocarbures
cancérogènes par voie intratrachéale, ce qui pourra servir
de base à la recherche de moyens préventifs applicables
à l’homme.

L’auteur se déclare convaincu que la prophylaxie du
cancer est possible, et que les recherches et expériences
entreprises lui donnent une base scientifique.

REFERENCES

Bogovski, P. A. (1960) [Occupational skin tumours
induced by products of the processing of mineral fuels],
Moscow, Medgiz
Danetskaya, O. L. (1952) Gig. i Sanit., No. 10, p. 26
Dikun, P. P. & Chushkin, S. G. (1959) Vop. Onkol., 5,
No. 7, p. 34
Dikun, P. P. & Nikberg, I. I. (1958) Vop. Onkol., 4,
No. 6, p. 669
No. 3-4, p. 254
Gorelova, N. D. & Dikun, P. P. (1958) Vop. Onkol., 4,
No. 4, pp. 398, 405
ROLE OF EXPERIMENTAL RESEARCH IN THE PREVENTION OF MALIGNANT TUMOURS

Monastyrskaya, B. I. (1952) [Some new experimental data on the prophylactic role of chronic inflammation in the genesis of skin cancer induced by carcinogens]. In: *[Symposium on Problems of Oncology]*, vol. 4, p. 136
Prokofyeva, O. G. (1938) *Arh. biol. Nauk.*, 51, No. 3, p. 120
Shabad, L. M. & Dikun, P. P. (1959) *Atmospheric pollution with the carcinogen 3,4-benzpyrene*, Moscow, Medgiz