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A number of modern scientific data indicate that it is possible to prevent cancer. We distinguish two ways of cancer prophylaxis: the prevention of its appearance and that of its development.

Observations of so-called occupational cancer had long ago demonstrated that in some cases certain chemical products or exposure to radiation could produce tumors in man. This includes cancer of the skin found in chimney sweeps and in workers of other industrial branches subject to the action of the products of combustion; cancer found in roentgenologists; cancer of the bladder found in workers of the aniline dye industry; cancer of the lungs found in miners of Shneyeberg and Yakhimov caused by radioactive substances, etc. Numerous experimental investigations were conducted with a view to interpreting these observations and to finding out precisely to what reactions the malignant tumors were due in these cases. The results of these investigations formed the basis of modern experimental oncology and led to the discovery of cancerogenic or, a better expression, blastomagenic substances (since they cause not only cancer but also other kinds of tumor) as well as to the possibility of studying more extensively the appearance and development of tumors of various types.

Various tumors and leukemias can now be induced experimentally by chemical blastomagenic substances or certain radiation effect, and their different types and localization can be systematically studied.

Let us emphasize that we speak not only of cancer of the skin at the spot where cancerogenic substances were smeared or various types of sarcomas at the area where they were introduced subcutaneously, but also of a number of tumors of the internal organs. In our laboratories we obtained and studied tumors of the mammary glands induced in mice with estrogen and fluorene (Ye. L. Prigozhina and L. L. Malyugina); adenomatous tumors of the lungs in mice effected with hydrocarbon and uretan (L. M. Shabad and L. A. Gritsyute); cancer of the cervix in mice

induced by the introduction into the vagina of tampons impregnated with tar or cancerogenic hydrocarbon (Ya. L. Klenitskaya) and of the uterus brought on in rats with large doses of synestrol (Ye. L. Prigozhina); tumors of the ovaries developing in mice as a result of general irradiation with X-rays (I. D. Nechayeva); cancer of the prostate effected in rats by the introduction of 9,10-demethyl-1,2-benzanthracene (B. V. Klyucharev); cancer of the testicles in mice caused by estrogen introduced in fractions (V. P. Konoplev); cancer of the liver induced in mice and rats with cancerogenic aminoazo-compounds and 2-acetylaminofluorene (L. S. Morozenskaya, V. I. Gel'shtein and L. L. Malyugina); adenomas and adenocarcinomas of the kidneys in male hamsters induced by the introduction of large doses of diethyl stilbestrol or synestrol (R. I. Pol'kina), etc. All these experiments have demonstrated that cancer does not appear immediately but that it is the last link of a long chain of changes which we can rightly designate as precancerous or pretumorous.

We distinguish 4 stages of precancerous changes:

1) Diffused irregular hyperplasia.

2) Focal proliferation.

3) The so-called benign tumor.

4) Malignant tumor.

L. M. Shabad, Z. V. Gol'bert, Yu. M. Vasil'yev and L. A. Cherkasskiy also demonstrated that under the effect of blastomagenic hydrocarbons and radioactive substances, they observed definite presarcomatous changes in the subcutaneous tissue, glossar muscles and bones of mice, rats and rabbits under various experimental conditions.

The mechanisms firmly established in experiments compel us to search very carefully for precancerous changes in the pathology of man and to study them in detail. It has been known for a long time that many malignant tumors develop in man as a result of changes which we consider as precancerous. We bear in mind that there is a connection between an adenocarcinoma of the stomach or of the rectum and adenomatous polyps; between cancer of the breast and proliferating fibroadenomatosis or fibrocytic mastopathy with epithelium growth; between cancer of the cervix and persistent cervical pseudoerosions with the proliferation of epithelium; between cancer of the larynx and its pachyderma, etc. However, in a number of tumors in man changes regularly preceding them remain unexplained and little studied. The main difficulty lies in finding out whether malignant tumors appear merely in the background of these or other changes or whether they develop out of them. Only in the latter case can one speak of precancerous significance of such changes in the true meaning of this word.

The concept of precancer was conceived in the clinic. Experimental research gave it specific substance. At present, it is possible to use experimental data for investigating further precancerous conditions in the clinic and for deepening the concepts of precancer. We think that each case of cancer has its precancerous stage. In a number of cases, it still remains to find out precisely which changes preceding cancer have a direct relation to its development and are stages in the process representing true precancerous changes.

The discussion above proves that it is possible to prevent cancer. If every malignant tumor appears not suddenly but gradually and if it develops from determined precancerous changes, then a timely recognition and removal of precancer will break the chain of the process, i.e., will become the means of cancer prophylaxis. This proposition has already been proved in practice. Another means of cancer prophylaxis is to prevent the action on the organism of different agents, capable of producing malignant tumors. First of all, this refers to blastomagenic chemical substances in man's environment and to methods of their removal.

Modern experimental research on the appearance of tumors grew out of observations of occupational cancer in workers of certain industries. However, research on occupational cancer proved to be not only one of the ways of finding out the etiology and pathogenesis of tumors. It also proved that it was possible to prevent cancer and marked the way for developing methods and organizing cancer prophylaxis.

Thus, cancer of chimney sweeps, the classic type of occupational cancer, is now practically non-existent. This has come as a result of changes in work conditions, a decreased contact with harmful effects, a number of technical measures taken to protect the organism, and personal hygiene. In brief, we can say that in persons engaged in this occupation, it was possible to prevent the harmful effect of blastomagenic agents on the organism or, in any case, to decrease it significantly. This proposition proves that, in principle, cancer prophylaxis is possible, particularly in cases where its causes are concealed in the environment and their effect on the organism can be removed or significantly decreased.

If cancer in chimney sweeps no longer presents any real danger, the same cannot be said of many other forms of occupational cancer and, in particular, of cancer of the bladder in workers of the aniline dye industry. In this branch of industry it is also possible to prevent systematically the appearance and development of cancer by decreasing contact with dyes by hermetically sealing certain manufacturing processes (I. L. Lapkin) and by making systematic cystoscopic examinations with a view to finding out and removing precancerous processes (I. S. Temkin). But many products of the chemical industry, which may present cancerogenic

danger, remain insufficiently explored. For instance, everybody recognizes that beta-naphthylamine is a highly active cancerogenic agent; the same is not clear regarding alphanaphthylamine. For this reason, opinions on this subject differ. Benzidine has been recognized as a cancerogenic agent whereas a number of substances related to it still remain insufficiently or not all studied. Blastomagenic properties of dichlorbenzidine were established in our laboratory for the first time only in 1958 (G. B. Pliss). This substance introduced to rats and mice in food or in subcutaneous injections produced various often numerous malignant tumors in about 80% of the rats and 40% of the mice. Some tumors developed at the site of subcutaneous injections (sarcomas) and others away from it (cancer of the mammary glands, of the sebacious glands, of the liver, papilloma of the bladder, etc.). Our findings on the marked blastomagenic effect of dichlorbenzidine were fully confirmed by Williams in Manchester, England.

The chemical industry produces a great quantity of entirely new substances with which people at times have to remain in a close contact over a long period of time under industrial or everyday conditions. Some of these substances may produce blastomagenic effect. Therefore, a timely testing of the new substances on experimental animals is an important task. According to our data, the latent period for the development of tumor is equal to one-fifth of the life span, constituting 15 to 18 years for human beings and 6 to 12 months at the most for experimental mice or rats with a life span of 30 months. This permits us to test out the blastomagenic properties of one or another substances in experiments before finding out their effect on people.

Our experiment has indicated the importance and effectiveness of this type of investigations. In the last 3 years, in collaboration with the K. Ye. Voroshilov Scientific Research Institute of Dyes, we systematically examined a number of new products of the chemical industry; among them were cyclohexylamine, dicyclohexylamine and dicyclohexylamine-nitrite. As demonstrated in the experiments of G. B. Pliss, the first substance did not produce tumors; the second produced sarcoma in the injected site; and the third produced tumors in several internal organs. The blastomagenic activity of dicyclohexylamine-nitrite was discovered for the first time. These two substances can be considered as relatively weak blastomagenic agents since they produced tumors only in 20% of the experimental animals and appeared only 12 months later; however, the results obtained are very significant. A new group of blastomagenic substances was discovered, studying them is of great practical importance.

It is quite natural that we should continue investigating systematically in experiments on animals a number of new products put out by the chemical industry to discover any possible blastomagenic effects. This

is one of the conditions for preventing occupational cancer. However, in thinking more carefully about the results of such work, it appears that they exceed the bounds of combatting occupational hazards. Blastomagenic hazards may spread from occupational into everyday ones. This occurs when wide masses of population come into a close contact with them instead of the narrow circle of workers in a given production. Many products of aniline dye industry and of coloring may come into the hands of people.

For instance, at one time several countries used for coloring foods, particularly butter, margerine, flour and macaroni, a substance called "Butter-gelb" or "Butter-yellow." This cancerogenic substance is dimethyl aminoazobenzol, which causes tumors of the liver in rats and mice. This was demonstrated by Kinosita already in 1937. Substances suspected of possible blastomagenic activity can be found even now among numerous dyes and preservatives used in the modern food industry. The special International Conference assembled in Rome in 1956 dealt with this problem. In the proceedings of Roman Conference (see the Russian translation in the journal "Modern Problems of Oncology," 80, 1957), we can find the list of food colors found harmless, the list of those not permissible for using in foods and, finally, extensive lists of colors and of other substances (which may possibly penetrate into food products) not sufficiently analyzed and which need to be further explored.

Let us give another example of an occupational hazard growing into an everyday one. Remember the classic cancer of chimney sweeps. There is no doubt that this type of occupational cancer was caused by the products of pyrogenic processing of fuel with tar, soot and smoke. Chimney smoke escapes into the atmospheric air. Therefore, it is natural to think that air becomes polluted with cancerogenic hydrocarbons contained in coal tar and its similar products. The interesting point is not that such pollution actually occurs but rather that this fact has only recently been established with modern precise spectrofluorescent methods.

About 10 years ago we conducted investigations in collaboration with hygienists (B. P. Gurinov, V. A. Zore, A. A. Il'ina and L. M. Shabad, 1953) to determine atmospheric pollution with 3,4-benzpyrene, a strong cancerogenic substance; we established that it was present in a number of the USSR towns. Subsequently, as a result of investigations conducted with P. P. Dikun, Ya. M. Grushko, I. I. Nikberg and other scientists, we assembled many records of the quantitative distribution of 3,4-benzpyrene in the air of different towns and of different sections of one and the same town. We also established that this pollution on a number of sources from which 3,4-benzpyrene escapes into man's environment. Analogous foreign data published by Weller in 1952,

and Cotin in 1954, demonstrate that in many towns of England and the USA air pollution with cancerogenic hydrocarbons is considerably greater than in the USSR.

We shall not dwell any longer upon the study of atmospheric pollution with cancerogenic substances. This subject draws the attention of many scientists and, apparently, is firmly implanted among the problems of national general and communal hygiene and of experimental oncology. However, we wish to emphasize one feature of this subject, i.e., it is possible to combat successfully this pollution and to prevent (or decrease considerably) the escape of 3,4-benzpyrene into the air. In applying a number of technological and sanitary engineering measures, the process of fuel combustion and of catching smoke products can be improved. It always is very important to plan rationally the layout of towns and to use extensively distrist heating plants and electricity. P. P. Dikun and I. I. Nikberg made a special investigation in the town of Makeyevka where old-fashioned coke ovens were reconstructed, there was a sharp decrease in air pollution with 3,4-benzpyrene. In collaboration with hygienists we made a comparative study of snow samples taken from two closely situated towns of Siberia, Irkutsk and Angarsk. Our tests indicated that in Angarsk, a new well planned town where residential quarters were separated from the industrial area by a green zone and district heating plants were in use, minimum amounts of 3,4-benzpyrene were present. In the old town of Irkutsk air pollution with 3,4-benzpyrene was not any smaller than in other large industrial towns.

Research on atmospheric pollution with 3,4-benzpyrene presents a great interest in connection with the problem of lung cancer. At the present time, it is universally recognized that the incidence of lung cancer has increased. Many authors consider that one of the reasons for this is the presence of cancerogenic substances in the air inhaled by man. It is known that there is a greater incidence of lung cancer among city dwellers than among the rural population and in large towns rather than small ones. Our data obtained together with P. P. Dikun indicate that, characteristically, atmospheric pollution with 3,4-benzpyrene is more marked in large towns than in small and that it is practically non-existent away from towns and industrial projects. Thus, to prevent the incidence of lung cancer it is necessary to purify air from cancerogenic substances. Considerable theoretical work remains to be done along this line; statistics of lung cancer need to be studied in relation to one or another degree of pollution with cancerogenic substances of man's environment; also experimental models of lung cancer near to the pathology of man should be developed. However, sufficient data are available even now to carry out systematically practical work of sanitizing the atmosphere.

Cancerogenic hydrocarbons can penetrate into the lungs not only from their suspension in atmospheric pollution but also by the means of tobacco smoking. The idea of a possible relation between lung cancer and tobacco smoking has been formed from clinicostatistical and physicochemical investigations. Clinostatistical data obtained mainly in the USA and England lead to a conclusion that lung cancer is found considerably more often in tobacco smokers than in non-smokers. For instance, according to Doll, the death rate from lung cancer among heavy smokers (over 25 cigarettes per day) is 5 to 15 times higher than among non-smokers.

A number of authors determined by spectrofluorescent research methods the quantity of cancerogenic hydrocarbons of 3,4-benzpyrene inhaled in smoking 100 cigarettes. According to Wright and Winder (1956) the quantity is 0.8 g; according to Cooper and coworkers (1954-1955), 0.8 to 1 g; according to Latarge and coworkers (1956), 1.2 g; and according to Bonn and Neykom (1957), 2.2 g. We collected in our laboratory smoke produced by a special apparatus imitating tobacco smoking and then extracted tar matter from the smoke. The data of P. P. Dikun and S. G. Chushkin indicated that they extracted 1.1 g of 3,4-benzpyrene from a 100 "Belomor-kanal" cigarettes, and 1.6 g from 100 "Avrora" cigarettes. In this way, our results corresponded with those of the foreign authors. Cancerogenic substances are actually contained in cigarettes although in small quantities. The same was confirmed in experiments on animals (painting the skin with various tobacco tars or injecting them under the skin). According to Winder and coworkers (1953 and 1957), by using this method they induced papillomas and skin cancer in mice, which developed only 18 months after the treatment.

We should continue to study the role of tobacco smoking in the occurrence of cancer. A direct experimental evidence of obtaining lung cancer in animals with tobacco products is still lacking. Tobacco products should be investigated for other harmful substances besides 3,4-benzpyrene and, in particular, for arsenic. It is necessary to explore extensively the connection between the appearance of cancerogenic substances in the tobacco smoke and the burning rate of tobacco and the nature of smoking. The facts already assembled make it possible to organize a number of ways for preventing this cancerogenic hazard. These may be, on the one hand, cutting down on smoking or giving it up altogether and, on the other hand, improving the manufacture of tobacco products. This includes the development of special filters, retaining cancerogenic products, specially prepared cigarette paper, etc.

Earlier we spoke much concerning the content of cancerogenic hydrocarbons, particularly of 3,4-benzpyrene, in various kinds of smoke. It is natural to consider the possibility of their presence in

smoked food products since the latter are at times subjected to an extended processing by smoke. Smoke components may not only settle on the surface of the product but also penetrate inside it. In 1954, Czech scientist Yan Shula and collaborators discovered 3,4-benzpyrene in smoked meat. N. D. Gorelova and P. P. Dikun systematically determined in our laboratory the content of 3,4-benzpyrene in certain types of smoked fish and sausage. A spectrofluoscent investigation revealed that in 1 kg of fish cured by hot-smoking there were from 3.3 to 6.7 g of 3,4-benzpyrene with 38% of it penetrating inside the fish (in relation to its content in the whole fish). In smoking strips of fish as much as 87% penetrated inside. Considerably greater quantities of 3,4-benzpyrene were found in fish cured in smoke; they varied from 27 to 53.3 g per 1 kg of fish weight. The content of 3,4-benzpyrene inside the fish with this method was only 4 to 11% of the total content. In various kinds of sausages, N. D. Gorelova and P. P. Dikun found from 1.9 to 10.5 g of 3,4-benzpyrene per 1 kg of weight with 65% of this amount penetrating inside the products. In speeding up the smoking operation with electricity, the total quantity of 3,4-benzpyrene remained the same as in the slow smoking process but with only 30% of 3,4-benzpyrene penetrating inside the sausage products.

The data given above indicate that cancerogenic substances are actually present in smoked food products. What is their pathogenic significance? We must emphasize that the amounts of 3,4-benzpyrene presented above are extremely small. However, they should not be disregarded particularly in cases where for one reason or another smoked foods are an important part of man's diet. We can illustrate this situation by the following example.

In collaboration with E. A. Voytelovich, P. P. Dikun and L. Yu. Dymarskiy we made a comparative study of the incidence of malignant tumors in Tukumskiy Rayon of the Latvian SSR. We compared the data related to the fishing population of two seaside settlements with analogous indicators related to the population of six agricultural settlements in the interior of the same rayon. We discovered that the mean yearly incidence of cancer in the seaside settlements was equal to 318 per 100,000 people whereas in the interior settlements, it was equal to 149. This difference was conditioned by a significantly greater incidence of cancer of the intestinal tract of the seaside inhabitants. Tumors located in the intestinal tract were found 3 to 4 times more often than in the inhabitants of the agricultural district. The incidence of cancer of the breast, uterus and ovaries was equal in both groups. The seaside inhabitants used greater quantities of smoked fish in their diet.

The mechanisms observed demonstrate that smoked foods when used in large quantities may have a cancerogenic effect on man. This situation leads to the necessity of engaging in research with a view to decreasing the quantity of cancerogenic substances, such as 3,4-benzpyrene, or to preventing their presence in foods products.

Modern technology of smoking food products rests on a very ancient method used by primitive man, who suspended pieces of meat over the smoke rising from his campfire. It is natural that now new technological principles, based on recent achievements of physics and chemistry, should be developed for smoking food products. In developing these principles, we should take into account the necessity of preventing cancerogenic admixtures from food products. We indicated above that the use in our experiment of electricity or of smoke generating method did not decrease the quantity of 3,4-benzpyrene in smoked foods. It is difficult to imagine a way of decreasing the quantity of 3,4-benzpyrene or, even more so, of eliminating it completely from smoke, which is a very complex and difficult-to-control mixture of substances. That is why our attention has recently been drawn to the methods of curing without smoking or of reducing the time of this operation to the minimum. We mean curing by a smokeless process or by a process with little smoking. This involves the use of pickling solutions for processing the food products by a so-called wet curing.

Many attempts were made in our country and abroad to use curing solutions for preserving food products. However, they have not been successful up to now and have not been introduced into practice. We did not succeed in developing cured products with a satisfactory taste, appearance or preservation. Recently (in 1958) I. I. Lapshin reported on the method he developed for the preparation of pickling solutions and for the use of a wet and a combined curing. In our laboratory, N. D. Grelova and P. P. Dikun made a spectrofluorescent analysis of the quantity of 3,4-benzpyrene present in the pickling solutions and in the products cured with these solutions. They discovered that 3,4-benzpyrene was not contained in a number of samples of the new pickling solution proposed by I. I. Lapshin. In some samples there were only traces of it. In analyzing fish samples processed with his pickling solution only traces of 3,4-benzpyrene were found and in fish samples processed by combined curing (pickling solution and quick smoking) only minimum quantities of this substance were found, approximately 30% less than in an ordinary smoking. At the same time, it was found out that the flesh removed from the inside of fish contained much less 3,4-benzpyrene when processed by the two methods than the flesh of fish processed by ordinary smoking. Thus, the use of pickling solution appears to be the sure way of decreasing significantly the quantity of cancerogenic hydrocarbons in cured food products.

In evaluating the pathogenic significance of small quantities of cancerogenic substances capable of passing into the stomach from the environment, one should not forget conditions of the effect of these substances depending on many factors. To illustrate this statement we can indicate the significance not only of the doses but also of the solvents and of the ways by which cancerogenic substances are introduced, which greatly influence the localization and incidence of the occurrence of these or other tumors. We know that experimental cancer of the stomach or rather of the rumen can be obtained in mice with cancerogenic hydrocarbons (L. F. Larionav and N. G. Soboleva; Ye. Ye. Pogosyants; T. V. Shemyakina and others). T. V. Shemyakina demonstrated in our laboratory that triethylene glycol used as a solvent for cancerogenic hydrocarbon caused considerably more experimental rumen cancer (in 93.3% cases) and much earlier than when triethylene glycol was introduced in the same dose and by the same method but in a suspension of glycerine. We can well imagine that under man's pathological conditions some factors may contribute to the manifestation of cancerogenic effect of even small doses of blastomagenic substances, which penetrate into the organism from the environment.

Materials assembled in this article indicate that cancer prophylaxis has now become a practicable problem although it is still a very difficult one.

One of the ways for preventing cancer is to discover blastomagenic substances in environment and to develop measures directed to lessening or eliminating their effect on the human organism, i.e., the prevention of tumor occurrence. Another way, as we have indicated at the beginning of this article, is to prevent the development of malignant tumors, i.e., to discover in time precancerous conditions and to treat them radically.

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