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Geographical Differences in the Distribution of Malignant Tumours *

Trends in Research on the Etiology of Human Tumours

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Malignant tumours are encountered among all races and in every type of geographical zone, but there are marked differences in different areas in the prevalence of particular forms of tumour—differences that are to a greater or lesser extent dependent on factors such as the climate and geography of the region and the habits, customs and occupations of the people. The study of these factors in relation to the occurrence of malignant tumours is of great importance in reaching an understanding of the etiology of tumours in man.

In this paper the author discusses the many problems involved in the study of regional features in the prevalence of malignant tumours, with special reference to the difficulties of ensuring comparability of the data from widely differing regions and population groups. He concludes the paper with a review of some known facts regarding the distribution of malignant tumours at various sites in which he compares data obtained in surveys in the USSR with those obtained in other countries.

OUTLINE OF THE PROBLEM AND BASIC LINES OF APPROACH

An important aspect of research on the causes of cancer in human beings is the study of regional differences in the distribution of malignant tumours. Climatic and geographical features, ways of life and types of occupation are all factors that to varying degrees affect the human organism and that need to be studied in relation to the prevalence of malignant tumours if an explanation is to be found for the preponderance of certain types of tumour among some races and population groups and their extreme infrequency among others. Malignant tumours are encountered among all races and in every type of geographical zone, but there are marked differences in the frequency of tumours at particular sites—differences that are reflected in the structure of morbidity and mortality alike. To discover the causes of these differences means to understand the conditions that favour the more frequent occurrence of particular forms of tumour.

In addition to the numerous experimental, morphological, biochemical and clinical investigations that are being carried out on the question of the causes and mode of development of malignant tumours, a study must be undertaken of the whole complex of conditions of human life that over the course of years and decades may lead to the development of pathological changes in particular organs and tissues of the human body. Some of these changes can be regarded as pre-malignant—that is, as constituting a background for the development of tumour growth.

Clinical and statistical studies carried out in a number of countries in recent years have brought to light several important facts concerning the geographical distribution and frequency of malignant tumours, but data on local differences in the distribution of tumours are still scanty. It is extremely difficult to establish associations between the frequency of occurrence of particular forms of malignant tumours and such factors as ways of life and types of occupation, since living habits and working conditions are constantly changing and many harmful environmental influences are being removed.

On the question of environmental hazards, Cowdry (1955) considers that the physician can

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identify a carcinogenic agent or combination of carcinogenic agents in less than 1% of cancer cases. It seems to the present writer, however, that by intensive analysis of the facts and a thorough study of the history of the disease it is possible to detect various specific and non-specific influences on the organism in a significantly higher percentage of cases.

At the present time an association between cancer and several environmental conditions has been established beyond doubt. For example, climate, composition of soil and water (content of radioactive elements and presence or absence of a number of other substances), ethnic group and economic status are all factors of definite significance. Some of these factors are purely external and objective, i.e., governed by the geographical characteristics of the locality; but others are also, to a large extent, subjective, depending upon local features of the life of the people—their habits, customs and hygienic practices.

At the Symposium on Geographical Pathology and Demography of Cancer held in Oxford, England, in 1950, the following basic principles regarding the systematic patho-geographical study of carcinogenesis in man were recognized:

1. Study of the geographical distribution of malignant tumours is an essential branch of research on carcinogenesis in man.

2. Such a study must be based on close and well-thought-out co-operation between scientists of different countries and of different specialities: oncologists, pathologists, statisticians, nutritionists, etc.

3. An important aspect of the study, particularly in the initial stages, is the collection of pathological and anatomical data.

4. Comparison of data from examination of biopsy and autopsy material obtained from well-defined geographical areas is an integral part of the geographical study of malignant tumours.

5. The exchange of histological material among participants in the study working in different geographical areas should be easy to effect at no great expense.

6. Close co-operation between the participants in the study during the actual work should yield valuable results.

7. Problems arising from the study must be subjected to experimental investigation.

Study of the geographical pathology of cancer is fraught with great difficulties. For the purposes of comparison, an exact definition is needed of the geographical territory and of the period of time in which the study is carried out (the important point here is that the regions to be compared should differ distinctly from one another in geographical and other features); full information is required on the morbidity and mortality from various types of cancer in different age-groups and sexes; the diagnosis of malignant tumours must be quite accurate and it is extremely important that a unified system of nomenclature should be used in describing them and that the method of obtaining the figures should be correct. National habits and customs must here be taken into consideration.

One of the principal lines of approach to the study of the geographical pathology of tumours is the carrying out of special surveys. In the opinion of the author and his former colleagues in the USSR (Chaklin, Sviatukhina & Orlovski, 1961), the chief objectives of such surveys should be:

1. To collect statistical material on the prevalence of malignant tumours and pre-malignant conditions and on cancer mortality in the district being studied. (Such data must, of course, be carefully checked for reliability before they can be used as a basis for the study of geographical pathology.)

2. To subject sample groups of healthy people to medical examination in order to determine the general level of health of the population in the district under study and to evaluate its ethnic characteristics; and to inspect groups of patients with the forms of malignant tumours most frequently met with in the given district, paying particular attention to case-histories. In connexion with the latter, not only should questions bearing on the disease itself and its cause be asked; information on living and working conditions must also be sought so that different harmful environmental influences may be brought to light.

3. To obtain a full ethnographical description of the population in the given locality, together with details about the geographical features of the district—climate, types of soil, composition of waters, etc.

4. To attract workers in cancer centres, hospitals and medical schools to the study of the distribution of malignant tumours in their respective districts.

Since 1950, the International Union Against Cancer has been carrying out systematic research

on the geographical incidence and demography of malignant tumours. The results of this research have been presented at a number of conferences and symposia—Oxford, 1950; Washington, 1954; São Paulo, 1954; Rome, 1956; Uganda, 1957; London, 1959; Johannesburg, 1959; Brazil, 1959; Bogotá, 1960; Tokyo, 1960; Uganda, 1961; and Philadelphia, 1962.

The International Union Against Cancer has established a Committee on the Geographical Pathology of Tumours consisting of the following seven members: A. V. Chaklin (USSR); I. Clemmesen (Denmark); I. N. Davies (West Africa); G. Higginson (USA); M. Segi (Japan); R. E. J. ten Seldam (Australia); and G. L. Stewart (USA). In addition two sub-committees have been established, one for Africa, headed by D. Gilman (Johannesburg), and one for Latin America under N. Prudente (São Paulo).

The Committee recognized the following as the basic data required for evaluating the importance of geographical factors in the pathology of tumours: mortality and morbidity statistics in respect of malignant tumours; records of cases of the main forms of malignant tumours in hospitals and clinics; and records of autopsies of persons dying from malignant tumours.

A prerequisite for the accumulation of such data is the establishment of tumour registration centres in different countries. Personal study of the organization of cancer control and tumour statistics in a number of countries (Austria, Bulgaria, Canada, Czechoslovakia, Denmark, Finland, France, Great Britain, Hungary, Israel, Italy, Luxemburg, Norway, Poland, Romania, Sweden, Switzerland, Uganda, USA and USSR) has convinced the writer that only by concentrating information concerning cases of malignant tumours in single centres and by coding and processing the basic material, taking into account all the information given in the records, can data suitable for comparison be provided; moreover, even then, the data will only be truly comparable if a uniform system of nomenclature has been used.

Several authors (for example, Dunham & Dorn, 1955; Steiner, 1954; Tromp & Diehl, 1955) have stressed that, when computing the data on patients with malignant tumours, the structure of the population in a given area in relation to race, sex and age must be taken into consideration. Further, in drawing conclusions from the data, it is also important to consider such factors as the relative proportion of in-patients to out-patients observed the frequency of malignant tumours in relation to that of all diseases, and the number of deaths from malignant tumours registered and the number of post-mortem examinations performed in a given district. An appraisal must be made of the medical institutions supplying the above data, together with an estimate of their efficiency. Finally, it must be remembered that a given population's occupations, customs and habits may alter quite rapidly, as Dunham & Dorn (1955) have pointed out, so that a description of the current social and occupational features, as well as of climatic and other geographical features, of the area is needed for the proper evaluation of the data on the distribution of malignant tumours.

IMPORTANCE OF UNIFORM TERMINOLOGY

The foregoing review of the lines of approach to be followed brings us to the question of terminology —first, the question of agreeing upon a single name for the whole problem under consideration. In the literature there are various preferences on this point:

1. Demography of cancer.
2. Geographical pathology of malignant tumours.
3. Epidemiology of cancer.
4. Endemiology of cancer.
5. Local pathology of tumours.

In our view, none of these suggestions is entirely satisfactory and it would be better to designate all such research " the study of local differences in the distribution of malignant tumours ", including under this designation the whole complex of factors mentioned above.

The importance of uniformity in terminology cannot be overemphasized. For example, if morbidity and mortality data on malignant tumours are to be of value, it is essential that a single nomenclature of nosological types, with a single numbering system, should be used, since the use of non-equivalent synonyms would lead to the comparison of data that were not, in fact, comparable. Here it must be borne in mind that, when comparing data derived from different sources, mistakes can arise not only from the existence of undiagnosed or incorrectly diagnosed cases and the absence of a unified terminology, but also from a lack of agreement on various general concepts—for example, the basic concept of " malig-

nancy". Often, sarcomas and other malignant neoplasms are included among carcinomas and this, according to Hamperl (1955a, 1955b), can lead to incorrect conclusions. The same applies to the pre-cancerous mole, which is very difficult to distinguish from a squamous-celled carcinoma. And it should be noted that there is insufficient clarity in the meaning of malignancy in certain tumours of the ovaries, bones and various other sites.

Hamperl's suggestion to include as cancer all malignant tumours, and to exclude from cancer all non-malignant tumours, is still not the complete answer. In some countries, sarcomas, leukaemia, Hodgkin's disease, and other tumour processes with a certain degree of malignancy are listed separately from carcinomas. Would it be correct to count them as cancers? Are there certain properties that characterize all malignant tumours? These and similar questions must be agreed upon at the start among investigators doing research on the distribution of malignant tumours.

As mentioned above, to obtain comparable data on the distribution of malignant tumours it is essential that a single international system of registration and a single nomenclature should be adopted. Nowadays, most countries use the 1955 revision of the International Classification of Diseases (World Health Organization, 1957). WHO has already established international reference centres for the histological nomenclature and classification of lung, mammary and soft-tissue tumours and leukaemias, and, in the near future, will set up similar reference centres for bone, ovarian, thyroid-gland, oral and salivary-gland tumours. The existence of such reference centres will enable every pathologist to follow the same system of nomenclature and classification, and the attainment of uniformity in this respect will be most valuable for all kinds of study and especially for epidemiological investigations.

METHODOLOGY

General considerations

In order to study local differences in the frequency and in the distribution by site of malignant tumours, it is necessary to compare the relevant statistical data for different countries, for different regions and different national groups in the same country, for men and women, and for persons of different ages. The question of methodology is of great importance in this connexion. For example, to ensure comparability of the data from observations made in different places and at different times, it is necessary to establish the sex-age composition of a central population to be used by all research workers studying standardized indices. It is also necessary to assess the statistical methods of research; to indicate methods for studying the records concerning the living and working conditions of patients with the forms of malignant tumours that are met with most often in certain geographical zones; to devise methods for defining the ethnological and climato-geographical characteristics of regional foci of certain forms of malignant tumours; and to establish a procedure for carrying out surveys.

After checking the reliability of the basic statistical data and introducing the necessary corrections, we are faced with the question of how to determine which sites are responsible for greater or lesser damage from malignant tumours in the populations of the regions that are being compared.

Determination of the relative weights of different forms of cancer in the total morbidity from malignant tumours depends, like that of other statistical indices of morbidity, on the completeness and quality of reporting of cases and on the quality of diagnosis. At the present time, thanks to the higher qualifications of doctors, the equipment of medical establishments with special diagnostic apparatus, the improvement in statistical reporting and the growing health-consciousness of the population, it is possible to speak with greater conviction about various regularities that have been observed in the distribution of different types of malignant and pre-malignant tumours in different provinces, republics and regions of the USSR.

In the analysis of data on different forms of cancer in a given population, the ratio of men to women among the patients with malignant neoplasms and pre-malignant diseases must be taken into account, since there are sex differences in the frequency of certain types of tumours. The question of sex differences will be discussed in greater detail later (see pages 342 and 343).

Value of mortality and morbidity data

In the world literature, there is a great deal of information on cancer mortality, but mortality records for malignant tumours are not, by themselves, a sufficient basis for the study of local differences in the distribution of tumours. Data on causes of death cannot, on their own, give a true representa-

tion of the level of morbidity in the population for any given disease; they can be used only as supplementary data. In the case of cancer, the death-rates depend to a large extent on the age composition of the population (the older the population, the higher the death-rate) and on the completeness of reporting. In the majority of countries, information on total mortality from malignant tumours is still lacking. It is not unusual for cases of malignant tumours to escape diagnosis or to be wrongly diagnosed and, if no autopsy is performed, a death due to cancer may be recorded as being due to some other cause (old age, myocardial infarct, apoplexy, etc.). Furthermore, on the basis of mortality data alone, it is difficult to assess fully the distribution of different types of malignant tumours. It must always be borne in mind that the outcome of different forms of cancer is very variable. There is, for example, high mortality from cancer of the lungs, oesophagus, subgastric glands, stomach and ovaries, whereas cancer of the skin, lower lip, and breast is relatively more rarely fatal.

Another circumstance militating against the use of mortality data in studying the distribution of malignant tumours by site is that not all countries are as yet using the international classification of causes of death, and this makes the data from different countries so variable that comparison is extremely difficult.

It would therefore be methodologically unsound to base conclusions as to geographical differences in the distribution of malignant tumours on mortality data alone. It might be mentioned here, however, that if careful autopsies were performed in all cases of death from malignant tumours, one could profitably compare general cancer mortality rates and mortality rates for a particular form of cancer in different localities and thus obtain an estimate not only of the general morbidity from malignant tumours, but also of the morbidity from tumours of specific organs.

As to the use of morbidity data for the study of local differences in the distribution of malignant tumours, indices of composition are better calculated in relation to the number of newly diagnosed cases of malignant tumours than in relation to the total number of cases on the books of the oncological institutions, since the latter figure will include many patients who have already had treatment and are under observation, and this would be liable to distort the numerical expression of the indices.

Morbidity data based on hospital statistics alone are not sufficient for studying local differences in the distribution of malignant tumours, for the following reasons:

1. Not all cases of malignant neoplasms and pre-malignant diseases are hospitalized, approximately 15% of patients being treated as out-patients.

2. Some patients enter hospital a second time, with relapses and metastases, if there are indications for special or palliative treatment, and to distinguish such patients from among the total number hospitalized is, from hospital statistics, just not practicable.

3. The majority of patients in the late stages of malignant tumours (up to 70%) spend the last months of their lives, and die, at home.

Thus, the results of observations based on hospital records of patients with malignant tumours should be interpreted only with great caution and having regard to the above points.

The incompleteness of hospital statistics in respect of cancer morbidity can be demonstrated in the case of cancer of the stomach. The stomach is the most common site of malignant tumours in many countries; but out of the total number of cases of stomach cancer, usually only 60-65% are accounted for in hospital records, as compared with 80-95% in the records of the local physicians.

For studying the relation between cancer incidence and ways of living, especially diet and other factors that may be associated with conditions producing malignant tumours, data based on hospital records alone will in many instances not be sufficiently specific for conclusions to be drawn from them, since the selection of patients for hospitalization always depends on a number of circumstances. In analysing hospital statistics, it is necessary to take into account changes occurring during the period in question in the composition of the population and also to bear in mind that, even if no substantial population changes occurred during that period, there could have been changes in respect of the selection of patients for hospitalization, associated with improved equipment, widening of the clinical coverage and higher oncological qualifications of the doctors working in the area under study. Furthermore, the composition of hospital patients will vary according to the type of institution. For example, institutions that specialize in the treatment of certain forms of malignant tumours (especially cancer of the stomach, oesophagus, and lungs) are likely to have patients come for consultation or treatment from distant areas. Such patients are sometimes mistakenly registered as new cases in the locality in question,

thus creating the mistaken impression that in the said locality there is a particularly high frequency of one or another form of cancer. The same situation arises when the records of deaths from malignant tumours in a given locality include the deaths of non-residents.

Importance of age-sex composition of the population

A well-known difficulty in the study of local differences in the distribution of malignant tumours on the basis of mortality and morbidity data is created by differences in the age-sex composition of the population groups that are being compared.

Age mortality rates from cancer differ widely, and unless age rates or general standardized rates are calculated, the statistical data on geographical pathology cannot be analysed. For the purposes of analysis, it is necessary to note that the mean age of patients with cancer of the skin, lower lip, oesophagus and corpus uteri is much higher than that of patients with cancer of the cervix uteri, breast and stomach. This factor can have a definite significance in the assessment of the general composition of malignant tumours if data are known about the age composition of the population.

As mentioned earlier, and discussed in greater detail below, there are sex differences in the frequency of certain types of malignant tumours, so that information on the sex composition of a given population is also required for a proper appraisal of the morbidity and mortality data.

Indices for comparison

In addition to studying the distribution of cancer and other malignant tumours according to localization in different organs, it is worth correlating the distribution of tumours by anatomical site with their distribution by histological type. Such correlations are very important in themselves and, with correct methodology, comparison of the rates obtained may yield interesting results in respect of local differences in the distribution of tumours. For example, there is great significance in determining the respective rates of the squamous-cell and basal-cell forms of skin cancer and in comparing the rates of cancerous tumours and melanomas on exposed areas of skin with those on covered areas. When using the latter index of comparison, however, it is necessary to define the terms " exposed " and " covered ", since the details of dress differ widely in different countries, almost the whole surface of the skin being covered in some, while in others not only the face and neck, but also the arms and part of the chest are exposed.

In research on the geographical pathology of tumours, the following ratios in respect of different anatomical sites have great interest:

(*a*) ratio of cancer of cervix uteri to cancer of corpus uteri;

(*b*) ratio of cancer of breast to cancer of uterus;

(*c*) ratio of cancer of stomach to cancer of oesophagus;

(*d*) ratio of cancer of stomach to cancer of large intestine;

(*e*) ratio of cancer of lungs to cancer of larynx;

(*f*) ratio of cancer of lungs to cancer of buccal cavity.

In examining the data for tumours of a particular site, it is worth while to evaluate the following indices:

(*a*) ratio of cancer of covered to cancer of uncovered areas of skin;

(*b*) ratio of basal-cell cancer to squamous-cell cancer of skin;

(*c*) ratio of cancer of lower to cancer of upper lip.

It is also of interest to calculate the ratios of various pre-tumour processes in a particular site to malignant tumours at the same site. For example:

(*a*) ratio of leukoplakia of buccal cavity to cancer of buccal cavity;

(*b*) ratio of pre-tumour processes in cervix uteri to cancer of cervix uteri;

(*c*) ratio of chronic pneumonia and bronchiectatic disease to cancer of lung.

Another interesting index of comparison is the male to female ratio in respect of certain forms of cancer. Although, on the average, men and women are equally attacked by malignant tumours of all forms, in the composition of both morbidity and mortality there is a significant difference in the frequency of individual forms—a difference that exists even if tumours affecting only one sex (tumours of male and female sex organs) are disregarded. For example, cancer of the buccal cavity, upper respiratory passages, and subgastric glands occurs more frequently in men than in women, whereas cancer of the thyroid gland, liver and gall-bladder is found considerably more often in women than in men. For tumours of the digestive tract as a whole,

the male to female ratio is of the order of 15 : 1; for cancer of the lower lip it is 8 : 1. The ratio is appreciably lower for cancer of the buccal cavity and there is practically no difference between the sexes for cancer of the oesophagus, stomach and rectum.

Analysis of a number of records from the Institute of Oncology of the Academy of Medical Sciences of the USSR and from surveys carried out in the USSR on the geographical pathology of tumours has clearly confirmed the constant predominance of certain types of cancer in men or in women. For example, in our material, the male to female ratio for malignant tumours of the buccal cavity was 4 : 1, of the oesophagus 3 : 2, of the stomach 1 : 1, of the rectum 1 : 1, of the larynx 5 : 1, of the lungs 3 : 1 and of the breast 1 : 15.

The question of the significance of sex in the etiology of particular types of human tumours is of importance in the study of geographical pathology, and one of the objectives of the investigation of local differences in the distribution of malignant tumours is to clarify the position with regard to sex differences in the frequency of certain forms of cancer.

Various authors consider that the difference in the morbidity rates for different forms of cancer in men and women are associated not only with sex, but also with the place of residence and living habits of the population and with various ethnic characteristics. On the grounds of external factors or biological or hormonal peculiarities, it is possible to explain the existence of the sex difference in respect of the majority of the forms mentioned above.

From the foregoing it can be seen that data in respect of sex and age must be interpreted with great caution from the point of view of drawing conclusions concerning local differences in the distribution of malignant tumours.

Value of mass preventive medical examinations

Of great significance in the study of local differences in the distribution of malignant tumours is the analysis of data on the detection of malignant tumours and pre-malignant conditions in mass preventive medical examinations of the population. Carried out on a large scale, such examinations provide an excellent opportunity of evaluating the occurrence of tumour diseases.

With mass-screening records it is possible to compare not only the levels of occurrence of malignant tumours in general, but also to assess the relative frequency of particular forms of malignant tumours, in defined population groups. Moreover, from such records, conclusions can be drawn about a number of regularities in the changing proportions of cancers of various sites in different localities—regularities that have been noted, for example, in respect of patients with newly diagnosed cancer of the skin, breast, oesophagus, and various other sites.

Mass medical examinations are a necessary component of the survey method of studying local differences in the distribution of malignant tumours since, in addition to providing data on the detection of patients with cancer, such screening examinations can elicit information about the working conditions, habits and customs of the population group examined. It is of great value to obtain details of the personal and medical history of all cancer patients in a given locality, and of particular interest in the case of patients suffering from the form of cancer most frequently encountered in that locality. For example, careful questioning of patients with cancer of the oesophagus in a region with a high morbidity from this form of cancer may reveal a preference for very hot food, while study of the case-histories of patients with cancer of the floor of the mouth or with leukoplakias or papillomas of the buccal cavity in an area where these conditions are rather prevalent may disclose an association between them and the habit of chewing betel or *nass* (tobacco mixed with ashes, lime and certain vegetable oils) and inquiry into the personal histories of patients with lung cancer may show that the majority of the patients are smokers.

Representativeness of population groups studied

Great danger lies in the possible artificial selection of cases of a particular form of malignant tumour for study. Before taking, for instance, some of the patients with cancer of the buccal cavity and studying the state of the mucosa in relation to the chewing of betel or *nass*, and then extrapolating the conclusions to embrace the total number of cases of this form of cancer, it is necessary to consider whether the group studied is sufficiently representative of the whole and whether it has in any way been artificially selected. It should be realized that such selection can be quite unpremeditated. In all instances in the analysis of statistical data on groups of patients with malignant tumours and pre-malignant diseases, comparable data obtained from the interrogation of groups of healthy people are required. The numbers of people in the control groups must be sufficient to ensure the statistical validity of the rates being compared.

STUDY OF ENVIRONMENTAL FACTORS

Occupational tumours

Characterized very frequently by long latent periods of development, occupational tumours are one of the most important and interesting aspects of the geographical pathology of malignant tumours. In any area where industry has developed, where the extraction of minerals is going on or where large-scale work involving the use of any kind of carcinogen is in progress, there may be an increase in tumour morbidity. The study of occupational factors has revealed the undoubted effect of chemical, physical and biological carcinogens upon man.

Exposure of a large group of the population to any chemical or physical irritant, however, leads to disease only in a small group. How can this fact be explained? Do carcinogens of a particular kind result in an increase in the total number of cancer patients, as Steiner (1955) suggests? Are there imperceptible components of man's environment that are carcinogenic and lead to the production of the so-called "spontaneous" tumours and to what degree do unnoticed carcinogens contribute to disease? To what extent do industrial workers suffer from various forms of malignant tumours and is there a difference in tumour morbidity between industrial workers and other population groups or the general population? All these questions, though difficult to study, are of the greatest interest. Much work on the investigation of social and economic factors is at present being done in Great Britain, Norway, Sweden, the USA, the USSR and some other countries.

Dietary influences

The study of local differences in the distribution of malignant tumours of the digestive tract in the light of already accumulated medical knowledge is not possible without a thorough investigation of the dietary peculiarities of different population groups. This involves collecting information on a series of points, the main ones being the following:

(*a*) rhythm of meals;

(*b*) heat features of common foodstuffs (preference for very hot or cold food;

(*c*) very frequently consumed foodstuffs (frequency of taking meat, fish, vegetables, spices, mixed foods);

(*d*) consumption of alcoholic drinks (strength of the drinks, frequency of consumption);

(*e*) local peculiarities in the preparation of food;

(*f*) consumption of cereals (millet, rice, maize) and special ways of preparing them;

(*g*) dental condition of the population and the organization of dental care.

Peculiarities of diet apparently have an influence on the production of cancer of the stomach, liver, buccal cavity and larynx. The majority of authors consider that in order to arrive at definite conclusions as to this influence, it is necessary to carry out special research on the relationship between cancer of the stomach and methods of preparing food, with particular reference to the temperature to which fat is heated. Methods of food preparation differ among different peoples; there are three basic ways of preparing food:

1. Heating vigorously by frying or roasting in fat, grilling on a spit, stewing, etc. (These methods predominate in industrialized countries with a large urban population, but are also used by other peoples; the Eskimos, for example, cook over seal-fat lamps.)

2. Slow cooking in hot ashes and on hot stones. (These methods are mainly used in the South Pacific and in South-East Asia; in most instances the food does not reach as high a temperature as it does when cooked by the above methods.)

3. Boiling in water. (This method is mainly used for preparing broths and gruels from various vegetables and cereals; the food is not heated above the temperature of boiling water. The Bantu people primarily cook in this way.)

In assessing the dependence of an increase of malignant tumours upon peculiarities of diet, one ought to consider not only the general level of morbidity and mortality from tumours of the gastro-intestinal tract, but also the frequency of such tumours according to site: buccal cavity and tongue, larynx, oesophagus, stomach, liver and gall-bladder, small intestine, large intestine and rectum.

Finally, in order to evaluate the influence of nutrition, in the broad sense of the word, on carcinogenesis, one must have information on the nature of the diet (particularly on the use of highly spiced food) and on the nutritional level of the population.

Role of trace elements and influence of soil

The trace elements present in various dietary products play an extremely important role; they exert a direct influence upon the health of the population through their action as biocatalysts

providing regulators of the living process. The sources of trace elements in the human body are mainly food products of animal and vegetable origin and, to a certain extent, water sources and the atmosphere. Both a deficiency and an excess of any trace element may be of great significance for health. For example, endemic goitre is associated with iodine deficiency; fluoroses, with an excess of fluorine; Ourovian endemic disease, with a reduction in calcium, accompanied by a reduction in strontium and barium; and—an important factor in the study of local differences in the distribution of tumours—the development of malignant tumours, with a reduction in magnesium, with increased radioactivity of soil, etc.

The soil has an influence on the human organism both directly, through its radiations, and indirectly, through food, since the chemistry of plants depends to a well-known degree on the soil in which they grow. Therefore, in studying the local pathology of tumours, special attention has to be paid to peculiarities in the composition of soils, which are the sources of trace elements in dietary products.

The level of radioactivity of the surface of the earth and of the air is an important factor influencing human health. Alpha-rays stimulate the processes of respiration and oxidation; beta- and gamma-rays facilitate the processes of reconstruction and hinder respiration. Since, in cancer, the processes of oxidation are reduced, one would suppose that alpha-rays would hinder the occurrence and growth of tumours. However, Rosner (1954) examined data on cancer morbidity in Austria and Italy and found that, in localities where the soil contains much potassium and where radiation with beta- and gamma-rays is low, cancer morbidity was high.

Tromp (1955) studied the soil characteristics in various parts of the Netherlands, and related them to the average urban cancer mortality rates per 100 000 population aged over 50 years during 1900-1940. He established that the average death-rate was much higher in localities with drained-peat soil than in localities with sandy soil or in localities where the soil was covered with woody vegetation. The lowest death-rates were observed in the last-mentioned localities. Correlation of the results of chemical analyses of soil and drinking-water with cancer death-rates led Tromp to postulate that the carbonates of calcium, magnesium, manganese and sodium hinder, and silicon oxide stimulates, the development of cancer. In localities where an increased morbidity from goitre was observed, there was also an increased morbidity from cancer of the thyroid.

Tromp's observations showed that the mortality from cancer was very low in regions where the population uses well water and was high in those where the people use river water.

Much work has been devoted to studying the relationship between morbidity from malignant tumours and the content of magnesium in the soil. This work has revealed the fact that in regions where the soil has a high magnesium content, cancer of the stomach is observed infrequently, whereas in regions with black soil containing a minimal amount of magnesium, cancer of the stomach is often encountered.

There is a further relationship to which attention has to be drawn—namely, that between the presence of coal, shale and silica dusts in the air and the development of a number of lung diseases, in particular, cancer of the lung. It is known, for example, that inhalation of coal dust over a long period often produces anthracosilicosis. However, data on lung diseases among miners require very careful analysis, since radioactive substances may be present in the minerals being extracted. The discovery of a high morbidity rate from malignant tumours and pre-tumour diseases in a mining district would be a clear indication for carrying out organizational and scientific investigations.

For the collection of data on the influence of soils on the production of individual forms of malignant tumours, a map of the regions studied, indicating the composition of the soil, must first be drawn up through the co-operation of geologists, physicists, soil chemists and other specialists. The morbidity and mortality rates from different types of tumours for the population in each region can then be calculated with reference to the necessary indices (age-specific and standardized rates) and compared in respect of the composition of the soil on which the population is living. For such a comparison it is essential that the population groups studied should be similar as regards demographic characteristics.

Importance of population migration and ethnic characteristics

A very real difficulty in the study of local differences in the distribution of malignant tumours is caused by population migration—i.e., the transfer of large groups of people to what is, for them, a new geographical, climatic and, possibly, working

environment. Estimation of the morbidity from malignant tumours in particular population groups is always difficult when considerable population migration has taken place. But it is quite indispensable to examine the morbidity from malignant tumours separately for the indigenous population and for the immigrants. If the average length of life of the indigenous population is, in general, different from that of the immigrants, morbidity rates for the two population groups can be compared only after standardization by age and sex. When studying population groups directly after migration into new localities, care must be taken not to draw hasty conclusions about the morbidity rates for different forms of malignant tumours.

Difficulty arises also from the presence of different ethnic groups of population. Comparison of the cancer morbidity in different national groups of migrants has indicated that ethnic differences may exist in respect of the frequency and site of malignant tumours (Steiner, 1954). However, the general conclusion from the study of different forms of malignant tumours in migrants is that external environmental factors, rather than national characteristics, play a role in the production of malignant tumours. The long-term observation of certain national groups after migration has shown that the frequency of occurrence of forms of cancer such as cancer of the skin, stomach and buccal cavity changes under the influence of the different environmental conditions.

While differences in the living and working conditions in different ethnic groups are undoubtedly influential factors in the ethno-pathogenesis of malignant tumours, the significance of racial factors is still not well understood. In the world literature there are numerous references to comparative studies of different ethnic groups living in the same geographical region. Most of these studies have been concerned with differences in the anatomical distribution of malignant tumours rather than with differences in the over-all morbidity from them. Interpretation of the findings is particularly difficult in cases where several population groups have been studied under conditions of migration and in cases where the same region has been subject to several influxes of migrants. The great work on this subject is that of Haenzel (1961b).

One can quote the following examples:

(*a*) In the USA negroes have been found to suffer less often than whites from cancer of the skin and stomach.

(*b*) The anatomical distribution of malignant tumours in American negroes has been observed to be quite different from that in African negroes. (It is, of course, true that the American negroes are actually emigrants from Africa, although they have been living in the USA for a long time.)

What is the basic cause of these differences—heredity or environmental conditions? The facts indicate that environmental conditions are the decisive factor. The influence of the racial factor must not be ignored, but it would perhaps be better to speak not of race or even of racial pathology, but of ethnological characteristics.

Surveys in the USSR

As mentioned earlier, an important method for studying local differences in the distribution of malignant tumours and determining the influence of environmental conditions upon tumour pathology is the survey method. In the USSR surveys were organized in 1955 by the Institute of Oncology (Leningrad) of the Academy of Medical Sciences of the USSR, with the participation also of the Institute of Health Education of the Ministry of Health of the USSR, the Institute of Experimental and Clinical Oncology (Moscow) of the Academy of Medical Sciences of the USSR and workers in a number of oncological clinics.

The surveys were carried out in districts in the northern Caucasus, the coast of the Caspian Sea, in districts of western Siberia, on the shores of the White and Barents Seas, in a number of republics of Central Asia, in districts of the Pre-Baltic, in the Ukraine, and in Moldavia. Very different areas as regards climate, living conditions, ways of life and industrial development were covered and much useful information on the effect of environmental conditions on tumour pathology was accumulated. Some of the data obtained are presented in the final section of this paper.

Importance of data on etiology

Data on the pathogenesis of malignant tumours should ideally be studied side by side with data on etiology, since factors which provoke the occurrence of tumours must exert an influence also on the further stages of tumour development—particularly on the rate of growth of tumours. A question of principle arises here: is it possible to limit the study of geographical pathology simply to peculiarities in the occurrence and distribution of malignant tumours, or is it necessary to examine also the

question of differences in the course of malignant tumours in different regions?

As regards differences in the course of tumour diseases, some authors have suggested the following lines of study:

(*a*) consideration of the presence and course of pre-tumour processes;

(*b*) determination of the elective dislocation of the primary focus and its connexion with the precise application of the specific irritant;

(*c*) assessment of the latent period in a group of patients subjected to the differing influences of carcinogens as etiological factors. (In this way both the rate of the pre-tumour process and the rate of development of the tumour itself can be examined.)

Can all these questions be covered in research on local differences in the distribution of malignant tumours? The course of the tumour process is very individual, depending on many circumstances and causes. With already existing tumours, the methodology of interpreting influences of the external environment must be very precise. Attempts in the USSR to compare various differences in the course of tumour development in various parts of the country have clearly indicated that the differences are directly dependent on how soon the patient goes for medical care, on the nature of the treatment provided, on the biological reaction of the organism, and on the rate of growth of the tumour.

It would therefore be premature, at the initial stage of the investigation of local differences in the distribution of malignant tumours, to study at the same time differences in the course of development of tumours. Such a study would only distract the attention of the research worker from the fundamental question of the existence of differences in the distribution of malignant tumours in the population.

Role of international organizations

Many authors [1] are currently engaged in work on the regional features of the distribution of malignant tumours and facts are being accumulated in many countries. Further development of the study of regional features in tumour distribution is planned by the World Health Organization. WHO studies, now nearing completion, have been undertaken in Dublin and Belfast on the distribution of lung tumours in relation to multiple factors such as air pollution and smoking habits. A parallel study, carried out within the framework of a project on differing incidences and rates of morbidity and mortality, is under way in Norway and Finland. And a third study, on the distribution of tumours in Israel (a country whose different ethnic groups form a good human laboratory for epidemiological study), is in its early stages.

In this connexion it is planned to establish WHO teams, which will set up an information system and study data on cases of malignant tumours. These teams will carry out long-term surveys and it is expected that, on completion of their labours, the research will have been so organized that it can be continued by local physicians. An extensive programme of study for the next few years has been mapped out by WHO. The research will be based on the epidemiological studies, data concerning the frequency of malignant tumours being compared with data on various environmental factors. It is recognized that, at present, satisfactory information on these lines is available only in some European countries and in the USA. In these countries the effect of environmental factors has been observed to be quite similar. A comparison of material on the incidence of malignant tumours in these countries with that which might be obtained in respect of a number of peoples in Africa, Asia, South America and Australia will be of particular interest in the study of regional features of malignant tumour distribution. The carrying out of all this work will require close co-operation between WHO, the International Union against Cancer, the International Federation of Gynecology and Obstetrics and other organizations that could be of assistance in the planning of such studies.

The fact that regional differences in the distribution of malignant tumours exist can be considered as established, though at the present time data are available only for some tumour sites. Study of the literature and analysis of the writer's own material have shown that there are relevant data for cancer of the skin, the lower lip, the mouth, the nasopharynx, the larynx, the oesophagus, the stomach, the liver, the lungs, the mammary glands, the uterus and ovaries, the prostate, the urinary bladder, the penis and the thyroid gland.

Study of the above-mentioned types of cancer and of the special features of their onset has shown that in investigating their distribution various

[1] Dorn, Steiner, Clemmesen, Heller, Segi, Khanolkar, Haenzel, Stocks, Logan, Saxén, Denoix, Ericksen, Peters, MacMahon, Wahi, Wynder, Doll, Afifi, Mosbech, Kozlova, Shilovtsev, Bazikyan, Vepkhvadze, Mats, Merkov, Mironov, Petrov, Shaverdov, Shakhovtseva, Chaklin, Sviatukhina, Orlovski, Kmet, and others.

approaches will be necessary. For example, skin cancer and cancer of the lower lip may be linked with climatic factors; cancer of the oesophagus and stomach with dietary features; cancer of the mouth, oesophagus and lungs with certain habits and customs; cancer of the mammary glands, cervix uteri and penis with features of sexual activity; and cancer of the stomach, thyroid gland, etc. with special features of the soil and its composition. It is because these factors are characteristic in particular regions and nationalities that we speak of regional features in the distribution of cancer.

In the following section, facts are presented regarding various tumour sites and a number of suggestions are put forward for the differential study of the regional features of the distribution of malignant tumours at those sites. The writer's own material is compared with data from the literature.

SOME KNOWN FACTS REGARDING THE DISTRIBUTION OF DIFFERENT TYPES OF MALIGNANT TUMOUR

Malignant tumours of the skin

Significant features in the appearance and development of skin cancer have been noted in a number of countries, the basic determining conditions, as generally accepted, being the degree of skin pigmentation, the degree of ultraviolet irradiation, and the amount of time spent by the population in the open air.

In 1955, Heller, Cutler & Haenzel carried out a survey of 10 municipal districts in the USA with a population of 14.6 million and found that the frequency of cancer per 100 000 of the population in the USA was 305 in males and 331 in females, and that it was 333 among the white population, as compared with 272 among the coloured population. The authors explain this difference by the low incidence of skin cancer among negroes (after excluding skin cancer, the figures for the white and coloured populations are closer: 286 and 267, respectively). In the southern states of the USA the frequency of all forms of malignant tumours among whites and negroes is almost 50% higher than it is in the northern states, mainly because of skin cancer and cancer of the oral cavity and lower lip.

The inverse relation of the frequency of skin cancer to pigmentation was noted by Blum (1956) and Steiner (1955). In contrast to the white population, the negro population shows no difference in the incidence of skin cancer in the southern and in the northern states of the USA. Here we have a difference in histological characteristics. Basal-cell cancers are more frequent in light-skinned people and keratous-cell cancers in people with dark skins. Smith (1956a, 1956b, 1956c) states that skin cancer is extremely rare among the American Indians.

According to Khanolkar (1958), among the indigenous population of southern India, skin cancer accounts for only 2% of all forms of cancer, whereas among the light-skinned non-indigenous population it may be more than 10 times as frequent. This is explained by the intense solar radiation, which favours the appearance of skin cancer on the exposed portions of the body. Observations show that cancer of the unexposed portions of the body in the inhabitants of India develops most frequently in the inguinal folds and in places where clothing strings cause systematic irritation of the skin. The practice, in Kashmir, of warming the body by carrying under the clothes a *kangri* (an unglazed earthen pot packed with smouldering dry maple leaves) frequently induces erythema and eczematous symptoms and, in several instances, has led to the development of skin cancer.

In North Africa, according to Montpellier & Eisenbeth (1953), skin cancer is relatively more frequent on the trunk and extremities than on the face. According to Camain (1954) it is the living conditions, and not the racial features, that determine the fact that the basic group in the structure of cancer morbidity among Africans is comprised of primary tumours of the liver, skin epitheliomas and sarcomas.

The study of local differences in the distribution of cancer of the skin in the USSR shows an increase in the frequency of skin cancer in central as compared with northern districts, and in eastern as compared with northern districts. Analysis of the prevalence of skin cancer in towns in the south of the country has revealed a remarkable regularity. In the southern towns the prevalence rate for skin cancer is between 18.8 and 48 per 100 000 population, while in towns in the central and northern parts of the country the rate is much lower, between 6 and 14.7 per 100 000.

During our surveys we became convinced that the prevalence of skin cancer is undoubtedly associated with the climatic and geographical character of the district. Such an association was particularly clear in the comparison of prevalence rates among

population groups living on the shores of the Caspian, Black and Baltic Seas and of Lake Baikal. Investigations were made on fishermen and members of their families living on the western shore of the Caspian Sea (450 persons), on the eastern shore (225 persons), on the shore of the Black Sea (285 persons), on the shore of the Baltic Sea (270 persons), on the shore of Lake Baikal and in districts of the Buryatsk ASSR (213 persons)—a total of 1443 persons. A control group was composed of people living a long way from the shore and not engaged in work involving a prolonged stay in the open air. This group consisted of industrial workers (398 persons), non-manual workers (478 persons) and people working in the home (365 persons)—a total of 1241 persons. Comparison of the two groups showed that the frequency of pre-malignant conditions of the skin of the face among people living in districts by the sea was two to three times higher than that in districts far from the sea. Further, it was established that, in the seashore districts, cancer of the skin accounted for 18-23.5% of all forms of cancer, while in districts away from the sea the corresponding proportion was 6-12% (Chaklin, Sviatukhina & Orlovski, 1961).

An association has been demonstrated between the frequency of cancer of the skin of the face and the type of head-dress worn in the case of certain central Asiatic republics of the USSR. The head-dresses worn in various districts of Central Asia differ quite considerably, ranging, for example, from turbans (Tadzhikistan) to large fur caps (Turkmenia) and small skull-caps (*tyubetenki*) (Uzbekistan). In these republics one of the principal occupations is cotton-growing, which involves an exceptionally long period of stay in the fields. Comparing groups of cotton-growers in Tadzhikistan, Turkmenia and Uzbekistan, we established that cancer of the skin among them was 1.8 times higher in Uzbekistan than in Turkmenia, although the average temperature in Turkmenia is higher. The prevalence rates for cancer of the skin in the Tadzhik SSR are similar to those in Turkmenia.

The prevailing site of cancer of the skin is interesting. In our surveys we noted that the principal site for cancer of the skin was the face. But while in the North Osetnisk ASSR, the Groznensk and Irkutsk provinces, the Moldavian SSR and the Azerbaidzhan SSR cancer of the skin is localized on the face in more than 90% of the cases, in the Buryatsk ASSR the proportion is 81.5%; in our opinion this is not a chance difference, but is associated with the Buryatsk people's practice of protecting the face from mosquitos.

The survey data showed that there was a big difference in the frequency of cancer of the skin between the extreme north and the south of the country. The scarcity of sunny days in the Far North reduces the insolation of the face of the inhabitants and special fur clothing protects them against the effects of wind and cold.

Comparison of data on the frequency of skin cancer at various sites on the face and trunk has confirmed the existence of certain relationships in respect of the regional features of the distribution of this form of cancer. Thus, while skin cancer is relatively rare in Sweden, Finland, Denmark, Norway and Great Britain, it is frequently encountered in Bulgaria, Greece, Italy, Spain, the south of the USA, and Australia. An increase in the frequency of melanomas is found as geographical latitude decreases and the tropics are approached; in the opinion of Lancaster (1956) this is due to changes in the level of ultraviolet irradiation with changes in latitude.

Skin cancer is detected three-and-a-half times as frequently in prophylactic examinations in the southern regions of the USSR as in the northern regions. Information obtained during surveys has confirmed the data indicating a relatively high frequency of skin cancer and pre-tumoural lesions of the skin in fishermen and sailors; this is evidently due to long exposure to extreme variations of air temperature, bright sunshine, biting winds and other external factors which manifests itself particularly in the appearance with age of hyperkeratosis, wrinkles, folds of skin, chronic eczematous rashes and other changes on the basis of which tumour growth may arise.

Another very interesting problem is the distribution of Kaposi's sarcoma—a disease that exists in many countries, but particularly in the central African areas. Davies (1961) reported a high prevalence of Kaposi's sarcoma in Uganda, mostly in children. Some reports indicate that there could be a relationship between Kaposi's sarcoma and the presence of certain insects in districts; combined studies by physicians and entomologists might be carried out to test this hypothesis. The possibility of virus etiology in several types of human malignant tumours has been suggested and is under investigation.

Malignant tumours of the lower lip

The factors governing the incidence of cancer of the lower lip in many respects duplicate those

governing skin cancer, although the former type of cancer possesses some histological and biological features of its own.

Naturally such factors as exposure to sun and wind, the settling of dust and suspended particles of earth in the folds of the labial mucosa, burns suffered while working in the chemical and metallurgical industries and, finally, smoking must be given due weight; these factors operate in various parts of the world, including the various regions of the USSR.

According to our data, in prophylactic medical examinations of people in the northern regions of the USSR, cancer of the lower lip was detected in 0.02% of cases. The corresponding figure for the southern regions was 0.08%, i.e., four times as high. It was established that cancer of the lower lip is much more frequent among rural inhabitants than among town-dwellers.

It has been observed that cancer of the lower lip develops rather frequently in people with a fine dry skin with little pigment, particularly if they spend a great deal of time exposed to the sun and wind. Most of the patients observed in the Latvian SSR were collective farmers (63.5%). The second place was occupied by manual workers, particularly people doing heavy physical work such as dockers, navvies and watchmen (22.4%). The least affected people were the office workers and dependants.

The role of external factors is reflected in yet another set of observations: the much greater frequency of lesions of the lower lip among men than among women. According to most of the statistics, 95% of all persons suffering from cancer of the lower lip are men. But the more southerly the region, the greater is the proportion of women among sufferers from cancer of the lower lip. A relatively high frequency of cancer of the lower lip was noted among workers in the metallurgical industry (Nizhni Tagil). Material has been published that shows the relatively high prevalence of cancer of the lower lip in a number of countries in Southern Europe (Bulgaria, Greece, Italy and Albania) and the comparative rarity of this form of cancer in northern countries (Scandinavia and Canada).

Malignant tumours of the oral cavity

The frequency of cancer of the mouth is linked with a number of factors, including the habit, widespread in some regions of Asia, of chewing tobacco or betel leaves. Statistical material clearly shows a difference between the frequency of cancer of the oral cavity in various countries and towns throughout the world. For instance, Khanolkar (1955) presents figures according to which cancer of the oral cavity accounts for 36% of all forms of cancer in Bombay, India, whereas the corresponding figures for New York and London are 16% and 6.7%, respectively.

The highest prevalence of oral cancer recorded was in Travancore, India, where 1000 out of 2171 cases of cancer (46%) were cases of malignant oral tumour. Four surveys carried out in India, in the States of Bombay, Uttar Pradesh and Andhra, confirmed the earlier observations that the greater frequency of oral cancer in some districts was associated with the practice of chewing or sucking tobacco or betel leaves and also with the smoking of locally made cigarettes called *bidis*. The surveys also showed that the methods of preparing chewing-mixtures of betel nuts or leaves vary from district to district and that the frequency of oral cancer was higher in districts where a larger proportion of lime is added to the betel. Moreover, it appeared that cancer of the mucous membrane in the oral cavity was found among betel chewers predominantly in cases where the betel was mixed with lime or was chewed together with a mixture of tobacco and lime.

Khanolkar concludes, from an investigation of the chewing and smoking habits of a large number of Indians, that tobacco chewing favours the development of cancer of the oral cavity, that smoking and tobacco chewing together favour the development of cancer of the root of the tongue, and that smoking alone favours the development of cancer of the oesophagus and lungs.

Most authors affirm that in tropical countries, particularly Indonesia, Thailand, Ceylon and Indo-China, cancer of the oral cavity is more frequent than in other countries and that the greater frequency of this form of cancer is to a large extent linked with the habit of chewing tobacco and betel mixed with lime.

Having studied the prevalence of cancer of the digestive organs among the population of Viet Nam, Vu-Cong-Hol (1953) points out that, as a whole, cancer of the digestive organs is approximately twice as rare in Viet Nam as in Europe. In Viet Nam cancer of the oral cavity and pharynx accounts for 77.7% of all cases of cancer of the gastro-intestinal tract. Malignant tumours of the stomach, oesophagus, colon and liver are comparatively rare.

In the USSR, areas with a high prevalence of cancer of the buccal cavity have been identified.

These are districts in Central Asia, particularly districts of Bokhara, Samarkand, Chardjou, Krasnovodsk and several other towns of the central Asiatic republics. The people of these districts, in addition to smoking *papirosy* (cigarettes with long cardboard holders), also take *nass*; about 80% of the adult men and up to 20% of the adult women indulge in the habit of chewing or sucking *nass*. Investigations of population groups carried out at various times by Shilovtsev (1941), Chaklin, Sviatukhina & Orlovski (1961) and others have revealed the presence among *nass* users of a large number of leukoplakias, papillomas and fissures in the mucosa of the floor of the mouth. In these same districts the prevalence of cancer of the buccal cavity has been found to be much higher than in all other parts of the country, the rate being between 15 and 21 per 100 000 population, as compared, for example, with 2-3 per 100 000 population in the Pre-Baltic area.

Data have been calculated to show the relationship between the frequency of cancer of the floor of the mouth and that of cancer of the lung in districts where *papirosy* are smoked but *nass* is not chewed and in districts where the opposite is true. In the former districts the rate for cancer of the lung is between 13 and 21 per 100 000 population and that for cancer of the buccal cavity is between 2 and 9 per 100 000; in the latter districts the rate for cancer of the buccal cavity is between 15 and 21 and that for cancer of the lung is between 4 and 8 per 100 000 population.

During the third Pre-Caspian and the sixth Central Asiatic surveys we came across about a dozen sorts of *nass*, differing in their composition and method of preparation. It is interesting that in three districts of Central Asia where the *nass* is prepared without the admixture of lime the prevalence of cancer of the buccal cavity is between 6 and 11 per 100 000 population, while in districts where the *nass* contains a high content of lime, the prevalence of cancer of the buccal cavity is about twice as high, between 19 and 21 per 100 000.

Cancer of the oesophagus

As for cancer of the oesophagus, there are comparatively few published works in which this form of cancer is evaluated from the standpoint of regional pathology. Usually, the main attention in a study of a group of patients with cancer of the oesophagus has been paid to the case-history and, particularly, to the patient's living habits.

Mosbech & Videbaek (1955), in Denmark, surveyed the living habits and profession of 169 persons who died from cancer of the oesophagus and drew attention to the fact that 65% were alcoholics and 21% were persons whose professions were connected with the consumption of alcohol. These authors consider alcohol to be one of the factors which favour the development of cancer of the oesophagus.

Analysis of the statistics for the hospital centres in Cannes, France, for the period 1952-54 shows that 88% of the patients with cancer of the oesophagus were accustomed to consume large amounts of alcoholic beverages before their illness.

Despite the fact that a fondness for excessively hot food, especially tea, has been observed to be a feature of the population in Mongolia, in various regions of China and in some of the Indonesian islands, comparatively few studies have been made on the distribution of cancer of the oesophagus in these countries and it is impossible to carry out a comparison on the basis of the available material.

Local differences in the distribution of cancer of the oesophagus in the USSR have been determined both on the basis of clinico-statistical investigations and by surveys in a number of districts in the country. From a comparison of data on the relative frequency of cancer of the oesophagus in several countries of the world it may be noted that the USSR occupies an intermediate position.

Analysis of the prevalence of cancer of the oesophagus in various towns in the USSR per 100 000 population revealed that the highest rates were in the following towns: Guryev, 42; Krasnovodsk, 36; Nebit-Dag, 28; Chimkent, 24.6; Semipalatinsk, 24.6. In several towns an exceptionally low prevalence of cancer of the oesophagus was observed: Mogilev, 1.8; Chernovits, 0.8; Minsk, 1.9; Stalino, 1.9.

What is particularly necessary for the evaluation of regional features in the distribution of oesophageal cancer is more accurate diagnosis. An analysis of 2360 cases in which a preliminary diagnosis of oesophageal cancer had been made showed that in 8.8% non-tumoural diseases were involved. Among these cases of non-tumoural conditions, inflammatory processes accounted for 2.1%, cardial and oesophageal spasm for 4.1%, and diverticula for 0.7%, while scar tissues were found at the site of burns in 0.5% and the oesophagus was under pressure from mediastinal tumours in 0.1%. It should be noted that 8.5% of the persons in whose cases a

primary diagnosis of oesophageal cancer had been made were actually suffering from cardial stomach cancer.

In the literature, attention has been drawn to the relative frequency of oesophageal cancer among commercial travellers, hotel workers and waiters (Clemmesen, 1958); the greater prevalence of this form of cancer in Switzerland than in Denmark or Great Britain has been attributed to the fact that the hotel trade is particularly well-developed in Switzerland. The highest indices of oesophageal cancer have been recorded in Switzerland, Mongolia, a number of districts of China, some of the Indonesian islands, Singapore, Bombay and a number of regions of Central Africa. The main question here is the role of thermal and physical irritation of the oesophageal mucosa due to dietary habits in the production of malignant tumours of the oesophagus.

In the USSR relatively high rates for cancer of the oesophagus have been recorded in the Yakutian ASSR (Mironov, 1959), in the Kazakh SSR, in the Karelian ASSR and in districts of the Far North. It was established in these areas of high prevalence (by interrogation and examination of 10 218 persons) that very hot food was favoured by the majority of the people: amongst the Buryats, 79%; the Nentsy, 85%; the Turkmens, 92% (in district of Krasnovodsk); the Kazakhs, 96% (in district of Guryev), 88% (in other districts). The people living in these districts like very hot tea, sometimes with pepper or roasted millet and sometimes with lumps of roasted or dry meat.

In districts where people are engaged in fishing and in the processing of fish, a factor that can be recognized as being injurious to the mucous membrane of the oesophagus is the inclusion of bony fish in the diet. On the shore of the Caspian Sea, where the population is primarily engaged in the fishing industry, the prevalence of cancer of the oesophagus is 3 to 4 times higher than it is in agricultural districts situated a long distance from the sea.

In areas where oesophageal cancer is prevalent, a relatively high frequency is noted among people under 40 years of age and the ratio of cancer of the upper third of the oesophagus to other forms of cancer is higher than in districts where oesophageal cancer is relatively rare.

The dietary habits of the population—for example, their love of extremely hot food and the frequent eating of over-cooked food in some regions and the consumption of dairy produce, vegetables and fruit in others—undoubtedly have an influence on the structure of malignant tumour morbidity and particularly on the incidence of stomach cancer.

Cancer of the stomach

In most countries cancer of the stomach takes first or second place in the structure of malignant tumour morbidity. Since it is an established fact that in a clear majority of cases cancer of the stomach develops on soil prepared by pre-tumour processes, studies of the frequency of gastritis, ulcers and polypous ailments of the stomach in different parts of the world have been carried out by a large number of research workers. In these studies, as a rule, much importance has been attached to the relation between the development of these processes and the nature of the nutrition, the types of produce consumed, the amount of fruit and vegetables eaten, the way in which the food is prepared, the rhythm and manner of feeding, and the action of alcoholic beverages, tobacco, various spices, etc. on the stomach.

Analysis of a number of works shows that cancer of the stomach is actually less widespread in the tropics than in Europe and North America. Thus, in a group of cancer patients, cancer of the stomach accounts for 4.1% in South America, 2.2% in Rhodesia, 1.7% in Dakar, 3.9% in Nigeria and 1.8% in Kenya. Among negroes in tropical America the corresponding figures (according to post-mortem records) are 20.5% for men and 10.2% for women. As a whole, cancer of the stomach in the USA accounts for 23% of all cancer cases in men and 11.2% of all those in women. In South-East Asia cancer of the stomach is rare among Malays and relatively common among Chinese and Filipinos, and was found to be more common among the Tamils than among the Singhalese and more frequent in North Viet Nam than in South Viet Nam.

The possibility of a connexion between the frequency of cancer of the stomach and the nature of the soil has been suggested by several workers—Tromp & Diehl and Davis & Vingiface in England; Feisinger, Grillau, Molière, Robinet and others in France (quoted by Tromp & Diehl, 1955).

An extremely important question is that of the influence of nutrition, in the broad sense of the word, on carcinogenesis. This question has a bearing not only on the frequency of cancer of the stomach, but also on that of cancer of the liver, the oral cavity and the pharynx. As mentioned earlier (see page 344), studies should be carried out on the relation between cancer of the stomach and methods of prepar-

ing food and data collected on the nature of the diet and on the nutritional level of the people.

Primary cancer of the liver

A great deal of research has been devoted to the study of the prevalence of cancer of the liver among the population in different areas. Most authors who have studied the distribution of cancer of the liver in Africa have noted a high frequency of this form of cancer among the indigenous inhabitants. This high frequency, they believe, is not due simply to nutritional features but is also related to other etiological factors. There is an exceptionally large number of published works on the prevalence of liver cancer among negroes of the Bantu tribe in South Africa (for example, Gilliam, 1954; Denoix, 1956; Berman, 1958; Higginson, 1956). According to some data, more than 90% of the deaths from cancer among Bantu negroes are due to primary cancer of the liver, whereas in Western Europe and among the American negroes this form of cancer represents only a little over 1% of the total mortality from cancer.

Interesting figures on liver cancer are given by Denoix (1956). The yearly incidence of this form of cancer in the USA is 17.1 per 100 000 for men and 19.2 per 100 000 for women, while in Denmark the corresponding figures are 20.0 and 25.4. Cancer of the liver is comparatively common among the negroes in French West Africa (55% of all cancer cases in men and 17% in women).

In the USSR primary tumours of the liver are rarely encountered, except in Siberia. A point requiring study is the link between the greater frequency of liver cancer in some districts of Siberia and the higher prevalence of opisthorchosis in those districts.

Of the influences which have been suggested by various authors to play a part in the causation of cancer of the liver, those of genetic and climatic factors would appear to be of very doubtful significance. Much more convincing are the data relating to the importance of the nutrition factor in carcinogenesis of the liver. That the role of nutrition is important is proved by the fact that cancer of the liver and pancreas can be easily induced experimentally in animals by the inclusion of carcinogenic substances in the diet. Moreover, it has been shown that the development of malignant tumours of the liver can be accelerated or inhibited by the feeding of specific substances. In the writer's opinion, therefore, it may be firmly stated that primary cancer of the liver is a disease where there is no doubt as to the existence of regional variations in distribution.

Cancer of the lung

The prevalence of cancer of the lung has been particularly widely discussed recently in the world medical literature. It has been proved beyond doubt that cancer of the lung is much more common in towns than in rural districts, in men than in women, and in smokers than in non-smokers. A connexion between between the number of cigarettes smoked per person per year and the frequency of lung cancer has been noted in most of the studies.

Attention has been drawn to the great increase in the frequency of lung cancer in some countries in recent years. The rates have been particularly high since 1930 in England, the Netherlands, Switzerland, Finland, the USA and Denmark; in Japan, on the other hand, they have been relatively low.

The basic factors considered to influence the frequency of lung cancer are: (*a*) the inhalation of noxious substances in certain occupations (uranium dust, containing arsenic; chromium dust; etc.); (*b*) the pollution of the atmosphere by the carcinogenic substance benzpyrene, which is contained in the smoke from factories and the exhaust from motor vehicles; (*c*) infection of the respiratory passages; (*d*) smoking.

Not all aspects of the problem of lung tumour epidemiology have been dealt with here since there are many published works on the subject, particularly regarding the relationship between cancer of the lung and air pollution, smoking and chronic bronchitis (Doll, 1950, 1954; Shabad, 1960; Shabad & Dikun, 1959; Dorn, 1943, 1958; Haenzel, 1961a).

Malignant tumours of the mammary gland and of the female reproductive system

In studying the factors which favour the development of mammary-gland cancer, it has been established that there is a connexion between the frequency of malignant tumours of the breast and a number of features of women's lives, habits and customs. All this falls within the scope of regional features of the distribution of cancer, in view of the similarity of habits and customs within particular racial groups.

The frequency of cancer of the mammary gland varies both from country to country and, to a certain extent, within the same country. Numerous

authors have attempted to explain these differences in the frequency. There have been some who incline to the racial theory, asserting that women of certain races have a predisposition to cancer of the mammary gland. Most authors, however, attach decisive significance to such factors as the frequency of feeds, the frequency of births and abortions, and the sexual life of the women.

According to the material of the Committee on Geographical Pathology of the International Union against Cancer, cancer of the mammary gland is comparatively common in England (35 deaths per 100 000 women), Switzerland (29.2), New Zealand (28.4), Denmark (27.5), Australia (25.5) and Canada (24.5), and is comparatively rare in Chile (3.9), Japan (3.9) and Israel (3.6).

Khanolkar (1961) and Segerdahl (1955) have noted that cancer of the mammary gland is comparatively common among women who marry late and also among well-to-do women.

Several studies have shown that mammary cancer is commoner among women living in towns than among women living in the country. For example, in Norway the mortality rate from breast cancer is 31.9 per 100 000 women in the towns, as compared with 18.7 in the villages (Maisin & Langerach, 1955). The considerable increase in mortality from mammary-gland cancer in some countries during the last 40 years can be attributed partly to urbanization. In Australia, New Zealand, South Africa, Denmark, Italy, Sweden, Norway and the Netherlands, mortality from this form of cancer has increased twofold.

In many cities and regions of the USA, more and more use has been made during recent years of various vitaminized food mixtures for feeding babies. Thus, women after childbirth bind up their breasts and do not feed their babies with their own milk. Of 238 000 women who contracted cancer in the USA in 1955, 52 000 had mammary-gland cancer, which was foremost among all forms of malignant tumour.

The study of local differences in the distribution of malignant tumours of the mammary gland and of the female reproductive system is facilitated by the fact that there are, on the one hand, large population groups where the women breast-feed their children for a lengthy period and where neither abortion nor contraception is practised, and, on the other hand, large population groups, mainly in towns, where the women do not breast-feed their babies at all, or breast-feed them only for a very short time, and where various forms of contraception that prevent physiologically normal sexual intercourse are practised and there is a high abortion rate.

The inverse relation between the frequency of mammary-gland cancer and that of cancer of the cervix uteri has been described by a number of authors and has also been observed in surveys in the USSR. In most countries, lower breast cancer rates are accompanied by higher rates for cancer of the cervix uteri, and *vice versa*. Exceptions are Japan and Israel, where the frequency of both forms is low.

In a group of women suffering from mammary-gland cancer, the number of breast-fed children per woman was 1.21, whereas in a control group of healthy women of the same age the number was 4.22 (Segi, 1955; Segi et al., 1957).

In a number of districts of Africa and East Asia, on the island of Capri, and in Greece (Symeonidis, 1950) and southern Italy, a relatively high frequency of gynaecomastia has been recorded along with an increased frequency of mammary cancer in men.

Frequent trauma during childbirth is one of the factors that favour the development of cancer of the cervix uteri. The high prevalence of this form of cancer in some districts of many countries is related to the fact that the suturing of post-natal lacerations of the cervix is not regularly practised in those areas and that the mass preventive medical examination of women is not developed, so that pre-malignant conditions of the cervix are not always detected. The detection of these pre-malignant conditions through systematic medical examinations is of great importance in the prevention of cancer of the cervix. The institution of such preventive measures has reduced the prevalence of cancer of the cervix in a number of towns in the USSR; in Leningrad, for example, the frequency of cancer of the cervix showed a definite decline during the period 1949-60.

As for the distribution of cancer of the breast in the USSR, quite low prevalence rates have been observed in a number of districts and republics: Kabardin-Balkarsk ASSR; Buryatsk ASSR; Guryevsk Province of the Caucasian SSR; Nenetsk National District; and the Turkmen SSR. In comparison, the rates for many towns in the USSR are somewhat higher.

Analysis of the data collected in the districts surveyed showed that pre-cancer and cancer of the breast were extremely rare among the women of the following ethnic groups: Buryats, Karels, Nens, Turkmens, Tadzhiks and Uzbeks. In comparison, the prevalence of cancer of the breast among the non-indigenous settlers in these districts (women of

Russian or other nationality) was definitely higher. In the districts investigated, the frequency of breast cancer was much lower among women living in villages than among those living in large towns. From these observations it can be concluded that the frequency of cancer of the breast is associated with racial habits and customs and does not depend on climatic or geographical conditions. In contrast to the women of Russian or other nationality, the women of the indigenous ethnic groups in the districts surveyed begin their sexual life early and practise regular sexual intercourse in marriage, do not use contraceptives, have more frequent and more prolonged lactation periods, and rarely have recourse to abortion (the number of induced abortions is about 10 times higher among the women living in towns than among those living in villages). All the above factors play an important role in the prevention of breast cancer, since they promote the active physiological function of the breast and protect it against pre-malignant changes and cancer. The survey findings have thus opened up the possibility of reducing the frequency of pre-cancer and cancer of the breast through the dissemination of suitable propaganda among the population.

As for cancer of the uterus, this form of cancer also has its own distribution features. In this connexion it is most interesting to study the correlation between cancer of the uterus and cancer of the mammary gland and between cancer of the cervix uteri and cancer of the corpus uteri. Cancer of the cervix uteri occupies first or second place in a number of regions in the world.

There are many published works on the correlation between the rates for cancer of the cervix uteri and for cancer of the corpus uteri. In North Africa, the ratio of cancer of the corpus uteri to cancer of the cervix uteri is higher than it is in Europe. According to Hochmann (1955), from 1933 to 1947 at the Oncological Institute in Jerusalem the rate for cancer of the cervix uteri was lower than that for cancer of the corpus uteri among Jewish women. Herberger (1956) concludes that childlessness and restraint from sexual activity protect a woman from cancer of the cervix uteri. A survey of 13 000 nuns revealed no case of cancer of the cervix uteri and only 12 cases of cancer of the corpus uteri.

The connexion established between the frequency of cancer of the cervix uteri and the various conditions of sexual life suggests that research should be carried out along two lines: (*a*) determination of the significance of abstinence from sexual intercourse for a certain period after menstruation, as prescribed by Jewish law (this could be done by collecting the necessary information from Jewish women suffering from cancer of the cervix uteri); (*b*) determination of the effects of circumcision on carcinogenesis of the cervix uteri (for this, information must be collected on the relative numbers of women with cancer of the cervix uteri who have lived in sexual relations with men who have and with men who have not been circumcised).

Other forms of malignant tumours

As to local differences in the distribution of other forms of malignant tumours, there are data indicating that such differences exist in respect of various forms—for example, cancer of the larynx, the thyroid, the ovaries and the penis—but in the majority of cases the material accumulated cannot be accepted as sufficiently complete. An exception is the material on cancer of the thyroid, which is recorded more frequently in districts known to be foci of endemic goitre (high mountainous districts such as the Himalayas, Andes, Alps, Urals, etc.) than in goitre-free districts.

Leukaemia

The problem of leukaemia epidemiology is a very large one. As recent articles by MacMahon (1962) and Grais (1962) have shown, the frequency of leukaemia varies in association with a great many epidemiological factors.

THE POSSIBILITY OF PREVENTING CANCER

Research on the geographical pathology of tumours must be properly co-ordinated in order to provide a reliable basis for the organization of preventive measures. Combined efforts must be directed at obtaining complete data on all malignant tumours and pre-malignant conditions, on the life, customs and habits of various peoples, and on the possible injurious agents that act on the human organism over a long period. Only after unification of registration and proper statistical analysis of the full material can conclusions be drawn and practical methods for the prevention of various forms of cancer developed. Preventive measures must be directed primarily towards active control, on the part of local doctors, over the working and living conditions of the various population groups so that

carcinogenic or co-carcinogenic influences in the environment are eliminated or reduced to a minimum.

It is essential to take preventive action against pre-cancerous conditions by warning the population of habits that are harmful to health and by improving hygienic standards. The need for wide dissemination of reliable health information was clearly revealed in the USSR surveys. Personal interrogation of more than 10 000 people in the districts surveyed showed that the overwhelming majority was not well informed about those diseases from which cancer can develop and neither knew nor took protective measures.

Study of the organization of health education work in the survey districts showed that the dissemination of information on the prevention of pre-malignant conditions receives practically no attention. Various doctors are attempting to spread this kind of propaganda, but in many cases serious methodological mistakes are being made.

The study of the geographical pathology of tumours has an important bearing on the proper organization of preventive measures. The strict individualization of measures of preventing particular forms of cancer can be formulated only after thorough study of all the factors causing the occurrence of a given form of tumour. Furthermore, the establishment, for example, of the fact that certains forms of tumour are very rare in a certain population group can facilitate the determination of those physical conditions for human life under which the possibility for the development of given forms of tumour is at a minimum.

The basic question remains unsolved—are all exogenic and endogenic influences (carcinogens, dyshormonal processes, physical and actinic factors) a direct cause of the genesis of pre-tumour processes, leading in individual cases to the development of malignant tumours (cancer or sarcoma), or do they prepare the ground for the action of the tumour virus? Nevertheless it can be concluded that all the factors involved in the regional pathology of tumours are of undoubted importance since, besides indicating some patterns in the increasing frequency of individual forms of malignant tumours in various countries and in different regions of those countries, they may also serve as a scientific basis for the prevention and control of these diseases.

The development of research on the etiology of human tumours is every year bringing to light new facts. The interpretation of these facts is sometimes difficult. There are today two main views as to the etiology of cancer: one upholds the virus nature of cancer, the other stresses the role of a combination of chemical, physical and biochemical carcinogenic agents. Basic research should provide an answer to this general question. But whatever the answer, the importance of epidemiological studies of cancer is beyond question.

RÉSUMÉ

Toutes les races humaines, sous quelque climat qu'elles vivent, peuvent être atteintes de néoplasmes; mais il est des régions où certains types de tumeurs sont plus fréquents que d'autres. Ces différences dépendent dans une certaine mesure du climat, de la géographie, des mœurs et des occupations des habitants. Il est de toute importance pour l'étude étiologique des tumeurs d'examiner l'action de ces divers facteurs sur la fréquence des tumeurs malignes.

L'auteur passe en revue les données actuellement recueillies sur différents types de cancers, en fonction de leur répartition géographique et climatique et de leur fréquence. Les tumeurs de la peau sont en relation avec la pigmentation, l'intensité de l'irradiation ultraviolette, la vie en plein air et la protection plus ou moins efficace contre le soleil et les intempéries; les tumeurs de la cavité buccale se rencontrent particulièrement parmi les populations qui mâchent le bétel, surtout s'il est additionné de tabac et de craie. Le cancer de l'œsophage — pour lequel les indices les plus élevés ont été trouvés en Suisse, en Mongolie, dans certains districts de la Chine et de l'Afrique centrale, à Singapour et à Bombay — semble dépendre d'une irritation thermique ou physique. Le cancer de l'estomac — qui, dans la plupart des pays, occupe la première ou la deuxième place dans les causes de morbidité par cancer — peut être reproduit expérimentalement par l'addition au régime alimentaire de substances cancérogènes. On a beaucoup étudié le cancer primaire du foie, en particulier en Afrique, où il est très fréquent dans les populations indigènes. Certains travaux évaluent à 90 % la proportion de décès par ce type de cancer chez les Bantous (contre 1 % chez les Noirs d'Amérique), Quant au cancer du poumon, plus fréquent dans les villes que dans les campagnes, chez les hommes que chez les femmes, chez les fumeurs que chez les non fumeurs, dans l'atmosphère polluée des villes et de certaines usines, il fait actuellement l'objet d'études épidémiologiques et étiologiques étendues.

Les tumeurs du sein et des organes génitaux de la femme sont de fréquence variable selon les pays: 35 décès par 100 000 femmes en Angleterre, 29,2 en Suisse, 28,4 en Nouvelle-Zélande, et 3,9 au Chili et au Japon, 3,6 en Israël. Des études comparatives ont été faites sur ces types de cancers, en relation avec les habitudes des populations: allaitement au sein ou sevrage, usage de contraceptifs, avortements, etc.

Une partie de l'article est consacrée aux recherches à poursuivre et à entreprendre, à la nécessité d'user d'une terminologie uniforme qui permette de comparer les résultats d'un pays à l'autre, à la méthodologie, à la valeur que l'on peut reconnaître aux statistiques de morbidité et de mortalité par cancer dans les divers pays, aux rapports à établir entre la fréquence de divers types de tumeurs, entre les sexes, et enfin, à la valeur, dans la prévention du cancer, des examens médicaux systématiques de la population.

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