The epidemiology of gastrointestinal cancer with special reference to causation¹

A great deal of evidence is now available to show that the incidence of gastrointestinal cancer varies from place to place and from time to time. Moreover, the incidence among migrant populations is, in general, intermediate between that found in their original homeland and that in the country to which they have emigrated. It is evident, therefore, that environmental factors play an important part in the development of these cancers and that many of them may be preventable.

AETIOLOGICAL FACTORS

GASTRIC CANCER The most striking observation relating to the incidence of gastric cancer is the rapid decline that has taken place in the U.S.A. during the last 30 years. A decrease has also occurred in many other countries, some, but not all, of which originally showed a high incidence, but it is not universal and there has been little or no change in Japan. In general the decrease has begun first and been more marked in women than in men. The incidence varies at least tenfold between different countries. The disease is common in Japan, Iceland, Finland, Poland, parts of the U.S.S.R., China and Chile, relatively rare in the white population of the U.S.A. and very rare in many parts of the native populations of Africa, South America, and India. Striking contrasts are provided by Uganda (rare) and part of Kivu province of the Congo (common) and in Java by the Chinese inhabitants (common) and the native Indonesians (rare).

The incidence varies to a considerable extent within countries, and even within quite small countries. It is commoner in North Wales than in south-east England and in the Alpine and Pannonian plain regions of Slovenia than in the Mediterranean littoral. In general it is commoner in the northern parts of countries in the northern hemisphere than in the southern parts, although no such difference is revealed in Norway.

¹Report of the proceedings of an international working party held under the auspices of the World Organization of Gastro-enterology at the Ciba Foundation, London, on 17 to 19 October 1963. The members of the working party were as follows:—

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In industrialized countries it is notable that the disease occurs principally among the poor, but this rule does not hold in South Africa where it is several times commoner among the Cape Coloureds (who are largely westernized in their manner of life) than among the poorer Bantu workers. There is little to suggest that there are any important specific industrial risks, but it is notable that the disease tends to be unduly common among miners—and possibly also among their wives.

Urban-rural differences are small and when they occur the incidence is usually higher in the countryside. This makes it difficult to believe that the correlation with domestic coal consumption that has been observed in 83 British towns is directly due to atmospheric pollution. Britain may, however, be an exception as, in that country, the urban mortality is approximately 25% higher than the rural and the correlation with atmospheric pollution persists even after the more important 'social factor' (a measure which may be identified with poverty) is allowed for. The possible effect of atmospheric pollution might be explored further by examining the incidence of the disease among men employed in a specific occupation but resident in different areas.

Local variations in incidence have been attributed to differences to the geological formation and to the nature of the water supply. There is no conclusive evidence of a correlation with any particular constituent in soil or water, but the incidence has been reported to be particularly high in regions where the soil is peaty and the water very soft (Britain, Czechoslovakia, Holland) or where there is a high content of zinc in the soil (Britain, Japan). Very soft water might exert an effect because of its ability to carry ionized metal in solution. The suggestion that the incidence of gastric cancer is inversely correlated with the degree of hardness of water, has however, not been borne out by the most recent British study (unpublished).

The consensus of opinion among members of the working party was that the main causes of the disease were likely to be found in the diet. Diet is, however, extremely difficult to analyse and questions to patients about the type of food eaten are almost useless. Information about the type of food eaten more than a few years previously has proved extremely unreliable and no consistent differences

have been detected in response to questions about the type of food eaten immediately before the illness which preceded admission to hospital between patients with gastric cancer and patients with other, non-gastrointestinal, diseases. More retrospective inquiries of this sort are unlikely to be fruitful, unless a specific hypothesis can be framed about a particular foodstuff. A better method may be to ask general questions aimed at eliciting broad likes and dislikes; but the most promising method would appear to be an attempt to characterize the diet eaten in different rural areas in the hope that some features of the diet could be correlated with the incidence of the disease. In many rural areas diets are still traditional and the character of the traditional diet is largely determined by the type of food economically grown in the area. It is notable that the disease appears to be rare in most areas in which maize provides the staple food. Costa Rica appears to provide an exception and it might be valuable to compare the other elements of the diet that are eaten in that country with the other elements eaten by other maize-eating populations. Potatoes provide the most direct contrast to maize and the disease is believed to be common in nearly all areas where potatoes provide the principal source of energy.

In all considerations of diet, attention should also be paid to the method of cooking, the type of cooking utensil used, and the frequency of dental caries in the population.

Apart from direct studies of cancer incidence, attempts might be made to estimate the incidence of pre-cancerous conditions in populations with different dietetic habits. Estimates of the frequency of atrophic gastritis would be difficult; intestinal metaplasia can be defined and recognized more easily, but it is not adequate to look for it in small biopsy samples which are poor measures of the status of the stomach as a whole. A simple and physiologically satisfactory substitute might be an investigation of the incidence of achlorhydria by means of the 'tubeless test meal'. It would be interesting also to discover whether trends in the incidence of pernicious anaemia could be correlated with trends in the incidence of gastric cancer.

Pathological studies have so far failed to distinguish clearly any different types of carcinoma which might have different causes. There is, however, some evidence to suggest that the two extreme varieties, well-differentiated adenocarcinoma and scirrhous carcinoma, differ in respect of their sex and age distributions and this possibility should be pursued. A distinction might also be made between papillary and ulcerative growths and possibly even between growths at the proximal and distal ends of the stomach; but international comparisons between the

relative frequencies of the different types are unlikely to be fruitful until more exact definitions can be agreed.

OEESOPHAGEAL CANCER Oesophageal cancer differs from the other two principal gastrointestinal cancers in demonstrating a very variable sex ratio. The incidence among men provides little indication of the incidence among women and the ratio of the rates in the two sexes may vary between 1 to 1 and 5 to 1 irrespective of whether the disease is common or rare. It is common in France, Switzerland, Finland, Iceland, and the Karelian Soviet Socialist Republic; but very high incidences, of the same order as the incidence of bronchial cancer in Britain, are found in more localized areas, *e.g.*, the Transkei region of South Africa, part of the Chinese province of Honan, and the island of Curaçao. In Norway, Britain, Australia, and parts of Africa and among the white population of the U.S.A. the disease is relatively rare and in these countries the incidence among women may be as little as one-fiftieth of the rates recorded in other areas.

The very high incidence among the Bantu in parts of South Africa is a recent phenomenon and a new aetiological agent must have been introduced during the last 30 years. In countries where the disease is low, the incidence is generally decreasing.

Three factors are believed to be of aetiological importance. Alcohol consumption has been shown to be related to the disease in the U.S.A., Britain, France, Sweden, and Japan. The disease is concentrated among men and women who drink heavily, but there may also be a lesser risk at lower levels of consumption. Whether the effect is directly due to the alcohol itself is not known; the relationship could be indirect, in the sense that the disease might arise on the basis of a secondary nutritional deficiency. It is notable that French wines contain a high concentration of mineral salts, whereas Australian wines are, in this respect, relatively pure; it may be that some associated mineral is more important than the alcohol. Attempts to relate the disease among the South African Bantu to such contaminants of alcohol as tar, carbide, and arsenic have so far failed; the distribution of lead as a contaminant deserves further study.

Tobacco consumption has been related to the development of oesophageal cancer in the U.S.A., France, Britain, Sweden, India, and South Africa. The disease is not specifically related to cigarette smoking and some studies suggest that pipe and cigar smoking may be more important. Interpretation of the findings is difficult. The heavy drinker is also commonly a heavy smoker and some of the association with smoking (which is less strong than the

association with alcohol consumption) is likely to be a secondary ephiphenomenon. In some countries, the chewing of tobacco, with or without betel or other components, is also associated with the disease.

The third factor is nutritional deficiency. Carcinoma of the cervical oesophagus behaves in some ways like carcinoma of the hypopharynx and this type of oesophageal cancer occurs in women in north Sweden against a background of longstanding dysphagia and sideropenia. It has, however, not been possible to relate the disease directly to nutritional deficiency in any other country.

None of these factors appears to be capable of accounting for the disease in the areas where the incidence is particularly high. In Honan, in particular, the disease occurs in a part of the country where very little alcohol is consumed.

Excessively hot foods and drinks have been suggested as a contributory factor, especially in the cold climates of Iceland and Finland, but there is no direct evidence to implicate them.

Pathological studies provide no reason to suppose that the disease should be separated into distinctive histological types. Adenocarcinoma of the oesophagus nearly always arises from the stomach and such cases should be excluded. The division of oesophageal cancer into three groups according to whether it arises in the upper, middle, or lower thirds is arbitrary and figures based on these divisions are difficult to compare. An attempt should be made to separate cancer of the cervical oesophagus from cancer of the thoracic oesophagus since they may well have different causes. Cancers of the abdominal oesophagus should also be separated and, in the absence of histological proof that they are squamous celled, regarded as gastric.

CANCER OF THE LARGE INTESTINE Cancer of the large intestine is commonly considered to be two separate diseases: cancer of the colon and cancer of the rectum. This division is sanctioned by physiological and clinical considerations, but in practice it is often difficult to determine whether a particular cancer arises in the upper end of the rectum or in the lower end of the sigmoid colon. The junction between these regions is a common site for the occurrence of cancer, and some reported differences between the incidence of cancer of the colon and of the rectum in different countries may be due to differences in anatomical classification.

Pathologically there does not appear to be any conclusive reason for distinguishing between the two types of cancer and, in some circumstances, it may be better to class them together as cancer of the large intestine. There are, however, fairly strong epidemiological grounds for believing that cancers of all

parts of the large intestine do not have the same aetiology. Cancer of the rectum is everywhere commoner in males than in females, whereas cancer of the colon is usually commoner in females. This is not due to bias in ascribing cancer of the recto-sigmoid junction to the colon in females and to the rectum in males, since the female preponderance is most marked for cancer of the right half of the colon. Moreover, there is suggestive evidence that in countries where cancer of the large bowel is common, the excess incidence is most marked for the rectum and the left side of the colon. Clearly, therefore, information of value might be lost if cancer of the large bowel were studied as a single entity.

The gut immediately below the splenic flexure is a rare site for cancer and it might be more practicable to make the dividing line through this region and to study cancer of the colon up to the splenic flexure as one entity and to classify cancer of the left side of the colon with cancer of the rectum.

Whether this division would be more fruitful for aetiological studies remains to be proved. It is worth investigating but, in the meantime, the classical division between rectum and colon should not be abandoned. The different functions of these two parts of the bowel may be relevant to the reasons for the development of cancer in them and there are grounds for believing that the change in the sex ratio takes place close to the recto-sigmoid junction. Agreement on a practical way of separating cancers in this region is desirable before any international studies on cancer of the large bowel are planned.

Another possible source of error in comparing data from different countries is that, unlike cancer of the stomach and oesophagus, the survival rate is fairly high so that mortality is not necessarily a good indication of incidence. If the survival rate varies, and there is evidence that it may do so for reasons other than the availability of treatment, this will complicate the interpretation of mortality data.

Despite these difficulties it is clear that cancer of the colon and cancer of the rectum both vary in incidence in different countries, and that the range of variation is at least twentyfold. These diseases are particularly common in Scotland and Denmark; they are rare in Israel and are particularly rare in many parts of Africa. They are also relatively rare in all countries where there is a high incidence of gastric cancer, *e.g.*, Poland, Finland, Iceland, and Japan. In many countries the incidence is beginning to decrease.

There is very little evidence to implicate any particular factor as a cause of the disease. Study of the use of purgatives has been negative, except for some slight evidence to suggest that liquid paraffin

may contribute to the development of a small proportion of cases (together with some cases of cancer of the stomach). Variations in diet which lead to differences in faecal transit time through the bowel and to differences in faecal bulk, which might affect the concentration of a carcinogen in contact with the mucosa and the duration of contact, deserve investigation. In many African countries, where there is a very low incidence of large bowel cancer, it is customary to have the bowels open three or four times a day and the faecal bulk is high. There is, however, evidence to suggest that transit times, at least in some of these populations, are not notably different from those observed in Europe and North America.

Another possible line of investigation is to study the incidence of bowel cancer in patients with ulcerative colitis. Patients with this disease are particularly susceptible to colon cancer and many of them take restricted diets for many years. A co-operative prospective study might provide an opportunity for relating the occurrence of the disease to variations in diet that were maintained under direct medical observation.

GENETIC FACTORS For all these types of cancer there is evidence that simple genetic factors may sometimes play a part in determining susceptibility to the disease. By themselves, they are unlikely to be of overriding importance in more than a small proportion of cases; but knowledge of them may help to elucidate the nature of an environmental factor, by allowing a high-risk group to be defined in which the action of a carcinogenic factor can be more easily recognized.

ESTIMATES OF INCIDENCE

A great deal of information has been obtained in the last ten years about the incidence of cancer in different parts of the world. There are, however, still many countries for which little or no information exists and many others for which it would be desirable to have more detailed data about local variations. Incidence studies remain one of the most promising methods for obtaining new ideas about the aetiology of cancer.

COLLECTION OF STATISTICS Useful data can be obtained in several ways. Whatever the method, and the choice will often be governed by the resources available and the state of development of the area, the object is the same: that is, to obtain an estimate of morbidity which can be examined separately for such basic characteristics as the pathology of the growth and age, sex, and place of residence of the

subject. To achieve this all records must be classifiable according to such characteristics, and the populations from which the cases arise must also be known, or capable of estimation, with respect to the same demographic features.

The type of organization best fitted to provide an accurate measure of cancer incidence is illustrated by the permanent cancer registries that have been established in various parts of the world, some of which cover whole countries. In all such registries basic data are obtained by the compulsory, or sometimes voluntary, notification of all newly diagnosed cancers. Since, however, substantial numbers of persons with cancer die without a definite diagnosis having been put on record during life, the information from these notifications has to be supplemented by that from death certificates which identify persons said to have cancer but not previously notified. Questions asked in the course of registration and subsequent follow-up elicit relevant details concerning both the patient and his disease and the collection of such information on all cancer cases, when allied to the population data supplied by the comprehensive vital statistics system usually present in places where registries are maintained, makes possible the most accurate and detailed breakdowns of cancer incidence currently available.

Only a very small proportion of the world's population is, however, covered by cancer registries and in their absence we have to turn to other methods. One alternative, in areas with adequate registration of vital statistics, is the use of mortality data as an indirect measure of incidence. In the past, mortality records have been the mainstay of cancer epidemiology, their use being dependent on the very high fatality rates which allowed them to be considered as a close reflection of incidence for many types of cancer. While advances in treatment may perhaps be expected to distort this relationship in the future, cancer mortality statistics still retain a useful role in the epidemiology of many types of the disease, certainly including cancer of the oesophagus, stomach, and large intestine.

In other situations the method of choice may be an intensive short-term survey. Broadly, this consists of the ascertainment from all possible sources, throughout a short period of years, of cases newly diagnosed and of persons dying from cancer. Detailed planning will vary from area to area and the success of any particular study will depend on how closely survey plans can be dovetailed with such pre-existing local features as natural geography, local government boundaries, sites of hospitals or other medical agencies, and the lines of communication to and from them. If, for example, one or more hospitals provide the focal point of the inquiry then it is

necessary to define the area which is completely served by these hospitals for the purpose of cancer diagnosis among its population. Relevant details of the population in the area are also required and, if not otherwise available, may have to be obtained by means of a special sample census. This type of survey has been used in both highly developed and primitive communities and, at its most successful, can yield data comparable in type and quantity to that of a permanent cancer registry. Although carried out over a limited period its planning and execution require considerable time and resources.

While conscious of the need for further detailed morbidity studies of the calibre provided by cancer registries and special surveys, the working party recognized that any immediate and large-scale expansion in this field was unlikely. In view of this, consideration was given to the possibility of more efficient use of hospital statistics. Although such statistics were readily and widely available their interpretation, as measures of incidence, was inevitably handicapped by the general lack of related data on the populations at risk. Nevertheless, with suitable precautions, their collection from many different countries and areas may offer further indication of regions of specially high or low incidence. To minimize the distorting effect caused by the special interests (or facilities) of a particular hospital, such figures should be based on admissions to all hospitals in the local area and should relate only to patients normally residing there. A convenient period may be one calendar year, and the data collected should include the numbers of admissions, by age and sex, due to each of the main types of gastro-intestinal cancer. In the absence of any concrete data on the population at risk it would be necessary to seek some alternative baseline data to which hospital admissions for gastrointestinal cancer might be related. Suitable measures for this purpose may be admissions for other special types of cancer and for all types taken together. The use of necropsy statistics alone can be very misleading unless special steps are taken to ensure that they provide a reasonably representative sample of all local deaths.

PRESENTATION OF STATISTICS Detailed age and sex-specific rates provide the best foundation for any presentation of cancer morbidity data. By themselves they present a suitably detailed pattern of incidence and facilitate comparison between different populations. The age grouping employed may be in five or

10-year steps, the former being worthwhile only when the number of cases is very large. Often, however, particularly in international comparisons, it may be desirable to summarize the cancer experience of one area or country in a single rate and to make comparison with similar rates based on the experience of other areas or countries. In such comparisons the necessary allowance for differences in age structure between populations is made by means of some form of standardization. Many methods exist, all of them perfectly valid. The wide choice of method available has, however, caused some difficulty and confusion, since rates standardized by one method cannot be compared directly with other rates standardized in a different way. There would thus be considerable advantages if agreement could be reached on the use of one method. In general, the working party was in favour of adopting the population used by Segi as a common standard on which international comparisons might be based.¹ This population was obtained by pooling data from 46 countries and reducing the total to 100,000. As used by Segi, the population is divided into five-year age groups with a single final grouping at ages 75 years and over. Calculations can, however, be facilitated by fusing some of the age groups and rounding off the numbers in each group to the nearest 1,000, as follows:—

Age (yr.)	Population
0-15	31,000
15-24	17,000
24-34	14,000
35-44	13,000
45-49	6,000
50-54	5,000
55-59	4,000
60-64	3,000
65-69	3,000
70-74	2,000
75 and over	2,000
All ages	100,000

With this population the small weight given to the oldest age group reduces the error due to the unreliability of the data at these ages. Despite this, it may sometimes be valuable to compare rates for populations limited to persons under 75 years or even under 65 years of age.

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¹Segi, M. (1960). *Cancer mortality in selected sites in 24 countries*. (1950-57), Department of Public Health, Tohoku University School of Medicine, Sendai, Japan.