Cancer Detection

UICC Monograph Series · Volume 4

Cancer Detection

Prepared by the Cancer Detection Committee
of the Commission on Cancer Control

Springer-Verlag Berlin Heidelberg GmbH

ISBN 978-3-662-00161-5 ISBN 978-3-662-00159-2 (eBook)
DOI 10.1007/978-3-662-00159-2

Ursprünglich erschienen bei Springer-Verlag Berlin Heidelberg New York 1966
Softcover reprint of the hardcover 1st edition 1966
Library of Congress Catalog Card Number 66-29101

Title-No. 7514

Foreword

The activities of the International Union Against Cancer (U.I.C.C.) are carried out by the Commission on Cancer Research and the Commission on Cancer Control. The Commission on Cancer Control is concerned with the detection, treatment and social campaign against cancer and, to facilitate its work, has committees on cancer detection, cancer prevention, patient care, professional education, public education and voluntary organizations.

The Committee on Cancer Detection is concerned with programmes for the early diagnosis and registration of cancer and of pre-cancerous conditions with the object of achieving a reduction in cancer morbidity and mortality. The Committee is expected to study such programmes in the various countries and collect and evaluate the data and experience available. To this end meetings of the Committee were held in New York (1963), Oslo (1964) and Toronto (1965). This report is the result of these meetings and represents a considerable effort on the part of the Committee members.

Dr. E. PEDERSEN (Chairman) — Oslo, Norway
Dr. A. PHILLIPS (Secretary) — Toronto, Canada
Dr. E. DAY — New York, U.S.A.
Dr. M. GAITAN-YANGUAS — Bogotá, Colombia
Dr. R. GERARD-MARCHANT — Villejuif, France
Dr. K. GROSS — Prague, Czechoslovakia
Dr. T. KUROKAWA — Tokyo, Japan
Dr. A. NOVICKOW — Moscow, U.S.S.R.
Dr. L. ROBBINS — Washington, U.S.A.
Dr. G. TERZANO — Buenos Aires, Argentina.

In the preparation of the report the Committee was assisted by Mr. JOHN WAKEFIELD, Chairman of the Committee on Public Education.

It is the hope of the International Union Against Cancer that this review of activities in cancer detection in many countries together with the recommendations relating to the organization, procedures and techniques applicable to a cancer detection programme will prove helpful to those who are concerned with this phase of cancer control.

R. M. TAYLOR, M.D.,
Chairman,
Cancer Control Commission

Contents

Introduction

The concept of the examination of apparently healthy people for the presence of occult cancer originated some forty years ago. In the intervening years the techniques and methods, the groups surveyed and the results obtained have varied widely. Also, there has developed considerable diversity of opinion regarding the accomplishments and future promise of cancer detection.

Cancer detection is based upon three assumptions, first, that treatment of benign and precancerous lesions reduces cancer morbidity, second, that treatment of *in situ* lesions reduces the cancer morbidity rate since such lesions frequently develop into true invasive carcinoma, and third, that early diagnosis and treatment of cancer means better therapeutic results. It should be pointed out that none of these assumptions has received complete clinical, statistical or experimental confirmation although they are being studied in various countries. As far as *in situ* carcinoma is concerned these so-called preinvasive lesions are not truly malignant in the usual definition of the word; they are peculiar lesions which develop into cancer at an unknown rate of frequency. It is necessary, therefore, to record separately these pre-cancerous changes and *in situ* lesions in the statistics of cancer detection.

Another concern in cancer detection is the possibility of missing some cases since, for some sites, and with some detection techniques, there is a relatively high number of false negatives. It must be remembered that numerous cancers are not readily accessible to detection methods and false negative reports in such cases may lead to false feelings of security resulting in the disregard of future symptoms.

This report presents the specific procedures which have proved useful in the detection and early diagnosis of cancer in various areas of the body and discusses the efforts made towards a general screening test for cancer. Since the education of the public plays such a prominent part in the organization of cancer detection programmes, a chapter on public education has been included. This was prepared by the Committee on Public Education of the UICC under the chairmanship of Mr. J. WAKEFIELD, Manchester, England. Finally, the report includes a discussion of the evaluation of cancer detection programmes and summarizes those which were reported to the Committee from various countries.

The Cancer Detection Committee recognizes that the most important person in cancer detection is the practising physician in his own office. The overall purpose of this report, however, is to guide those who are concerned with advancing the clinical control of cancer by increasing to a maximum the number of cases found at an early stage. In some respects, the content may be considered as the standard for a cancer detection programme. However, the Committee recognizes that factors which may be unique in some countries make it impossible to propose standards which would prove applicable to all countries. It is

hoped that the report will prove helpful to those who contemplate the first steps in a cancer detection programme and, also, to those who wish to expand programmes already in existence. Enquiries concerning any aspect of cancer detection and requests for advice and assistance will be welcome and should be directed to the:

International Union Against Cancer,
3, rue du Conseil-Général,
Geneva, Switzerland.

Chapter I

Variations in National Patterns of Cancer Incidence and Mortality

Geographic differences in the amount and site distribution of cancer were first reported about the turn of the century, and although some of these observations and impressions could not be supported later and others had to be reinterpreted, there is now considerable evidence that significant differences exist between various countries in both cancer incidence and cancer mortality. An important aspect of the study of national differences is the identification of unusual tumours found in various parts of the world. The first interpretation of these unusual tumours was that they were "racial" and dependent on a special susceptibility, probably hereditary. It has been reported, for example, that the Indian was susceptible to betel-nut carcinoma, the Chinese to nasopharyngeal carcinoma, the European to gastric cancer and, more recently, the African Bantu to hepatoma. It now appears that these deductions were premature, for the more "racial" cancers are studied, the more apparent it becomes that they are not actually "racial" in the exact sense of the word. What appears at first to be "racial" in the genetic sense tends upon further examination to be "racial" only in the cultural or special environmental sense. The resistance of the Jew to cancer of the penis represents not inherent immunity of the cells but the consequence of the cultural custom of early circumcision. Similarly, the Negro has a low frequency of cutaneous carcinoma not because his cells are non-susceptible but because they are shielded by melanin from the commonest carcinogen.

SEGI has reported cancer mortality rates for 24 countries showing that, for all sites, the highest rate is about double the lowest. When individual sites are considered, the differences are much more striking and the highest mortality is usually five times the lowest, often more. Table I shows these rate differences for males and Table II for females.

These data are not in agreement with the hypothesis proposed by CRAMER in 1937, which, in brief, suggests that, when the incidence of cancer in a particular site is markedly increased in one population as compared with another, there is a compensating decrease in the incidence of cancer in one or more other sites. As a result, the total incidence of cancer in different populations remains on an even level. To many this is intellectual sabotage of epidemiology. It has been disproved repeatedly and the figures produced by SEGI for all sites show it to be unreal.

Many of the geographical differences in cancer distribution have been well documented and are universally recognized, but there still remain many extraordinary patterns of cancer distribu-

Table I. *Extremes of standardized cancer mortality rates (per 100,000) in 24 countries*

	Males			
	Lowest		Highest	
All sites	Portugal	104.6	Austria	193.0
Oesophagus	Sweden	2.6	France	12.5
Stomach	U.S. White	11.5	Chile	71.0
Colon	Japan	2.8	Scotland	15.8
Rectum	Chile	2.5	Denmark	11.9
Liver and biliary tract	Norway	2.7	Japan	15.1
Pancreas	Japan	3.0	U.S. Non white	8.7
Lung and trachea	Portugal	8.7	Scotland	66.0
Prostate	Japan	1.4	U.S. Non white	21.3
Bladder	Japan	2.0	South Africa	8.0
Leukaemia	Japan	3.4	Israel	9.3

Table II. *Extremes of standardized cancer mortality rates (per 100,000) in 24 countries*

	Females			
	Lowest		Highest	
All sites	Portugal	79.7	Chile	145.2
Oesophagus	Norway	0.7	Finland	5.1
Stomach	U.S. White	5.8	Chile	45.8
Colon	Japan	2.9	Scotland	15.7
Rectum	Chile	2.1	Denmark	7.1
Liver and biliary tract	England	2.7	Germany	11.5
Pancreas	Italy	2.0	Israel	6.0
Lung and trachea	Portugal	2.4	Scotland	8.7
Breast	Japan	3.8	Netherlands	24.2
Uterus	Israel	5.7	U.S. Non white	25.9
Ovary	Japan	1.6	Denmark	10.4
Bladder	Japan	1.0	U.S. Non white	2.6
Leukaemia	Japan	2.6	Israel	5.4

tion which have attracted considerable interest. For example, primary carcinoma of the liver is Africa's most challenging cancer problem. Of rare occurrence among all western people, whether they live in Europe, America, Africa or elsewhere, it is by contrast remarkably prevalent in the vast area south of the Sahara Desert. RAVEN has shown that, in over 7,500 cases of cancer in African races, 35% were primary cancers of the liver. In Canada, deaths from primary cancers of the liver amount to 160 to 180 annually in 24,000 cancer deaths — about three quarters of one per cent.

With respect to variations in different sites of cancer it has long been known that in Japan and Chile the death rate from stomach cancer in both males and females is the highest in the world. Recently, DUNGAL has reported that stomach cancer is frequent in Iceland, accounting for 45% of all male mortality from cancer and 31% of all female cancer mortality. The experience in Japan has received considerable attention and it

has been found that the Japanese have a high incidence of peptic ulcers. It seems to have been taken for granted that these are directly linked with gastric carcinogenesis, since some 25% of all gastric carcinomas have evidence of previous gastric ulceration. Emigrant Japanese populations have also shown an increased tendency to gastric cancer susceptibility, but SMITH has reported that the stomach cancer death rate in migrant Japanese is not as high as it is in Japan. In Hawaiian Japanese males it is 90% and in United States Japanese males only 72% of that of the homeland. Stomach cancer in Japan may be different pathologically from that in the West, since diffuse carcinomatosis of the mucosa is seen with multiple primary nodules. An extremely powerful stimulus for gastric carcinogenesis appears to be at work. There are many suggestive hints as to causative factors but these are based on whole population associations and not on cases with matched controls, so that the association may be very indirect.

Many countries have reported unique distributions of oral cancers, most of which seem to be related to local custom. Perhaps the best known of these are the so-called "betel-nut cancers". The "betel habit" involves the chewing of a quid composed of: (a) a leaf of the betel vine containing eugenol which is locally anesthetic, (b) the nut of the areca palm producing a red dye and containing alkaloids which stimulate salivation and sweating, (c) slaked lime, (d) uncured tobacco, and (e) various spices, e.g. aniseed, cloves.

Betel chewing has a long history; it is mentioned by Marco Polo in his account of his second journey about 1294, although the ingredients have undergone modification. Differences in the chewing habits occur in countries such as India, as also do differences in the distribution of the cancers. In Madras, cancer of the cheek is twice as common as cancer of the tongue, but in Bombay it is less than one-third as common.

In certain areas of India and South America, cigars are smoked with the lighted end in the mouth, and an associated cancer of the palate has been observed. Experiments with thermocouples have shown that the temperature of the tongue and palate are similar during smoking, so the cause is not simply attributable to heat. The flow of saliva over the tongue may help to remove any carcinogenic products of combustion or the palatal epithelium may respond differently; in any event the final explanation remains to be demonstrated.

The "Kangri" cancer of the skin of the lower abdomen and thigh has also been well described and is attributed to the custom among Kashmir people of carrying small wicker baskets filled with smouldering dry maple leaves under their clothes. This type of cancer appears to be caused by heat, although the probable influence of carcinogenic substances in the smoke has been suggested.

Insofar as cancer of the skin is concerned, the distribution throughout the world shows that the incidence is high in tropical and subtropical areas and it is generally accepted that the main carcinogenic factor is solar radiation. Of all countries, Australia reports the highest incidence rate, but it should be noted that Australia has virtually no coloured labour and whites do manual work in all of its various climates. Recently CARMICHAEL, and SILVERSTONE in Australia and AUERBACH in the United States have reported an inverse relationship in white males between skin cancer incidence rates and degree of latitude; skin cancer increases as latitude decreases. AUERBACH has illustrated the significance of this finding by showing that for 10 cities

in the United States the incidence rate is doubled for each 3° 48′ of latitude — approximately 265 miles.

These are but a sample of the geographic variations in cancer throughout the world. Undoubtedly, cancer detection programmes must be designed to recognize these differences in order that the maximum number of new cases will be found.

Chapter II

Evaluation of Cancer Detection

The critical evaluation of cancer detection must be based upon its effect on cancer mortality. This effect may be observed directly from the analysis of mortality data or it may be illustrated indirectly by showing that the ultimate prognosis of cancer uncovered by means of detection is better than that identified by more conventional means.

The effect of cancer detection on mortality is difficult to assess since the reliability of mortality statistics is affected by numerous factors. For example, in a review of 7,146 deaths due to cancer in a province of Canada, overdiagnosis of the disease was found in cancers of the lung, stomach and pancreas while underdiagnosis was found in cancers of the buccal cavity and breast. This tendency toward over- or underdiagnosis and the extent to which it has affected past mortality makes a retrospective analysis of mortality data unreliable. Added to this is the tendency to be more specific in death certification because of developing interest in cancer detection programmes. This is especially true in cancer of the uterus where greater specificity results in an increase of deaths ascribed to the cervix uteri. In Canada, for example, the proportion of deaths from cancer of the uterus, unspecified as to cervix or corpus, has declined from 30% to 21% since 1950. Undoubtedly, many of the cases now being more accurately recorded are in the cervix category hence it becomes possible for mortality from cancer of the cervix to rise temporarily in the face of a number of organized mass screening programmes.

In British Columbia, Canada, for example, a mass screening programme for cervical cancer was organized in 1950 and to date, approximately 75% of the female population over 20 years have been examined. The mortality experience indicates that there has been no significant change attributed to this programme.

Table I. *Crude death rates per 100,000 for cancer of the cervix in British Columbia: 1950—1963*

Year	Death rate	Year	Death rate
1950	8.7	1957	6.5
1951	7.9	1958	8.7
1952	9.9	1959	8.5
1953	8.4	1960	6.4
1954	8.8	1961	8.3
1955	8.3	1962	9.9
1956	7.7	1963	7.2

In light of the decline in the proportion of unspecified cases the experience in British Columbia indicates the need for specific mortality studies in order to evaluate cancer detection. This requires study of each death ascribed to cancer of the uterus in order to categorize accurately those which were truly cervix cases. The experience in such a study in British Columbia is shown in Table II.

A different attack on the problem of evaluation of cancer detection may be made through a study of the incidence of invasive cases in a population which

Table II. *A study of the reported deaths from squamous carcinoma of cervix in British Columbia, 1958—1962*

	1958	1959	1960	1961	1962
Reported deaths from squamous carcinoma of cervix	64	64	50	66	84
a) Shown not to have had carcinoma of cervix	15	13	5	14	24
b) Shown to have died of diseases other than carcinoma of cervix	1	4	4	6	2
Reported deaths from other diseases but shown to be due to squamous carcinoma of cervix	6	2	6	3	4
Actual number of deaths from squamous carcinoma of cervix	54	49	47	49	62

is participating in a mass screening programme. This has been done in British Columbia and results show that the incidence of invasive cancer of the cervix has declined significantly. For example, in an eight-year period (1955 to 1962) the incidence rate dropped 45%.

Table III. *Incidence rate per 100,000 of invasive carcinoma of cervix in women over 20 years in British Columbia: 1955—1962*

Year	Rate	Year	Rate
1955	28.4	1959	22.6
1956	27.2	1960	19.7
1957	26.0	1961	23.2
1958	23.7	1962	15.5

The evaluation of cancer detection would not be complete without mention of some of the ancillary benefits. As a beginning cancer detection offers a unique opportunity to study the natural history of cancer through its early stages and before the host environment has been altered by the disease. This can be accomplished by following all positive cases which, for one reason or another, remain untreated. Undoubtedly, this is the opportune time to investigate all factors in the internal and external environment which have produced positive signs of malignancy.

The value of cancer detection in the study of the natural history of the disease is followed by its contribution to the understanding of "pre-malignant" lesions. Here, information becomes available on the reasons why certain conditions must be considered precursors to cancer and, in addition, data are obtained on the biochemical and morphological differences between lesions with low and high cancer potential.

Since many cancer detection activities are planned to examine the same participants at periodic intervals, it becomes possible to study the growth potential and rapidity of cancer development in an individual at a measured interval of time and after a previous negative report. It is also possible to assess the relative sensitivity of detection techniques particularly in those who appear to have had cancer at the time of a clinically negative examination.

Among so-called "high risk" groups, cancer detection delineates those factors which characterize such groups and so establishes the criteria for selecting segments of the population which require the benefit of periodic cancer detection examinations. The relative values of age, sex, race, family history and environment can be assessed in an attempt to understand those factors which predispose to cancer or develop an immunity to it.

This section of the report has attempted to describe methods of evaluation in cancer detection, the main emphasis being placed upon its effect on cancer mortality. Most examples cited relate to detection of cancer of the cervix but there are implications for all sites which lend themselves to detection techniques. Although cancer detection is a relatively new approach to a disease problem its philosophy and practice can be subjected to critical evaluation.

Chapter III

A General Screening Test for Cancer

The cancer detection specialist continually probes for promising ways to find cancer early. Despite continual failures, many investigators are searching for a general test for cancer which will shorten the time from the development of malignant cells somewhere in the body to definitive treatment of the primary site. The zeal of the scientist who proposes a general test for cancer is great and his hopes are not easily dampened.

One of the most attractive possibilities of recent years to some investigators was the Penn Hall seroflocculation reaction for cancer. This work claims that a flocculation reaction is produced when a special bile-acid derivative is mixed with the serum of cancer patients. An antigen suspension of ethyl choladienate is mixed with the sera and the resulting mixture observed for large particles in a clear medium. In 1957, PEACOCK and WILLIAMS reported that, "this reaction is not suitable for general use as a screening test". The test either missed too many cancers or included too many false positives. The test is still being studied by some investigators but has produced no substantial promise in the intervening years.

The second cancer test, which has raised some hopes and is more specific for cancer in the urinary tract, is the urine test for lactic dehydrogenase isozymes or LDH as it is called. WACKER and DORFMAN found elevated levels of LDH activity in the urines of 19 patients with carcinoma of the urinary tract and no elevation of LDH activity in 9 out of 12 patients with non-malignant lesions of the urinary tract. Clinical studies by RIGGENS and KISER showed that elevations of urinary LDH were not specific for malignant disease and GELDERMAN *et al.* concluded that the elevated urinary LDH activity of patients with bladder disease is probably due to the presence of leukocytes or red cells in the urine. Here again was the story repeated of too many cancers missed and too many non-cancers called positive.

The Shutz-Dale technique, a sensitive immunological method using the sensitized horn of guinea-pig uterus, was applied by MAKARI. MAKARI showed good results which were corroborated by BURROWS but MAAS has been unable to confirm these findings.

For a time, the National Cancer Institute, U.S. Public Health Service, attempted to evaluate such general tests for cancer. This proved to be an almost hopeless task, for once a test had been shown to be worthless, it was changed to meet some objection and was then contending again for a general test for cancer which would have a high specificity, (exclude most non-cancers) and a high sensitivity, (include most cancers).

Seven tests for cancer were evaluated in the Public Health Monograph No. 12, published in 1953. One of the most promising of these was the Black-Kleiner-Bolker blood test. In 1947, Black reported that about 80—85% of the plasmas of patients with cancers gave very long reduction times for methylene blue. LATER, BLACK, KLEINER and BOLKER reported that plasma from cancer patients gave abnormally high turbidities when heated. BLACK and SPEER then obtained better results when these two tests were combined. When the above tests were subjected to careful analysis, ERIKSEN, ELLERBROOK and LIPPINCOTT among others found that the combined test was not sensitive enough as a routine screen for cancer, and not

specific enough to differentiate cancer from other diseases.

Another test was based on the power of serum from cancer patients to destroy the sugar pentose when added and incubated with the serum. MENKES claimed that the serum from cancer patients destroyed more pentose than serum from normal individuals. PEACOCK reported that there is doubt that serum destroys pentose as a pentolysis phenomenon, and reports that there is no basis for the use of the reaction in cancer diagnosis.

The Bolen test, developed in 1944, intrigued investigators for years. BOLEN claimed that "the blood pattern noted in a drop of blood on the glass slide — offer(s) the internist substantial aid in diagnosing cancer in various stages and to differentiate between benign and malignant conditions". KASDON and HOMBERGER evaluated the Bolen test. They even included BOLEN himself in the evaluation and gave him "unknowns" by which to examine the method, along with others trained in the technic. The Bolen test was negative in so many cancers in a group of cancer patients and positive in so many normal patients that the test was found to be "clearly unsuitable as a screening procedure". The evaluation added, "The sedimentation rate of red blood cells, while equally unspecific, was a more sensitive index for the presence of disease, benign or malignant".

Another test for cancer depended on the alleged production of lactic acid from red cells in cancer patients but not from the erythrocytes from normal patients when incubated with pentose. HILL, who evaluated this method, reported that there was a slight lactic acid formation from ribose by washed erythrocytes from individuals both with and without cancer and concluded that the reaction had no value in cancer diagnosis.

A fifth cancer detection method in the series was reported by the French investigators ACHARD, BOUTERIC and BOUCHARD. This was a fluorescence method and depended on the ability of cancer-sera to change the fluorescence of the sodium and calcium salt of fluorescein in a characteristic manner. HILL was given the task of checking on this method and reported: "This investigation was stimulated by reports that cancer sera selectively depress the fluorescence of a solution of sodium fluorescein and cause greater depression of the fluorescence of the calcium salt compared with the sodium salt of fluorescein". He further reported that there was no demonstrable difference between cancer and non-cancer patients.

A test using the level of plasminogen, a precursor of plasmin or "proteolysin", in the serum of cancer patients was studied by PEACOCK and LIPPINCOTT who reported no correlation between the plasminogen level and the nature of the disease.

The seventh and last test in the series was investigated by FISHMAN, BONNER and HOMBERGER. It had been proposed that "protein metabolism is abnormal in those patients who have malignant growths and indicates a new avenue of research in cancer studies". BEATON, MCGARRITY and MCHENRY suggested that protein metabolism be measured by "the determination of plasma glutamic levels by the method of PRESCOTT and WAELSCH in suspected cancer patients". The evaluators reported that the results obtained with this method in patients with and without cancer showed no difference.

From the above negative results from general tests proposed for cancer one might be led to conclude that there are no differences between patients with cancer and those without cancer except

for the presence of malignant cells which can only be distinguished histologically. However, future evidence may be forthcoming that there is an immunological difference between animals that have cancer and those that do not. It has been shown that implantations of tumor cells will not "take" in certain inbred mice if the mouse is given a previous experience with an implanted tumor. Although this protection is real but weak and is ineffective against large tumor implantation, it has convinced many observers that there is some degree of cellular immunity to cancer which reflects some kind of immune response to tumor antigen. This highly theoretical possibility is now being studied in many laboratories.

The above information does not lend itself to a test for cancer, at least at the present time. One hopes for a test that will demonstrate a "tumor-specific antibody" in the circulating blood of the individual with cancer. To date, however, no general tests for cancer have been found reliable when exposed to careful scientific scrutiny. The search is continuing because of the great significance of such a test to the early discovery of cancer.

Chapter IV

Cancer Detection by Site

The early detection of cancer of the buccal cavity

Morbidity and mortality

Cancer of the buccal cavity is not one of the most frequent cancers, nevertheless, it represents a serious problem when, in spite of its accessibility, diagnosis is made in the advanced stages of its evolution. Its frequency varies from one country to another and, within the same country, there are often areas with a higher incidence. Generally between 2% and 10% of all cancers are localized in the mouth (tongue, floor of the mouth, gums, cheek, soft and hard palate, anterior pillars and mucosa of the lip).

The majority of these cancers are squamous cell carcinomas. A few are adenocarcinomas arising from salivary glands and, more rarely, melanoblastomas. Sarcomas are exceptional. Excluded from this group are those tumours arising from the bone structures and from other supporting tissues of the mouth.

Prognosis

With the exception of the hard palate, each of the organs forming part of the mouth has a very rich lymphatic net hence a very early transportation of tumour cells to the regional lymph nodes occurs resulting in nodal metastasis. This explains why in approximately 5% to 10% of cases the first manifestation of the disease is metastatic nodules in the neck. This may explain also why present-day treatment results of 20% to 40% five year survival are not as high as in some other equally accessible sites.

On the other hand, dissemination of the disease by the mechanism of direct invasion is very rapid and destructive in carcinoma of the oral cavity. This is especially true in the tongue and floor of the mouth. Distant metastases, on the other hand, usually remain confined to regional lymph nodes and very seldom go beyond the lungs, brain, liver and bones.

Another very interesting aspect of carcinoma of the mouth is the frequency with which multiple lesions present themselves, whether simultaneously or in sequence. It has not been clearly defined

if these multiple lesions are different primaries which developed on the basis of special carcinogenic factors, or if they are produced by implantation in other sites of cells exfoliated from a primary tumour.

Detection techniques

1. Clinical examination

Direct examination of the mouth by inspection in good light and palpation are the most useful methods for detecting cancer of the buccal cavity. Unfortunately, they are not practised by doctors and dentists as frequently nor as thoroughly as they deserve. It is not the common procedure for a general practitioner to do a routine mouth examination in every patient. Even specialists in head and neck problems seldom do this for their interest is often limited to the eye, or the ear, or the nose. The same criticism can be directed to dentists; few of them making a complete examination of the entire buccal cavity. This problem becomes even more serious when, in addition to this lack of interest in complete examination, one considers the malignant potentiality of many benign lesions, for example, leukoplakia, chronic ulcerations, etc. It becomes imperative, therefore, that special emphasis be directed to changes in former existing lesions. Another handicap is the fear of taking biopsies, in spite of the simplicity of this procedure. This, together with the previous considerations explains why the diagnosis of oral cancer is often made at a late stage and why very advanced cases still present for treatment.

2. Exfoliative cytology

The oral cavity, including the anterior aspect of the accessible oropharynx, is covered by squamous-cell mucosa, the total area being one of the largest in the body. On this basis alone, one might assume that exfoliative cytology should be a useful method of detecting cancer in this body cavity. Encouraged by the results obtained with the Papanicolaou method in early diagnosis of cervical carcinoma, many authors have conducted special studies on the application of this technique to the diagnosis of oral cancer. In spite of the many publications on the subject, not one study has been undertaken to detect cancer of the buccal cavity by cytological techniques in large groups of apparently healthy people. Some studies have been made of small groups but with special emphasis directed to the differentiation between benign premalignant conditions and cancer. Other studies have been directed to the follow-up of treated cases.

A detailed analysis of available experience in the use of cytology in the diagnosis of buccal cancer leads to the following conclusions.

a) The technique employed is almost uniform; it consists in obtaining the desquamated cells by means of a swab from the surface of the lesion or by scraping the surface with a spatula. Colouring or dyeing techniques are then used in the preparation of the slide. In addition, a "mouth washing" technique for obtaining material for smears is being investigated in some centres.

b) Cytological examination provides an accurate measure for the diagnosis of malignant conditions in the buccal cavity with a reliability which, according to different authors, varies between 60% and 98%. False positives and false negatives seem to range between 2% and 15%.

c) One of the more important applications of oral cytology is in the differential diagnosis of benign pre-malignant conditions and true cancer. For example, it has great value in the study

of leukoplakia and in chronic ulceration. In these instances, cytology may disclose the presence of malignancy when the clinical aspect is doubtful.

d) Cytology is very useful for assessing the effect of radiotherapy on cancers of the buccal cavity. This is done by taking serial smears during treatment or after treatment has been concluded and provides a measure of the radio-sensitivity of the tumour and the cell-changes resulting from radiation.

e) When residual lesions are observed after treatment, especially after radiation therapy, it is often very difficult to know if the residual lesion is persistent tumour or if, on the contrary, it is due to an overdose of radiation and therefore trophic in nature. Under these conditions, a biopsy of the lesion is not recommended, the better method of investigation is through the cytological study of smears.

f) Cytology in the hands of some investigators and students of early oral cancer detection is promising and worthy of further study, especially in high-risk groups, such as chronic smokers or chewers of tobacco, older age groups with poor oral hygiene, or in those exposed to carcinogenic factors such as chewing betel nuts, cocoa leaves or some others.

g) In order that cytological techniques be of greatest value in the detection of cancer of the buccal cavity, a method is needed which permits a study of desquamated cells obtained from a saliva sample which has been centrifuged. Studies must be continued on the utility of some new techniques in high risk groups as described before.

h) Since the incidence of oral cancer is relatively low in comparison with other sites, the cytological method of detection cannot be considered economical. It has been estimated that, depending on the frequency of oral cancer, one case of cancer is found per at least 10,000 cytological smears.

In view of the above-mentioned considerations, exfoliative cytology is not yet a method to be recommended for cancer detection in mass screening programmes for the buccal cavity in non-high risk groups. However, it has a great value in:

a) The differential diagnosis between benign and pre-malignant conditions and cancer in patients already discovered by clinical examination.

b) The determination of the radiosensitivity of tumours during the course of treatment.

c) The differentiation between a persistent tumour and trophic alterations due to excessive dosage of radiation.

3. Biopsy

It is not necessary to insist on the simplicity of taking a biopsy, either by the general practitioner or by the dentist. However, it is worthwhile to insist that it must be obtained from the suspicious part of the lesion and in the case of leukoplakia it is advisable to excise the whole lesion and to make serial sections for study.

The early detection of cancer of the stomach

Morbidity and mortality

Stomach cancer is one of the most important diseases in respect to its relative frequency and actual mortality in many areas of the world. In Japan, for example, it accounts for over one-half of all cancer deaths in men and over one-third of all cancer deaths in women.

Prognosis

Until etiological factors in gastric cancer are better understood and preventive measures can be applied, early detection and surgical extirpation are indispensable for best control. In this presentation *early stage of stomach cancer* means that the cancer is limited to the mucous membrane or submucous tissue without regional lymph-node metastasis. When cancer is limited to the gastric mucosa, the 5 year survival rate approaches 100 percent, but when the disease reaches the muscularis propria, the 5-year survival rate is halved. These figures indicate the importance of early detection of gastric carcinoma.

Symptoms in the early stage of stomach cancer are limited to mild anorexia, mild pain in the epigastrium, and mild fullness of the stomach, which are not significant pathognomonic symptoms. It is by no means infrequent that there are no symptoms whatsoever.

As the disease advances the objective signs are: weight loss, increasing abdominal pain, occasionally anemia, and finally the so-called cachexia. It is usually late when the classical symptoms of anorexia, nausea, vomiting, and especially hematemesis and palpable tumor in the epigastrium appear.

As with all sites of cancer, screening of those individuals and groups in the population which have the greatest likelihood of developing the disease, i.e., the high risk groups, affords the most effective approach to control through early treatment. For stomach the high risk factors are:

1. Age over forty;
2. Country of origin;
3. Dietary habits including:

a) high proportion of white carbohydrate foods,

b) high salt content,

c) carcinogen-producing methods of food preparation;

4. Family history of gastric cancer;
5. Pernicious anemia;
6. Atrophic gastritis;
7. Gastric ulcer;
8. Gastric polyp.

Detection techniques

Four of many procedures helpful in the diagnosis of stomach cancer are:

1. Diagnostic procedures for gastric secretions;
2. X-ray examination;
3. Endoscopic diagnosis;
4. Cytological procedure.

Although each procedure brings about good results in the early detection of stomach cancer, a combination of these methods yields more exact early diagnosis. Consequently, it is usual to use two or more procedures in clinical practice.

1. Examination of gastric secretions and scanning procedures

Extensive studies of the stomach contents (gastric secretions), under fasting and stimulated conditions, have indicated variations in acidity and enzymes in relation to benign and malignant disease but have not proved to be broadly useful for diagnostic purposes. Screening for low or absent acidity has been used as a means of identifying those individuals in the older asymptomatic population who should be referred for further diagnostic examinations such as G.I. X-ray series, and can increase the yield of such procedures.

Techniques of scanning for early gastric cancer, such as fluorescence (tetracycline) and radioisotope diagnosis using radioactive phosphorous (P_{32}) for selective pick-up, have been developed but have limited applicability.

As a general rule, the early diagnosis of gastric cancer depends upon prompt

application of radiologic and endoscopic procedures, with cytologic and histologic examination, in all groups and individuals where there is a clinical suspicion or group likelihood of this disease.

2. X-ray examination

In advanced stomach cancer, X-ray findings are very obvious and diagnosis is easily made. However, in early stages the detection of the lesion by X-ray examination is by no means easy because the lesion is often limited to the mucous membrane and does not involve the entire thickness of the gastric wall. Roentgenographic changes in the gastric mucosa or gastric wall, at one time considered incidental, can now be identified as stomach cancer with the aid of gastric endoscopy. Since the introduction of the gastric endoscopic technique combined with the roentgenographic examination, the early detection of stomach cancer has made great progress.

The first phase of the X-ray technique is designed for viewing the mucosa. A small amount of barium sulphate suspension is swallowed in order to lightly coat the mucosa. To ensure even coating of all areas, outside pressure has to be applied ("graded compression") to the area with some type of "compressor" (wooden paddle or other blunt instrument). Using this method and a fluorescent screen, one can visualize irregularities of the mucosa. If any abnormalities are observed, a "spot film" should be taken with the patient assuming various positions, i.e., standing, supine, prone, the first oblique, and the second oblique.

To obtain an adequate "filling picture" of the stomach and proximal gastrointestinal tract, additional barium sulphate is administered. This mixture then fills the stomach and adjoining areas. The fluorescent screen or X-ray film will indicate any filling defects, i.e., rigidity, obstruction, constriction, etc. During fluoroscopy, spot pictures can be taken of any abnormal areas. Again, the patient should assume the aforementioned positions when spot picture studies are required.

Mention should be made of the recent development of the double-contrast method. After taking a sufficient amount of barium suspension, varying amounts of air are passed into the stomach through a tube. As a result, the gastric wall is distended and outlined by a thin layer of barium. This method clarifies small elevations or shallow depressions in early carcinoma and also interruptions of the mucosal folds. This method, in combination with the already-mentioned "graded compression" and rotation of the position of the patient, is very effective.

3. Endoscopic procedure

Gastric endoscopy has been used for a long time. At first a stiff metal tube was used with a light and mirror at the tip. The lesion is reflected by the mirror, and the lens in the tube outside the body makes an image. Therefore, the position of the patient must be such that there is a straight line from the mouth to the oesophagus and stomach (WOLFF's gastroscope). This caused the patient much pain. Later, a flexible gastroscope was produced, in which a multiple lens system was applied, but even this tube necessitated a straight line from the mouth to the throat, and did not eliminate all pain. In 1956, HIRSCHOWITZ applied extra-fine glass fiber to the gastroscope which is now called a fiberscope and the pain to the patient was almost completely eliminated. This flexible instrument enabled sufficient gross observation of the inner gastric surface and also color photography of findings. This invention brought about a great

advance in the early diagnosis of stomach cancer.

In Japan, for 10 years prior to the invention of the fiberscope, the gastrocamera had been widely used. This consists of a thin flexible tube with a small camera at the tip. Photographs of the inner surface of the stomach can be taken in 32 consecutive shots on 8 mm. color film by the light from a lamp through the lens. These pictures are very sharp and realistically demonstrate even a minute change in the gastric mucosa. This method greatly enhanced the rate of detection of early stomach cancer. The shortcomings of the method are blind-shot photography and difficulty in taking a picture of the cardia and fundus. The latter point was overcome by the invention of a retroflexible gastrocamera which takes pictures of the cardia and fundus. Now, the gastrocamera is used routinely in Japan for detection of stomach cancer.

The gastrocamera gives much clearer pictures than does the fiberscope, in spite of the shortcomings of its blind-shot photography. Recently, in Japan, the fiberscope with a camera at the tip, the so-called "fiber camera" was produced. With this instrument gastric lesions are observed through the fiberscope and photographed at the same time by the camera. This is an almost ideal form of gastric endoscopy providing intragastric observation and simultaneous photography.

Advances in endoscopy have resulted in a higher detection rate of early stomach cancer and, at the same time, have revealed the significance of previously neglected roentgenographic findings.

4. Cytological method

Observations made by roentgenography and endoscopy (with its related photography) are only those of gross morphological changes. Confirmation of malignancy requires the study of histological or cytological observations to find the cancer cell itself. In this study the procurement and staining of intragastric cells are important. At present, there are the abrasive balloon method, the washing method, and the pressure washing method. Other methods, such as washing with physiologic saline solution, papain solution, or kymotrypsin solution are also used. As for staining, there are Papanicoloau, May-Giemsa, aceto-gentian and fluorescence methods. Observation of fresh cells by the phasecontrast microscope is also a good method. It may be difficult to differentiate the cancer cells from non-cancer cells in exfoliating cells. The gastric juice also has an effect on the cells, for which reason the differentiation may become more difficult. At this point, the most correct diagnosis is given by intragastric biopsy and for histological study.

For this purpose a gastric biopsy resection of small pieces of the gastric lesion is performed under fiberscopic observation. At the Cancer Institute Hospital in Tokyo, intragastric biopsies are performed by means of small forceps attached to the top of the fiberscope.

It should be stressed that a combination of these methods brings about a greater degree of efficiency in the detection of early stomach cancer and increases the rate of detection.

At the Tohoku University Medical School, 1281 cases of stomach cancer with operative treatment were seen during the 20 years from 1943 to 1962. Of the total cases, 73 showed early stages of stomach cancer. Of these, only 18 cases (4.5%) were found in the first 10 years from 1943 to 1952 and 55 cases (8.3%) in the second 10 years from 1953 to 1962. Moreover, for the last 5 years — the last half of the decade — 41 cases

Table I. *The incidence of early stomach cancer*

Period	Operated for stomach cancer	Early stomach cancer				Total	%
		Mucosa	Sub-mucosa	Male	Female		
1949	120	1	0	1	0	1	0.8
1950	120	1	2	1	2	3	2.5
1951	153	1	0	1	0	1	0.7
1952	175	1	1	2	0	2	1.1
1953	146	1	2	2	1	3	2.1
1954	230	3	9	8	4	12	5.2
1955	233	2	4	5	1	6	2.6
1956	236	3	4	4	3	7	2.9
1957	258	7	9	11	5	16	6.2
1958	276	7	9	12	4	16	5.8
1959	254	6	12	10	8	18	7.1
1960	290	3	16	9	10	19	6.6
1961	252	14	18	14	18	32	12.7
1962	224	11	12	13	10	23	10.3
1963	227	9	17	14	12	26	11.5
Total	3194	70	115	107	78	185	5.8

(12.3%) were found to have early cancer. This indicates that in a roentgen era the detection of early stomach cancer was infrequent but with the appearance of the gastrocamera and fiberscope and with a combination of cytology and gastric biopsy, more cases were detected early.

At the Cancer Institute Hospital in Tokyo, 3194 cases of stomach cancer have been resected during the last 15 years (Table I).

The percentage of early cancer in all the resected stomachs with cancer was 2.5% from 1945 to 1953, 5.2% until 1958 and more than 10% recently.

Mass survey for stomach cancer

As mentioned already, there are no definite symptoms in the early stage of stomach cancer and this cancer shows the highest incidence in the malignancies of the gastrointestinal tract. Even when symptoms occur they are often very mild in degree, not enough to differentiate from gastritis or ulcer. For this reason, patients do not pay early visits to their physicians and even if they do, physicians often experience difficulty in finding the small lesion. Most people consult the physicians too late, when the diagnosis may be easily made, but with little likelihood for a curative operation.

For these reasons, a mass survey for stomach cancer has been undertaken in Japan. Fluoroscopies are performed in a large automobile equipped with an apparatus for X-ray examinations, taking indirect photographs of 4 to 6 shots on 70×70 mm. films, in various positions of the patients. This procedure enables the screening of many patients in a short time (approximately 3 minutes for one person), and 80 to 100 persons can be examined in a day. Furthermore, it is easy to move the vehicle in any local district, the cost is about $ 2.50 and the examiners need not expose themselves to X-ray by the remote control system.

In 1964, the total number of persons screened in mass surveys in Japan reached 884,594 and 1,048 cases of stomach cancer (0.12%) were found.