ADVANCES IN TUMOUR PREVENTION, DETECTION AND CHARACTERIZATION

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editor: C. Maltoni

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HUMAN CANCER. ITS CHARACTERIZATION AND TREATMENT

editors:
W. Davis
K.R. Harrap
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Proceedings of the Eighth International Symposium on the Biological Characterization of Human Tumours

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Human cancer. Its characterization and treatment

Eighth International Symposium on the Biological Characterization of Human Tumours

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The Ministry of Culture and Sciences, Greece

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Introduction

The goal of cancer prevention, though admittedly difficult to achieve, is today stimulating a considerable part of all cancer research. Improvements in diagnosis and treatment of cancer are still being sought, and important advances have been made, but still prevention attracts more and more attention.

This trend has been visible through successive volumes of proceedings of the biennial symposia on the biological characterization of human tumours. Fifteen years ago, the main aim of studying human tumours was to find the biochemical key that would provide the opening to a selective chemotherapy. Such work still continues and is well presented in this present volume, but the emphasis in cancer research has changed.

As studies of cancer causation developed, came the hope, that cancer could be prevented by discovering the aetiological factors, and removing them from the human environment. The epidemiological studies, for example, that established the association between cigarette smoking and lung cancer have not unfortunately led to the ending of exposure to the carcinogen. Instead scientists have been encouraged either to find a 'safer' cigarette, or to identify the markers that could indicate differences in individual susceptibility to the carcinogen. This recent development is clearly of great, and growing, importance. There are very few examples of a uniform human reaction to exposure to a carcinogen, and the identification of the individuals, or groups, who are at higher risk because of particular genotypic or phenotypic variants would have important public health consequences. The papers presented in this volume give an indication of the breadth of the research that is devoted nowadays to the monitoring of high risk groups.

The identification and removal of carcinogens from the environment wherever possible is still an essential task, and one that is particularly important in relation to diet. Some aspects of carcinogenic risks in food are presented, which may well be of significance for the cancers of the gastrointestinal tract dealt with in the subsequent papers.

The volume concludes with a selection of papers dealing with aspects of cancer chemotherapy.

On behalf of the Co-ordinating Committee, we wish to record our gratitude for the generous support received from the Greek Ministry of Culture and Sciences, from A.B. Leo, Sweden, from Lederle Laboratories, Great Britain, and from anonymous donors in Eire.

The Editors

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Chapter I

Monitoring of high-risk groups

THE ROLE OF CYTOLOGY IN STUDYING HIGH RISK GROUPS

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Cytology may be used to detect changes thought to precede the development of malignant disease (such as dysplasia or cellular atypia), or as a (diagnostic) test for the presence of in-situ and invasive cancer. This review is particularly concerned with the screening applications of such work, either in detecting precursors of cancer or invasive disease. However, the latter use merges into the contribution that cytology can make to the diagnosis of malignant disease; it is also necessary to consider the alternative means of achieving a diagnosis before dealing with one method applied to population screening. A rather separate aspect is that of research aimed at identifying groups within the population at high risk of developing malignant disease; this may be to identify individuals in whom some preventive steps may be taken to reduce exposure to an environmental agent, or in order to concentrate limited screening and diagnostic facilities upon those most likely to develop the disease.

BACKGROUND

The promise of cytology

In general, the collection of specimens for cytological examination is easier for the subject (patient) and the medical staff. Particularly in comparison with biopsy for histological examination, it is quicker and simpler, samples may be collected from a wider area, repeat samples may fairly readily be taken after short intervals, and less expensive facilities are required. However, as was made clear in the original papers by Papanicolaou (90, 94) the cells obtained provide a less complete picture than tissue removed to identify histological changes of malignancy. From the initial applications, it was hoped that the technique would facilitate 'earlier' diagnosis.

The quality of smears

The predominance of hospital-derived smears was an outcome of the initial use of cervical cytology in

diagnostic work in out-patients; subsequently the population campaign relied on smears taken in other locations. One of the important issues that required resolution prior to the expansion of population screening was the development of a simple technique for taking, fixing and transmitting a smear; Smith and his colleagues (118) reported on a suitable method for this. With the launching of the national campaign, kits were issued free to family doctors and clinics in England and Wales. Yule (143) showed that the proportion of unsatisfactory smears was sufficiently low to accept smears from all sources; a slightly higher percentage unsatisfactory from hospitals was a reflection that these are being taken from patients rather than 'well women'. Keighley et al. (60) report a particular source of false positive results - the transfer of malignant cells on non-disposable brushes used on endoscopy of a succession of patients with upper alimentary tract lesions. Katz et al. (59) confirmed the variation in effectiveness of different instruments for obtaining cervical smears; cotton-tipped applicators result in a significant excess of false negative smears, whilst there was no significant difference in clinical performance between wooden spatulas and plastic specimen collectors.

Laboratory Quality Control

Gad and Koch (38) analysed data from population rescreening and estimated that cytologist error occurred in 19% of the positives (i.e. through false negatives on initial screening). They suggested that patient compliance and inadequate medical follow-up can also lead to failure of care, but that reduction of cytology error seems the most promising avenue of progress. Wood and Hicklin (140) reviewed the value of rescreening 10% of negative slides as a method of monitoring the performance of cytoscreeners. They described how individual laboratories can adapt the general proposals to their own resources for checking and estimated error rates. Some data on variation in error from one laboratory to another has been obtained by a special study in which Evans and Sanerkin (30) circulated a small number of specimen slides (which included an artificially high proportion of abnormals) to a number of centres. However this material only went to a few selected centres and the technicians reading the specimens knew that a special study was in progress. Penner (101) described the US approach to routine quality evaluation of cytology laboratories, though no results were available.

Langley (69) has discussed the need for quality control in exfoliative cytology and some of the philosophical and mathematical issues that are involved. Examples of previous studies on this topic are given and suggestions made about further steps that could be taken to

improve quality control.

Due to the large volume of smears that have to be assessed in any population campaign, effort has gone into introducing automation of the preliminary examination of the smears. Husain et al. (51) presented results suggesting that malignancy can be detected by studying the size/density matrix of nuclei in cell populations as a basis of an automated screening system. Tanaka and his colleagues (125, 126) have described their approach and progress in automatic cytoscreening for uterine cancer. Husain et al. (52) described a new procedure for preparing slides for automated cervical cancer screening, which gave superior cell presentation compared with two earlier techniques. Despite the investment of considerable effort on this important but difficult issue, the final goal has proved somewhat elusive.

Population Screening

Pedersen (100) pointed out in order to test the effect of screening ideally a defined population should be randomly divided into two groups, one of which is then subjected to periodic mass screening. He discussed some of the points that make interpretation of studies difficult; the varying or low response rate, the detection of slow-growing lesions in the initial screen, difficulty in classifying some of the abnormalities that are detected, the influence of 'early' diagnosis upon survival (does the patient merely know they have cancer for a longer period), and the need to examine the overall death rates and the proportion of the deaths that are in persons not participating in the screening programme.

Dunn (27) emphasised that cytology may detect a lesion fourteen years before it would have presented as clinical cancer, thus emphasising the uselessness of conventional survival calculations for such subjects. The consideration of screening has generated a voluminous literature; there is also a growth in jargon and an awkward tendency for different workers to use different terms for the same concepts or the same term in different ways. The statistics of error rates have been examined by May (79), who indicated the need for agreed definitions and standard presentation of analysis of such errors. The World Health Organization, European Office (141) convened a working party whose report provided a definition of screening, discussion of evaluation methods, the procedures and services required in screening campaigns, comments on present barriers to progress, and the desiderata for a successful screening programme. Such references should be consulted for definition of screening, response rate, true and false positive or negative, sensitivity and specificity. The Lancet (68) has pointed out how such terminological matters are dull, but important. One term that appears frequently in this text is 'early': this term is

often used rather loosely to indicate lesions that are non-invasive, localised, or have not been associated with appreciable patient or diagnostic delay. The term should not be thought to imply that diagnosis of an 'early' lesion is indicative that the natural history of the disease can be altered.

CYTOLOGY USEAGE BY SITE

Coleman (19) reviewed the use of exfoliative cytology for population surveys for incipient cancer of the bladder, breast, bronchus, prostate, and stomach; she commented that results had been disappointing and contrasted this with the success in detecting in-situ cervical cancer. There now follows a brief review of cytology for a number of sites, which have been listed in ICD order. For each site the validity of cytology is compared with that for other diagnostic procedures; the ease of collection of specimens is also indicated. Each subsection indicates the specific uses to which cytology has been put, particularly where this has involved population screening or approaches to early diagnosis. The references are not comprehensive, but have been selected to illustrate the breadth of types of study and topics that have been explored.

Oral Cavity

The advantages and disadvantages of oral cytology have been presented (8); the types of lesions particularly suited to the use of exfoliative cytology were described. Zajicek et al. (144) reviewed the value of aspiration biopsy and cytological examination as a diagnostic test in salivary gland tumours. They suggested that, with adequate experience, diagnosis is feasible in most (93%) of the cases.

A group of over 50,000 workers in India were clinically screened for oral cancer between 1961-71 (117); the subjects were predominantly males 35 years and older. Over 27,000 oral lesions were examined by cytologic scrapings and 51 oral cancers diagnosed. However, only one cancer was detected which had not been suspected by the screeners on examination. Due to the low prevalence of oral cancer the technique is not thought of great value in screening, but useful as an adjunct to biopsy of clinically suspicious lesions.

Oesophagus and Stomach

Blendis et al. (9) studied various methods of diagnosing gastric cancer in hospital patients and suggested that saline lavage produced satisfactory specimens for cytology and was suitable for screening programmes. They stressed the difficulty in patients with pyloric

obstruction and that false negative results could be obtained with infiltrative lesions accompanied by limited exfoliation. Ackerman (1) carried out a postal survey of centres in the U.S., of which 108 (59%) replied. There was no evidence that gastric cytology had proved valuable as a screening test and in general clinical practice relatively few early cancers had been detected. Bedine and Cocco (6) evaluated the use of brush cytology, biopsy, and washings for alimentary tract cancers. They suggested that direct brushing provided specimens of higher diagnostic accuracy. Segal et al. (116) found gastric washing gave disappointing results due to unsatisfactory material and a high false negative rate. This contrasts with the relative ease with which brush cytology specimens may be obtained and their satisfactory nature (139). In a study of 100 verified malignancies of the oesophagus and stomach Witzel et al. (139) compared several diagnostic methods. One of two early cancers was only detected by cytology. Hishon et al. (46) suggested that barium swallow was the ideal screening procedure for oesophageal cancer, with per-endoscopic cytology for confirmation (though they were discussing the investigation of patients referred to hospital and not population screening). Kasugai et al. (58) reviewed the value of brush cytology and direct vision biopsy of oesophageal and gastric cancers and suggested that, due to the ease of biopsy, this procedure is first choice with cytology being examined where biopsy was inappropriate or had failed. Kobayashi and Kasugai (64) used endoscopy biopsy and/or brushing cytology to diagnose cancer involving the cardia and lower oesophagus. Combined use of both yielded a higher diagnostic accuracy than one or the other; they suggest that brushing cytology should particularly be used when endoscopy shows mucosal elevation, thick folds, or tight cardial stenosis. Behmard et al. (7) agreed that endoscopy with brushing cytology and biopsy provided the surest diagnostic technique in upper gastrointestinal lesions.

Hitchcock and Scheiner (47) used triple histamine stimulation to identify subjects with achlorhydria or hypochlorhydria; annual radiological examination was then performed on these high-risk individuals. The proportion of cancers detected with positive lymph nodes or local extension of the growth was lower in asymptomatic subjects; however, their 5 year survival was not better than 'early' cancers diagnosed in patients attending the surgical clinic. These authors did not think that conventional Papanicolaou smears were feasible for large scale screening, but suggested that improved methods of cytology should be developed. MacDonald et al. (74) identified 500 patients at risk of stomach cancer; 149 had pernicious anaemia and the remainder achlorhydria. Using cytology as a screening device three patients were found to have gastric cancer, but two were readily visible on X-ray and the third had evidence of metastases.

No potentially curable lesions were identified by cytology.

The British Medical Journal (13) suggested that various reports from different parts of the world should stimulate greater interest in 'early' gastric cancer. Ichikawa (54) discussed early diagnosis of stomach cancer and the Japanese programme for population screening. He described the technique used for double-contrast X-ray; endoscopy was reserved for doubtful or positive results. No mention was made of the role of cytology.

In contrast, Hisamichi et al. (45) indicated that cytology is an integral step in population screening. Individuals first had a double-contrast X-ray; 18% then required further investigation including direct X-ray, gastrocamera and fiberscopic examination, biopsy, and cytology. Ishioka et al. (55) acknowledged that cytology cannot be used as a first step, but for all patients identified at preliminary screening as suspicious they suggest it is the definitive test with few false positive or false negative results. These authors (45, 55) claim the impact of screening can be identified from improved detection of early gastric lesions and reduced mortality from gastric cancer. The results from both these authors are very impressive; however, they are insufficient to evaluate the specific impact of the cytology or overall gastric screening programme. Kaneko et al. (57) reported the results of a population survey for gastric cancer, carried out in one locality near Tokyo and a number of industrial concerns. They found an appreciable proportion of localised lesions with good five year survival, using a combination of endoscopy and radiography. Again no mention is made of the use of cytology in their study.

Nakajima et al. (84) performed peritoneal lavage at the time of laparotomy for 458 patients with gastric cancer. Peritoneal cytology was a good predictor of prognosis.

Colon and Rectum

Bader and Papanicolaou (5) used cytology as an aid to diagnosis in cancer of the large bowel. This was predominantly in symptomless patients attending for screening; the cytology was obtained from direct washing of lesions visible on proctoscopy or colonic washing for lesions identified on radiology. They suggested the technique is a dependable investigation, with particular usefulness for lesions beyond the reach of the proctoscope. (This study was carried out in 1950-51 - with no access to a colonoscope.) Burn and Sellwood (14) reported the use of cytology in 50 patients with symptoms of large bowel disorder. Twenty-three patients were subsequently diagnosed as having malignant disease and