GASTRIC CARCINOGENESIS

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Proceedings of the 6th Annual Symposium of the European Organization for Cooperation in Cancer Prevention Studies (ECP), London, UK, 7–8 March 1988

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Foreword

ECP (European Organisation for Cooperation in Cancer Prevention Studies) was established in 1981 with the object of fostering the development of studies of aetiology and prevention of cancer on a European basis, since the activities of EORTO (European Organisation for Research on Treatment of Cancer) were restricted to research on cancer treatment.

Since then annual symposia have been devoted to themes of high priority for cancer prevention: "Tobacco and Cancer" (1983), "Hormones and Sexual Factors in Human Cancer Aetiology" (1984), "Diet and Human Carcinogenesis" (1985), "Concepts and Theories in Carcinogenesis" (1986) and "Causation and Prevention of Colorectal Cancer" (1987).

While sitting over a particularly good dinner in Budapest when attending the International Cancer Congress in August 1986 the editors conceived the idea of bringing together the leading experts in the field of gastric carcinogenesis in an attempt to shed more light on the aetiology and especially the prevention of a cancer which, while steadily decreasing over the past 30 years, is still numerically one of the most common cancers worldwide. We were particularly gratified by the fact that only one of the list of participants then drawn up could not attend the eventual meeting.

This volume contains the proceedings of the 1988 ECP symposium held in London, UK at the Royal College of Physicians, on March 7th and 8th on "Gastric Carcinogenesis". The aim was to review our current knowledge of this topic under four headings: "Background", "General Aetiology", "Gastric luminal factors" and "The Future". The high level of contributors ensured an outstanding overview of this clinical problem, highlighting the benefits which improvements in socio-economic factors have already achieved in the past three decades, but also stressing the need for further preventive measures to be agreed, including the initiation of intervention trials in high risk groups, to reduce further the incidence of this lethal disease. The symposium was enriched by an especially valuable poster session, the abstracts of which have been published in a special issue of "Cancer Letters" (Vol 39, Suppl. March 1988).

We are indebted to the speakers for their contribution during the symposium and for their prompt submission of manuscripts. We are grateful to the sponsors, Glaxo PLC and Miss Mandy Lakin of Gardner–Caldwell Associates for assistance with the smooth running of the meeting.

Our special thanks go to Mrs Belinda Johnston for all the work associated with the organisation of the meeting, Miss Theresa Gallagher for preparing and typing the camera ready forms of all the manuscripts and Dr Steve Leach, Craig Mackerness, Kathy McPherson and Philip Packer for their assistance in checking these afterwards.

We hope that this will be the first of a series of symposia on gastric carcinogenesis to be held in the future.

The 1989 ECP Symposium will be on "Aetiological and epidemiological relationships between cancers of the breast, endometrium and ovary" to be held in Bilthoven (The Netherlands) on 1–2 May 1989.

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BACKGROUND

BACKGROUND

Gastric carcinogenesis. P.I. Reed, M.J. Hill, editors.

DIAGNOSIS AND SURGICAL TREATMENT OF GASTRIC CANCER

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INTRODUCTION

The diagnosis of gastric cancer at an early stage is often a very difficult feat. In countries where the disease has a very high incidence eg Japan (67 cases per 100,000 per annum), the application of mass screening or early diagnostic techniques can identify several cases at an early stage, as well as giving an initial high yield of some advanced cases on a large scale (26). In the United Kingdom the incidence of gastric cancer is much lower (27 cases per 100,000 per annum) and in common with most other countries in the world it has been declining steadily over the past 40 years. A recent survey (Fig. 1) defining the incidence in relation to age of the population in the United Kingdom reminds all of us involved in clinical work, to raise the index of suspicion of the diagnosis in patients over the age of 50 who have vague, persistant, yet often very mild upper gastrointestinal symptoms. From the data (Fig. 1) gastric cancer below the age of 25 is rare but in the fourth and fifth decades there is a steadily increasing incidence of the disease in both males and females. Another helpful strategy is the identification within the population of special high risk groups in which, for one reason or another, there appears to be an increased risk of the disease developing. A list of well-known groups at risk and risk factors is given in Table 1.

Diagnosis

Many diverse factors can help us in arriving at the diagnosis of early gastric cancer, not least of which is the fact that in a recent UK survey (de Dombal, personal communication) about 50-60% of cases were, in fact, symptomatic. This has been emphasised by Allum and his colleagues in Birmingham (2), whose open-access endoscopy clinic for males with persistant dyspepsia lasting longer than 6 weeks resulted in a higher pick-up rate than previously achieved in that region of the UK, together with a higher percentage of cancers at an earlier and operable stage. It can be seen from Table 1 that many of the conditions and groups listed result from a suppression of normal gastric acid secretion with hypo-or achlorhydria often associated with damage to the epithelium. Some of the detailed factors operating at the mucosal level will be discussed elsewhere in this book.

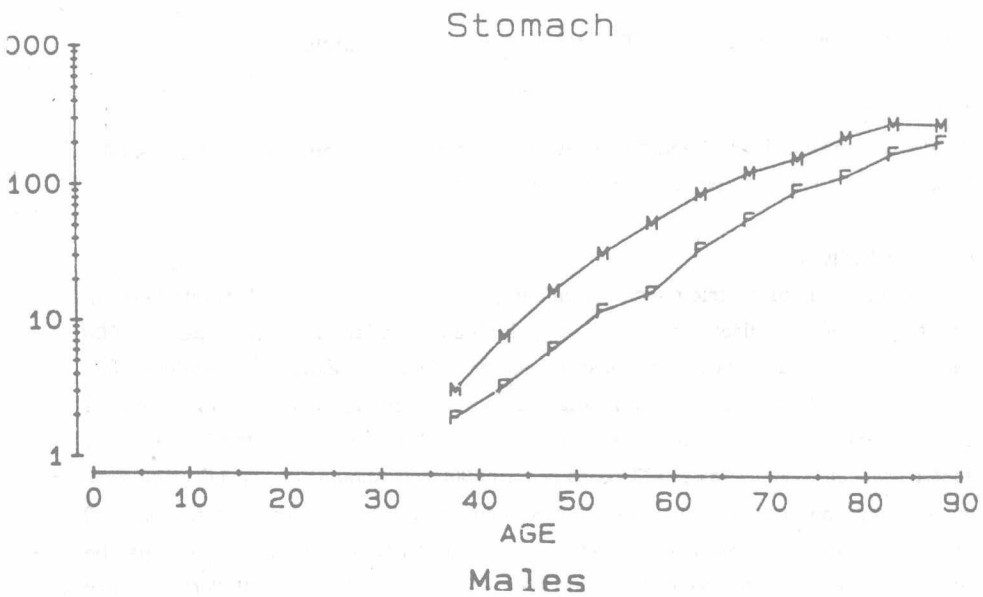

Fig. 1. Age-related incidence of gastric cancer in United Kingdom (Source: Registrar General Statistics).

TABLE 1

IDENTIFYING FACTORS AND GROUPS ASSOCIATED WITH INCREASED RISK OF DEVELOPMENT OF GASTRIC CANCER

Blood group A
Pernicious anaemia
Chronic atrophic gastritis
Intestinal metaplasia
Gastric resection
Bile reflux
Geographic and ethnic factors
Diet and salt intake
Truncal vagotomy

Team Approach

In order to efficiently achieve a diagnosis of early gastric cancer, it is essential

that colleagues form diagnostic teams comprising of a clinician with a high index of suspicion of the disease, an endoscopist (who may be the clinician), a motivated radiologist and pathologist. It is particularly important that a pathologist experienced in the diagnosis of dysplasia and of early gastric cancer is available (14,13).

Clinical Diagnosis

From the point of view of clinical diagnosis any areas of suspicion in the stomach should be biopsied particularly using the "spiked" forceps to obtain tissue below the mucosal surface, and if possible at least 10 biopsies within a circumscribed area should be obtained. Biopsy alone is not sufficient and brush cytology can also be extremely helpful in establishing the diagnosis but requires the availability of an experienced gastric cytologist. It is now widely accepted that fiberoptic endoscopy with biopsy and brush cytology forms the gold standard for the critical diagnosis of gastric carcinoma (3,38). Nevertheless, endoscopy has not been 100% successful in diagnosing cases particularly in areas of difficulty, for example at the oesophago-gastric junction. Mori et al (42) have shown that certain cases of early gastric cancer (EGC), a diagnosis made in 21 patients out of a total of 2,237 cases of gastric cancer, all lay within 2cms below the cardio-oesophageal junction and the lesions themselves varied from 1 to 4cms in size. The diagnostic point at issue lies in the fact that in 16 of their 21 cases of EGC of the cardia, the diagnosis was directed and suspicions raised by a double contrast barium meal study, so that the endoscopist could be guided to the particular area in question. This important clinical contribution also pointed out that these early gastric cancers in this part of the stomach were coincident in some cases with duodenal ulcer, gastric ulcer in others and, in a few cases, early gastric cancer was found elsewhere in the stomach. The role of radiology is also emphasised in a further recent pospective study of 385 patients with 'dyspepsia' by Shaw et al (1987) (58) who submitted their cases to double contrast barium meal and endoscopy without allowing either speciality access to the findings of the other. Analysis of the results in terms of diagnosis of gastric cancer suggested that carefully performed double contrast radiology of the stomach in some hands can compete with equal merit with that of fiberoptic endoscopy. In practice most patients will have an endoscopy and in cases of difficulty or doubt all diagnostic methods should be employed. Both diagnostic techniques are labour intensive of clinicians' time and have cost implications particularly relevant in countries where the incidence of the disease is relatively low, such that mounting large scale screening programmes, particularly by endoscopic methods, are beyond the means of available resource. This situation applies in the United Kingdom.

Histological and Morphological Classification

Our Japanese colleagues have been pioneers in clarifying the endoscopic

classification of early gastric cancer which is now used as a standard by endoscopists the world over (Fig. 2). This classification based on simple luminal morphology of possible lesions has, moreover, allowed endoscopists to examine critically mucosal abnormalities and has helped in the precise location of the site selected for biopsy (35).

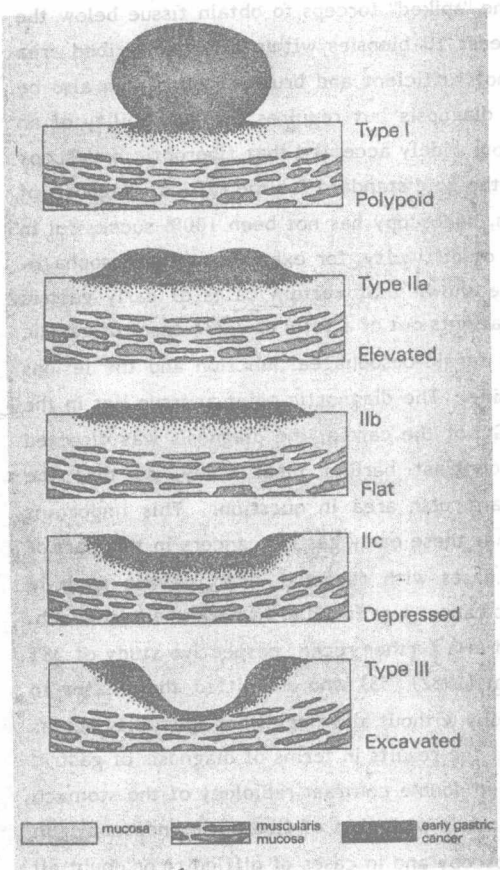

Fig. 2. The Japanese morphological classification of gastric cancer (Illustration reproduced by kind permission of Gower Medical Publishing Co).

A histological classification of gastric cancer from the work of Lauren (36) more than 20 years ago described two broad groups: the diffuse type and the intestinal type. Recent evidence has strongly suggested that the frequency of the diffuse type of carcinoma decreases markedly with increasing age, while the incidence of the

intestinal type accounts for over 60% of cases at the age of 70 or more (24). Clinically the world-wide decline in gastric cancers has primarily been found in those suffering from the intestinal type, strongly suggesting that it is a change in environmental factors which may well be responsible for this decrease (60,27,44). As in all pathological classifications there is some degree of overlap with areas of both types being seen in the one specimen and in a minority of cases (<10%) classification on this system is not possible at all.

Staging of Gastric Carcinoma - Relationship to Survival

A prime determinant of surgical treatment after making the diagnosis is the stage of the cancer. We are again indebted to our Japanese colleagues for defining the microscopic staging of early gastric cancer as adopted by the Japanese Cancer Research Society in 1963 (13). Early gastric cancer, therefore, has been defined as confined to the mucosa or submucosa as determined by depth of infiltration of the gastric wall, but has been associated with lymph node metastases in 15-20% of cases. The implication for successful surgical treatment is well-illustrated by the report of Takasugi et al (62) who showed that the post-operative 10-year actuarial survival rate for early gastric cancer confined to the mucosa was 100% and for that in the submucosa 95%.

Is there a Change in Clinical Pattern?

Changes in the clinical pattern of gastric carcinoma in North America and in England have recently been noted (41,47) suggesting that proximally based tumours have increased in frequency whereas carcinomas of the antrum and body have significantly decreased in incidence over the past 30 years ($p>0.01$). Whether these simply reflect the better diagnostic facility offered by the fiberoptic endoscope, or are a true reflection of a change of location of the disease with time will require further study from other geographic locations, but if such reports are confirmed then a greater index of suspicion and greater vigilance in the area of the cardia and proximal stomach will be required.

The Gastric Ulcer Dilemma

The diagnosis of gastric cancer associated with a gastric ulcer presents the clinician with difficulty. A recent report by Rolag and Jacobson (1984) (52) has helped to clarify these issues. 121 gastric ulcers benign at original assessment by biopsy and brush cytology were traced after 6 years. Many had undergone surgery for their original gastric ulcer on the dictum adopted by many clinicians that "if the ulcer fails to heal within 6 months, gastrectomy is advised because of the risk of malignancy". Others ($n = 17$) had died from unrelated causes and 22 with no clinical complaints who were traced refused further investigation, and 4 could not be found. However, a substantial majority ($n = 78$) were re-scoped and had multiple biopsies taken from the site of the previous ulcer or from any suspicious areas in the

stomach. One gastric cancer was found. None of the original ulcers removed at surgery were found to be malignant. This report emphasises the safety with which predictions can be made if a gastric ulcer is thoroughly assessed at the initial endoscopy, sampled by biopsy and brush cytology and serves to remind us that most gastric cancers are not associated with a classic gastric ulcer (10).

Tumour Markers - Future Possibilities?

The search for suitable markers for gastric cancer has intrigued many workers in recent years, particularly with the availability of monoclonal antibodies to the neoantigens Ca19-9, Ca50, Ca12-5 as well as the existing spectrum of oncofetal antigens originating with CEA (23). The problem has been that while some cancers are clearly identified, most of the markers are not sensitive or specific enough to be used routinely in vivo for the detection of gastric carcinoma (48,34). Recent studies with murine monoclonal antibodies with restricted antigen epitopes on CEA are more hopeful, picking up 72% of a pilot series (45). Since the majority of gastric cancers are associated with a degree of gastritis an exciting possibility using the serum pepsinogen groups 1 and 2 both individually and as a ratio as described by Samloff et al (55) might allow us to define the histologial state of the gastric mucosa from a simple serum sample submitted to the respective radioimmunoassays (Fig. 3). If applied on a mass scale after validation from the original reports in the siblings of a Finnish cohort with pernicious anaemia, then such a strategy may allow the definition of high risk groups with atrophic gastritis and hyposecretion, who could then be further investigated by endoscopy and cytology. Unfortunately the antibodies and antigens are not yet widely available particularly for the group 2 pepsinogens (ie those associated with the antrum of the stomach).

Another exciting possibility not only for identification of patients with gastric cancer but of malignancy in many other locations could result from application of the techniques described by Fossel et al (15,16). This group made use of the magnetic resonance-water-suppressed proton spectrum associated with the methyl and methylene groups in the lipoproteins of plasma. They described the almost complete separation of patients with varying types of adenocarcinoma including those of the stomach and the colon from age and sex matched normal subjects, and from the majority of those hospital control patients suffering from non-cancer diseases. However, the details in this report do not in any way reflect the stage of the tumour.

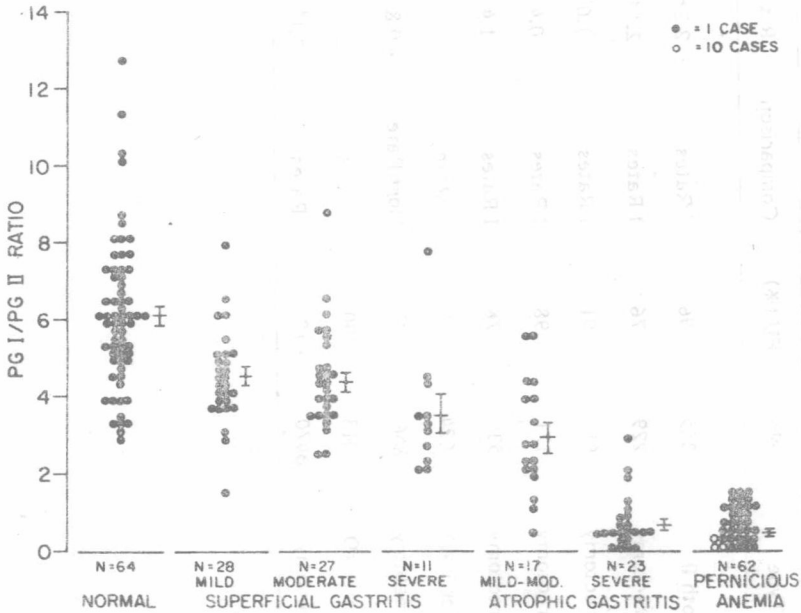

Fig. 3. The relationship between the ratio of Group I pepsinogens to Group II pepsinogens in the serum of siblings of pernicious anaemia cases and the histology of the stomach (by kind permission of Dr M Samloff, and Gastroenterology).

Gastric Polyps - A High Risk Group

Most polyps in the stomach are pseudoinflammatory and have nothing to do with gastric cancer (11) but the adenomatous polyp can undergo malignant change (Fig. 4). They are often seen incidentally in the investigation of a patient with mild dyspepsia or with gastrointestinal bleeding, and there is good prospect in the future that treatment by endoscopic laser techniques will allow ablation of such lesions without resort to gastrectomy (51).

Surveillance of the Post-Operative Stomach

Cancer of the gastric stump after gastrectomy or after truncal vagotomy and drainage for peptic ulcer has long been known by the relevance of the pre-operative diagnosis, the age of the patient at the time of original surgery, the particular