Flat and Depressed Colorectal Neoplasia in England and Japan (Foundation for Promotion of Cancer, Japan and the British Council)

To the Editor:

As a research fellow in Leeds, England, I have now come to the end of an interesting and stimulating month at the National Cancer Center Hospital (NCCH) in Tokyo and Kashiwa.

Our unit at the General Infirmary in Leeds had the privilege of receiving a Japanese expert colonoscopist for three months in 1995, when I learnt much about flat and depressed colorectal lesions and subsequently began to search for them. Whilst in Japan, I improved my technique and compared my findings with those of Dr T. Fujii and other Japanese colleagues. Here, I aim to put flat and depressed colorectal lesions into a Western context and to report on my own relevant experience in the UK, where, after Dr Fujii’s visit, I began to search for and remove flat adenomas, using endoscopic mucosal resection.

Traditionally, the colonoscopic training in the West has emphasized the importance of detecting polypoid lesions. This is due to the adenoma-carcinoma sequence originally proposed by Morson. According to this hypothesis, adenomatous polyps become increasingly dysplastic as they enlarge and eventually progress to adenocarcinoma. The evidence that carcinomas develop from adenomas is convincing: (1) adenomas are six times more common in patients with colorectal carcinoma than matched controls, (2) metachronous carcinomas are twice as common in patients found to have both a colorectal cancer and adenomas in the original specimen, (3) 75% of patients with synchronous carcinomas have additional adenomas, (4) dysplasia, aneuploidy and focal carcinoma may be observed in adenomas, (5) adenomas seem to precede carcinomas by an estimated 10–15 years, (6) patients with the highest risk of future cancer have multiple adenomas or adenomas greater than 1 cm in diameter and (7) there is evidence of genetic progression from adenoma to carcinoma.

Morson estimated that up to two-thirds of all colorectal carcinomas arose from adenomatous polyps. The origin of the remaining colorectal carcinomas is not known and some have suggested that they may arise de novo. An alternative explanation, proposed by Japanese workers, is that they arise as ‘flat’ or ‘depressed’ rather than as polypoid lesions.

Dr Fujii performed 208 examinations in Leeds and found 68 adenomas (32%) and 7 carcinomas (3.4%). In my own series, adenomas were found in 21% of examinations (154/722) and carcinomas in 1.7% of examinations (12/722). Dr Fujii found that 60% of his 75 neoplastic lesions were polypoid, 37% were flat and 2.7% were depressed. My own findings were identical: 60% of the 166 neoplastic lesions appeared polypoid but 37% were flat and 3% were depressed.

Dr Fujii found that 4/68 (5.3%) were severely dysplastic adenomas, 3/68 (4%) were Duke’s A carcinomas and 4/68 (5.3%) were more advanced malignancies. In my own series, 14 (8.4%) of the 166 neoplasias found were severely dysplastic, 6 (3.6%) were Duke’s A carcinomas and another 6 (3.6%) were Duke’s B or more advanced carcinomas.

Most important, however, Dr Fujii found that of the 7 early carcinomas, i.e. severely dysplastic adenomas or Duke’s A carcinomas, 4 (57%) were polypoid, 1 (14%) was flat and 2 (28%) were depressed. Of the 20 early carcinomas I found, 9 were polypoid (45%), 7 were flat (35%) and 4 were depressed (20%).

These findings have important implications for colorectal cancer screening protocols, the purpose of which is to detect early cancers, e.g. adenomas with high-grade dysplasia or Duke’s A carcinomas. Special training is needed to detect depressed lesions, as these tend to be smaller than the other lesions (8.5 vs 14 mm in my series) and usually only appear as erythematous patches. Without this training, I predict that the colonoscopic screening protocols will fail to detect between 20% and 50% of all preventable cancers.

The largest published trial supports this prediction: the National Polyp Study reported on the 6 year follow up of 1418 patients after colonoscopy to clear all polyps. This study failed to prevent up to 24% of all subsequent carcinomas.

If both a Japanese and a British colonoscopist have independently found that up to half of the early colorectal malignancies appear flat or depressed, why are these lesions not more widely recognized? There are several possible explanations. The bowel preparation must be perfect yet this may be unsatisfactory in up to 40% of patients. In Leeds we have used up to 4 l of a colonic lavage fluid, self-administered by the patient, the evening prior to a morning colonoscopy list. Patients undergoing afternoon examination are often given a sachet of Picolax 1 day before followed by two units of lavage fluid (Klean-Prep) in the hours prior to examination. This latter method gives a superior result but can only be used for afternoon lists. We are also assessing a phosphate-containing lavage fluid (Phospho-Soda), but the results, so far, have been very similar to those with our old method.

Then recognition of flat and depressed colorectal neoplasia is not easy. The depressed lesions are usually small and only appear as a red patch. In spite of this, they carry a high risk of malignant change. Another important group of lesions which may easily be overlooked are the non-granular laterally spreading tumours. To date I have found six such lesions, four of which contained intramucosal carcinoma. Crucially, the endoscopist must be familiar with the use of dye-spraying to highlight suspicious lesions. Once a lesion has been stained one should be able to assess the crypt pattern to determine the nature of the lesion. It was only after I was lent a magnifying colonscope (CF200Z) that my technique improved.

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Molecular Genetics and the Research Strategy of the NCCRI: an Outsider’s Impression

To the Editor:

I am writing this letter to share with you and your readers the impressions of my extremely productive visit of 6 weeks to the National Cancer Center Research Institute (NCCRI), Tokyo. The visit was sponsored by The Second Term Comprehensive 10-Year Strategy for Cancer Control, which aims at fostering international cooperation in cancer research, amongst other goals. I had already made one such visit some 12 years ago and, as a result, a trainee of the NCCRI eventually joined my laboratory, producing important observations about cytokine regulation of connective tissue homeostasis. He has long joined the faculty of Kanazawa University School of Medicine where he is pursuing research in liver diseases.

My laboratory has had a long-standing interest in the pathophysiology of connective tissue with particular reference to the structure, function and regulation of collagen and fibrillin genes. Our major accomplishments have been the cloning of the human fibrillar collagen genes and the establishment of causal associations between them and a variety of genetic disorders, including osteogenesis imperfecta and disproportionate dwarfism; the cloning of human fibrillin genes and the discovery of the genetic lesion in the Marfan syndrome; and the development of mouse models of these human diseases for pathogenic analyses and gene therapy. In more recent times, we have been interested in the identification of genes coding for molecules—transcription factors—which regulate commitment and differentiation of mesenchyme cell lineages. The scope of my visit to Japan was twofold.

First, I wanted to learn more about an interesting new model of limb organ culture recently developed by Dr Takahiro Ochiya at the Genetics Division of the NCCRI. The model allows one to follow in vitro several aspects of development, including limb outgrowth and digit formation, and under closely monitored conditions. Therefore, potentially it offers researchers the possibility to examine how environmental signals regulate limb development, which genetic determinants are sequentially activated during this process and when and where cell–matrix interactions participate in it. Each of these topics is of relevance to the etiopathogenesis of developmental abnormalities in humans, and also of deregulated cellular programs in cancer. The second reason for my visit was to test the hypothesis that cell type-specific regulators may also be involved in tumorigenesis by exploiting the wealth of biological material available at the Genetic Division of the NCCRI, in addition to the unique talent and expertise of its investigators. This pilot study was very successful and has eventually grown into a large-scale screening for tissue-specific transcription factors with deregulated expression in cancer cells and tumor tissues. The screen is being carried out principally by Dr Teruhiko Yoshida at the NCCRI in concert with our group in New York City.

Needless to say, my visit was productive; in addition, it was an educational experience for my own understanding of cancer biology and for appreciating the new directions in this important biomedical field. I must say that the NCCRI is at the forefront in these challenging tasks. During my stay, I had the opportunity to discuss with the Directors of most NCCRI Divisions their current work and future prospects. As a result, I came to realize that the overall mission of the Institute is solidly funded on a variety of basic and translational programs that range from genetic screening to gene therapy and from molecular analyses to clinical applications. The scientific stature and international reputation of individuals such as Drs Hirohashi, Ohki, Sekiya and Terada, to name only a few, are unquestionable and the congregation of these and additional outstanding investigators in the same place is unmatched even in highly competitive institutions of the USA. Indeed, the leadership should be commended for having built such a vibrant place and having brought together such a superb cadre of scientists.

In conclusion, I have benefited greatly from this visit and my research program has grown further along with my own knowledge. I am very much indebted to those who made this visit possible, in particular the Foundation for Promotion of Cancer Research, The Genetic Division and Dr M. Terada and all the scientists of the Research Institute. I hope they enjoyed having me around and were able to benefit a little from my ideas and suggestions. Finally, I am looking forward to making my relationship with the NCCRI even stronger in years to come.

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