The changing face of familial colorectal cancer
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“minimalists who still hankered after the old style of medicine . . . to do the least possible consistent with good appearances.”

The root of the reactionary culture, concludes Dame Janet, is the fact that elected members (all doctors) control the council. They see it as their job to represent doctors rather than regulate them. Dame Janet wants more medical members appointed rather than elected, something that is unlikely to please rank and file doctors who have rebelled in the past over “taxation without representation.”

The old guard or minimalists are not entirely philosophically bankrupt. They can gain some comfort from another woman with an incisive mind, Onora O’Neill. In her Reith lectures she argued that attempts to replace trust with accountability may have gone too far: “The efforts to prevent the abuse of trust are gigantic, relentless, and expensive; their results are far: “The efforts to prevent the abuse of trust are gigantic, relentless, and expensive; their results are always less than perfect.” There can never be so much transparency that trust is no longer necessary, and the challenge is to arrive at the correct balance of trust, transparency, and accountability.

The changing face of familial colorectal cancer
Young patients with colorectal cancer should be assessed for genetic predispositions

Colorectal cancer is predominantly a disease of elderly people in the developed world. The annual incidence of more than 35 000 cases in the United Kingdom means that many people have at least one affected relative. Colorectal cancer in elderly relatives may be due to shared environmental exposure rather than a true genetic predisposition, although the risk of developing colorectal cancer rises with the number of relatives affected. Genetic factors may have a role in up to 30% of cases, but only a small proportion (less than 5%) of colorectal cancers arise in families with strong histories in which tumours develop at a young age (less than 50 years) and represent truly high risk inherited predispositions. Even so, more than 1500 families per year need to be counselled and screened.

Most hereditary colorectal cancers are attributable to two recognised syndromes. Familial adenomatous polyposis usually has a clear phenotype, characterised by numerous (more than 100) adenomatous polyps in the large bowel by the second to third decades of life, which inevitably progress into cancers. This autosomal dominant condition, caused by APC gene mutations, has been a paradigm for the management of familial colorectal cancer. The use of registries, genetic testing, surveillance, and prophylactic surgery means that familial adenomatous polyposis now accounts for less than 0.5% of all new colorectal cancers, and patients’ life expectancy is much improved.

Hereditary non-polyposis colorectal cancer syndrome accounts for the bulk of familial colorectal cancer. The name is misleading as these colorectal cancers also arise from adenomas, but the degree of polyposis is less marked than in familial adenomatous polyposis. Hereditary non-polyposis colorectal cancer has a heterogeneous spectrum, and the phenotype is more difficult to define than in familial adenomatous polyposis. Some kindreds are predisposed to endometrial cancer, and other sites of cancer that may be associated include the stomach, ovaries, and urinary tract.

We now know that hereditary non-polyposis colorectal cancer arises due to mutations in mismatch repair genes. Mismatch repair proteins correct insertion and deletion mutations that occur when DNA is copied before cell division. Such errors accumulate markedly in microsatellites, where the DNA sequence is repetitive, and hence, these cancers are said to display...
Revised Bethesda guidelines for identification of patients who should be tested for microsatellite instability

Individuals with colorectal cancer before age 50 years
Individuals with synchronous or metachronous colorectal cancer, or other cancers related to hereditary non-polyposis colorectal cancer at any age
Individuals with colorectal cancer with MSI-H histopathology diagnosed before age 60 years
Individuals with colorectal cancer and one or more first-degree relatives with a hereditary non-polyposis colorectal cancer related tumour, with one cancer diagnosed before age: 50 years
Colorectal cancer diagnosed in two or more first or second degree relatives with tumours related to hereditary non-polyposis colorectal cancer, at any age

microsatellite instability. There are several mismatch repair genes and it appears that distinct gene mutation patterns may underlie variability in the clinical phenotype of hereditary non-polyposis colorectal cancer syndrome.

Stringent family history requirements, the Amsterdam criteria, were developed to identify families with hereditary non-polyposis colorectal cancer for genetic research. However, many families with hereditary non-polyposis colorectal cancer do not fulfil these criteria despite carrying mismatch repair gene mutations. Reliance solely on family history, which is often incomplete or limited by small family size, may hinder diagnosis. Improved understanding of hereditary non-polyposis colorectal cancer has led to the development of the Bethesda guidelines, (box) that identify with high sensitivity patients with colorectal cancer who may harbour a genetic predisposition and should undergo testing for microsatellite instability or mismatch repair protein immunohistochemistry. If mismatch repair defects are found the patient can then be appropriately counselled and further tested for specific gene mutations. Clearly, such services should be extended to patients’ families. Ethical issues surrounding the implications of tests that discern hereditary syndromes are complex, and the challenges posed by patients at high risk who decline testing are difficult but merit careful consideration.

Any young patient with colorectal cancer, or a patient with synchronous or metachronous tumours should best be assumed to have a genetic predisposition until proved otherwise. All patients under the age of 50 years with cancers associated with hereditary non-polyposis colorectal cancer should be appropriately counselled and offered further investigations. Clinicians dealing with these cancers should also be alert to the common histological features of tumours related to hereditary non-polyposis colorectal cancer—they are characteristically right sided, poorly differentiated, mucinous, and densely infiltrated by lymphocytes. Histopathology reports may therefore raise the suspicion of hereditary non-polyposis colorectal cancer in a patient, even when criteria regarding history criteria are not fulfilled.

The identification of such patients and their families is important because of the implications for counsel-ling, genetic testing, and surveillance. Screening for colorectal cancer in families with hereditary non-polyposis colorectal cancer has been shown to have notable benefit, but the value of screening extra-colonic sites needs further evaluation. Prophylactic surgery may be an acceptable option for some patients and should be discussed where appropriate. Hereditary non-polyposis colorectal cancers may also have altered prognostic outlook and selective chemosensitivity.

Genetics and clinical practice need to be integrated and additional resources assigned to the creation of formal links between district general hospitals and tertiary referral centres capable of providing comprehensive genetic and clinicopathological analyses. The potential benefits of surveillance and prophylactic surgery mean that the Bethesda guidelines (box) should now be a part of routine clinical practice.

Research into the genetic mechanisms responsible for familial colorectal cancer is pivotal to understanding this disease. An autosomal recessive form of polyposis associated with a gene called MYH has recently been characterised, and other genes or molecular pathways predisposing to novel variants of familial colorectal cancer may yet emerge. The genetic spectrum of familial colorectal cancer should be considered a “moving target” for the foreseeable future.

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