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Crohn's disease

Recurrence rates in Crohn's disease: predicting the future and predicting the past

D B Sachar

Phenotypic features at diagnosis of Crohn's disease may help predict subsequent disease flares and operations

"A guy ought to be very careful in making predictions, especially about the future." [Yogi Berra (1925–), professional baseball player and manager]

The Holy Grail of Crohn's disease—aside from finding the elusive cause and cure—is understanding its "natural history"; that is, how it develops, presents, evolves, and responds to different therapies. A principal objective of this level of understanding would be the ability to

predict the course of disease in any given individual or group of individuals. This aim has been the focus of clinical studies of inflammatory bowel disease for nearly four decades.

One of the earliest attempts to find clinical markers to predict outcomes was made by the late FT de Dombal in Leeds, who proposed a rise in serum β -globulin as an early warning sign of impending flare of ulcerative colitis.¹ Later efforts to develop laboratory predictors of Crohn's disease flares included studies by Brignola *et al* in Bologna.² A sharper focus on clinical predictors, as distinct from pure laboratory indices, was introduced by JP Wright in Cape Town.³ All of these studies were as well intentioned as, but not much more successful than, the search for the historical Holy Grail had been over the previous millennium.⁴

Meanwhile, a less sophisticated but perhaps more intuitive approach to forecasting the clinical course of

Crohn's disease emerged from separate studies in Leeds,⁵ Cleveland,⁶ and New York.⁷ These investigators called attention to the value of observing clinical "patterns" or "behaviour" of disease in predicting its subsequent course, especially, although not exclusively, leading up to and subsequent to surgery. This avenue of investigation has led to formal attempts in Rome, Vienna, and Montreal to construct standardised phenotypic classifications of Crohn's disease.⁸⁻¹⁰

Phenotypic classifications, of course, have a number of potential uses. They can serve as templates for molecular, serological, and genotypic correlations.¹⁰⁻¹¹ They can and indeed must provide stratification criteria for clinical trials, and they are now widely adopted as guidelines for therapy.¹²⁻¹³

Yet another application for phenotyping is the act of forecasting itself—*prediction* (from Latin roots for saying or telling in advance) and *prognostication* (from Greek roots for knowing in advance). While the earliest 14th century uses of the latter word in English predated that of the former by about 100 years, the specifically medical application of "prognosis" emerged only in the second half of the 17th century.

Today we continue our efforts to move beyond tea leaves and sheep entrails to forecast the fates of our patients. In this issue of *Gut*,¹⁴ a distinguished group of some of the top investigators in Europe report on a 10 year cohort study looking for phenotypic features at diagnosis that would help predict subsequent disease flares and operations (*see page 1124*). This is a worthy goal, important as the authors correctly indicate "for patient counselling and health care planning". Their abstract summarises four principal conclusions: (1) younger patients and those with upper tract lesions experienced more disease flares than others; (2) 31.6% of patients underwent surgery within 10 years of diagnosis; (3) patients with colonic disease were operated on less frequently than others; and (4) patients from northern Europe, especially Copenhagen, underwent resection more often than others.

To be sure, as in all scientific reports, there are a few spots where the supporting ice is a little thinner than in other places. For example, calculation of "non-surgical recurrence rates" implies a firmer measurement than the definition justifies. What we are really dealing with here is simply a "flare up" as individual patients and doctors might happen to record the event at various times in different centres. Likewise, interpretation of the effects of medical therapy appears to rest on shaky ground.

The association of aminosalicylates with *more* flares is postulated to represent "an epiphenomenon of recurrent disease rather than a risk factor," while the association of azathioprine with *fewer* flares is taken as "a sign of its potent immunomodulatory maintenance effect". The authors seem to be having some trouble sorting horses from carts.

Perhaps most puzzling is the fact that the surgical recurrence rates in this series are the lowest, slowest, and most widely variable ever reported. In the decade following diagnosis, fewer than 30% of all patients required operation, well under half the rate experienced in most centres worldwide. This finding might have been the result of enormous variability in rates among centres. Unfortunately, we are not given the actual data from each centre but we are told that "significantly less recurrences [*sic*]" were recorded in three centres that comprised 39% of the total population of the study, and "significantly more recurrences" in another centre (Copenhagen) that comprised only 16% of the total. The flavour of this stew is likely to be determined by the heaviest ingredient, as in the proverbial "horse and rabbit" stew concocted from one horse and one rabbit.

Yet even if the conclusions highlighted in the abstract remain solid despite the occasional weaknesses in the underlying data, they are only the smallest nuggets of information tossed to the surface; the real treasures lie below, hidden in the body of the text. Particularly noteworthy is confirmation of previously noted observation¹ that reoperation following initial resection is required in somewhat less than half of all cases,²⁻¹⁵ that most patients evolve from inflammatory disease behaviour at diagnosis into either stricturing or penetrating categories during the first 10 years after diagnosis,¹⁶⁻¹⁷ and that, curiously, a sizable proportion of cases *already* presented with penetrating or stricturing complications at the time of diagnosis.¹⁸ While the 25% proportion initially presenting with such complications in the present series is not as dramatically high as the 55% in a recent report from Italy,¹⁸ I call it "curious" because Crohn's disease is conventionally thought to present initially in an "inflammatory" phase and only after 5–10 years to progress to stricturing (Vienna Classification B2) or penetrating (B3) categories.¹⁶⁻¹⁷

The question must therefore arise: How and when does Crohn's disease actually *begin*, and where is it, and what is it doing for all the *past* time *before* it becomes clinically manifest?¹⁹ Perhaps continuing endoscopic study of fresh postoperative cases and video capsule studies of normal and genetically or

serologically "high risk" subjects will help answer this question. In the meantime, we shall have to keep struggling not only with the problem of predicting the future but also the challenge of "predicting the past."

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