EDITORIALS

Studying Inflammatory Bowel Disease in the Global Laboratory

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An axiom—almost a cliché—in our specialty is the observation that the inflammatory bowel diseases (IBD) develop from an intersection of genetic predispositions and environmental triggers. But how informative is this axiom? As of today, there are over 30 gene loci identified as each playing tiny roles in the susceptibility profile for IBD [1, 2]. But even the most robust among them, mutations at the NOD2/CARD15 locus, are present in only a minority of cases of Crohn's disease and appear to exert an influence only in certain populations and not others [3-5]. Even the indisputable phenomenon of familial tendencies for these diseases shed little if any light on the stubborn dilemma of the respective roles of genetic versus environmental factors [6, 7].

And as far as environmental triggers are concerned, except for cigarette smoking [8] and possibly a history of appendicitis [9], nothing but controversy and uncertainty swirl around hypotheses regarding agents as diverse as urban diets [10], Mycobacteria [11], toothpaste [12], dietary microparticles [13], and trace minerals [14].

Can any laboratory experiments clarify these issues? We cannot breed humans and we can hardly conduct lifelong randomized trials exposing controlled populations to various selected environmental elements. Where then can we turn? Perhaps our best laboratory is the planet itself. Global population distributions and migrations afford us opportunities to study both genetic and environmental associations with a whole spectrum of serological, clinical, and pathologic varieties of IBD.

Thus, the medical literature is replete with analyses of patterns of IBD in different countries. Indeed, in the last two years alone, papers have appeared describing the genetic and clinical patterns of IBD and its complications in Brazil [15], Finland [16], Malta [17], Spain [18], Barbados [19], Hungary [20], Puerto Rico [21], Iran [22], China [23], rural southern Germany [24], Poland [25], southeastern Norway [26], Sri Lanka [27], and French Canada [28], as well as across whole populations of Asians, Hispanics, and African Americans [29-31].

Now another in this series of publications about IBD from different parts of the world has recently appeared in the June 2009 issue of this Journal [32]. It is one of only a handful of studies of the clinical features of ulcerative colitis (UC) and Crohn's disease (CD) in Turkey. Besides contributing generally to the literature regarding IBD in various global populations, what specific lessons does this meticulous and ambitious study have to teach us about the fundamental nature of these protean disorders?

Besides learning that age patterns, extraintestinal manifestations, and clinical features of IBD in Turkey are generally similar to those in most other countries, I find two observations to be of particular interest. The first point was that Turkish patients resembled every other population in the precise parallelism of demographic patterns and risk factors between UC and CD for every variable studied (regions of origin, current areas of residence, educational levels, uses of oral contraceptives and NSAIDs) except smoking. Smokers are less likely to develop UC and have a more severe course of CD [8]. The consistency of this observation worldwide has been remarkable ever since it was first brought to wide attention over 25 years ago [33].

Equally of interest to me is a second point that can be extracted from the authors' wealth of data: namely, that the prevalence of UC in their series was 2.6 times higher than that of CD. Why do I find that particular fact noteworthy? The reason is that it reproduces the prevalence ratios noted in all countries of low prevalence before the diseases become increasingly common. Throughout much of the western world 10-20 years ago, UC tended to be more common than CD, while the past decade has seen UC decrease and CD increase in frequency to the point that the ratio is reversed in many places [34-36]. In other parts of the world, however, as

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in Turkey, UC is still more common than CD; yet, if current global trends continue, we can expect to see CD increasing in incidence and prevalence to the point that it will ultimately equal and perhaps outstrip UC.

Nobody yet fully understands what all these population trends signify, but to me they convey at least one definitive lesson. Gene pools do not change rapidly from one decade to another, but environmental factors do. For all the fashionable genetic science going on today in the field of IBD, let us not lose sight of the dominant role of as yet unidentified environmental agents. More studies from eastern Europe and other continents should illuminate this field further in the years ahead.

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