It's Not Just the Genes

The most common diseases are the toughest to crack. Heart disease, cancer, diabetes, psychiatric illness: All of these are "complex" or "multifactorial" diseases, meaning that they cannot be ascribed to mutations in a single gene or to a single environmental factor. Rather they arise from the combined action of many genes, environmental factors, and risk-conferring behaviors. One of the greatest challenges facing biomedical researchers today is to sort out how these contributing factors interact in a way that translates into effective strategies for disease diagnosis, prevention, and therapy.

The genes that contribute to complex disease are notoriously difficult to identify, because they typically exert small effects on disease risk; in addition, the magnitude of their effects is likely to be modified by other unrelated genes as well as environmental factors. Perhaps reflecting these difficulties, susceptibility loci for complex diseases identified in one study population often cannot be replicated in other populations (see the Report by Levinson *et al.*, p. 739).

This special section describes three complex diseases that together illustrate the difficulty facing researchers. Type II diabetes (see the News story by Marx, p. 686) has reached epidemic proportions in the United States and, in a particularly disturbing trend, is now striking people at a young age. The clear physiological link between this form of diabetes and obesity, whose incidence is also on the rise, makes a strong case for a causal role of diet and exercise level; at the same time, studies of diabetes-prone human populations and rodent models have begun to uncover tantalizing candidate genes that are also likely to influence disease susceptibility. In patients suffering from the autoimmune disorder lupus (see the News story by Marshall, p. 689), the immune system recognizes host tissue as foreign, sometimes producing serious organ damage. The working model for disease etiology suggests that people with lupus are genetically predisposed to have a hyperactive immune system, but the manifestation of symptoms is also influenced by environmental factors, including viruses, drugs, and exposure to sunlight. Sawa and Snyder (p. 692) review our current understanding of schizophrenia, a debilitating psychiatric disorder affecting an estimated 1% of the population. Intriguingly, three diverse investigative approaches—pharmacological analysis, brain imaging, and genetic studies—are implicating the same neurotransmitter systems in the disease, although the role of environmental factors such as viruses and birth trauma has not been excluded.

In a series of commentaries, three scientists who do not subscribe to the current "genocentric" view of disease argue that progress in understanding complex diseases will depend on additional branches of science. Willett (p. 695) discusses the importance of carefully designed epidemiological studies in disease-prevention research. Such studies have revealed that more than 70% of stroke, colon cancer, coronary heart disease, and type II diabetes is potentially preventable by life-style modifications. Rees (p. 698) discusses the critical role physicians play in diagnosing and treating patients with complex diseases. He notes that skilled clinicians have designed very effective therapies for common skin disorders such as psoriasis and acne simply through careful observational studies of patients and without any knowledge of the contributory genes. Finally, Strohman (p. 701) points out that systems-based approaches such as metabolic control analysis can yield important insights into complex diseases; however, progress in this arena will depend on the development of new technologies and better training of biomedical scientists in mathematics and quantitative biochemistry.

Can the puzzle of complex diseases be solved? With integrated approaches and coordinated efforts from researchers in diverse disciplines, there is much room for optimism.

–PAULA KIBERSTIS AND LESLIE ROBERTS

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***See also* Science's *STKE* on p. 611 and *Report* on p. 739.**

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