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Grant awarded **£44,838 (1 Year)**

Identification of the HLA susceptibility gene for colonic Crohn's disease by targeted positional cloning and microarray expression studies

Patients with Crohn's disease are known to have a genetic susceptibility that, in some way interacts with unknown environmental factors to cause chronic intestinal inflammation. This year the first gene (NOD2/CARD15), implicated in causing Crohn's disease in 20% of sufferers, was identified. During my period as the Leslie Parrott research fellow I have shown that this gene is associated with small intestinal Crohn's disease only, whilst other genes on chromosome 6 are associated with colonic and perianal disease. This genetic evidence confirms our clinical suspicion that Crohn's disease is not a single disorder but a family of closely related diseases, which although characterised by similar symptoms and signs, are each associated with specific genetic abnormalities.

The HLA region on chromosome 6 contains many genes that control the inflammatory process. The aim of this study is to determine precisely which particular gene in this area is responsible for colonic Crohn's disease. Genetic studies alone are unlikely to provide the answer, so this study employs a combination of approaches. First we propose to determine which genes are actually expressed in the inflamed colon using a technique known as an oligonucleotide array. Those genes shown to be expressed in the diseased colon, as opposed to the un-inflamed colon, will be studied in more detail to determine the mutations associated with Crohn's disease. In order to study the genes expressed in the very early stages of disease we shall study patients with colonic disease who have gone into remission following a defunctioning ileostomy. Biopsies will be obtained from the proximal colon (via the 'mucous fistula' leading into the colon) and then further biopsies taken following daily instillation of ileostomy fluid for 7 days. This technique has been shown to activate Crohn's disease in the isolated colon in previous studies in Oxford and Leuven, and provide the ideal model for this project.