Summary and Conclusion

Cells of the innate immune system, such as monocytes, macrophages, neutrophils, dendritic cells, and natural killer cells, recognize microbial products and host molecules expressed by pathogen-infceted and tumor cells.

Recognition of danger by the innate immune system is followed by the release of chemokines that direct inflammatory cells to the site of the danger and removal of the danger by the combined action of phagocytic cells, cytotoxic cells and cytokines, acute phase proteins, and complement.

Activation of the adaptive immune system requires the activation of T lymphocytes. T cells express clonotypic antigen receptors that recognize peptide fragments of protein antigens presented by major histocompatibility complex molecules on antigen-presenting cells.

Activation of a naive T cell requires a signal through its antigen receptor (signal 1) as well as a danger signal through a costimnlalory receptor (signal 2). This causes it to differentiate into an effector cell capable of subsequently mediating its effector function upon receipt of signal 1 alone.

Adaptive immune responses to danger can be either inflammatory responses involving cytotoxic T cells, Th1cells, and natural killer cells or antibody responses involving Th2 cells and B cells, mast cells, and eosinophils. Antibodies can neutralise toxins and viruses, opsonize pathogens for phagocytosis, cytotoxicily, and directed histamine release and activate complement.

Thl/Th2 cell differentiation, effector functions of the adaptive immune system, and termination of adaptive immune responses are controlled by cytokines released by T cells and cells of the innate immune system.

The innate and adaptive immune systems interact with and regulate each other. Dendritic cells and macrophages are central to both innate and adaptive immune responses. Some T cells have predominantly innate immune functions.

The common autoimmune liver diseases (type I autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis) do not exhibit simple Mendelian inheritance attributable to a single gene locus.

These autoimmune diseases are "genetically complex", arising from the interaction of both environmental factors and one or more host genes.

The alleles that are permissive for autoimmunity are common in the "healthy" population and by themselves are neither necessary nor sufficient for disease to occur.

Most of the evidence for a genetic component in the pathogenesis of autoimmune liver disease is based on case-control (association) studies. Informative (multiplex) families are rare, and conventional linkage data are not available.

The most consistent data we have suggest strong links with the major histocompatibility complex (MHC) on chromosome 6p21.3. Possible links with other susceptibility alleles on a number of chromosomes are more speculative.

Genetic effects on both disease susceptibility/resistance (i.e. disease risk) and disease progression (i.e.. pheno-type) have been documented. Identification of the former provides the necessary background for a better understanding of the disease pathogenesis. Identification of the latter alleles may be more immediately useful in developing predictive indices for disease prognosis.

Overlap syndromes and comparison with other autoimmune diseases indicate that there may be shared (common) disease susceptibility alleles acting as non-(disease)-specific promoters of autoimmunity. These findings indicate the activation of common pathways in the pathogenesis of autoimmunity and the processes underlying tolerance breakdown.

Current knowledge of the genetics of autoimmune liver disease is incomplete, but the Human Genome Project has identified an astounding degree of polymorphism in our genes; **5** yr on. we still face a major challenge in integrating the "new genetics" into medical practice.

The key issues for future investigators will be defining the genetic mechanisms whereby self-tolerance is broken: defining the genetic mechanisms that determine the role of disease progression and identifying genetic markers to predict both progression and malignancy.

The same HLA genes and haplotypes that are important in autoimmune liver diseases are also implicated in susceptibility and resistance to infectious liver disease, opening a new avenue for future investigations.