MOLECULAR MIMICRY IN AUTOIMMUNE DISEASE

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INTRODUCTION

Autoimmune mechanisms are thought to be important in causing a number of diseases including multiple sclerosis, insulin dependent diabetes mellitus, psoriasis, ulcerative colitis and rheumatoid arthritis. The precise sequence of events which initiate the autoimmune attack has not been elucidated but in recent years an exciting new hypothesis has been proposed which is based on the concept of molecular mimicry between antigens on the surface of micro-organisms and antigens on the surface of human cells.

Infection by viruses or bacteria provokes a specific immune response directed against foreign antigens on the surface of the micro-organisms. Some micro-organisms, however, have surface antigens which are similar in structure to antigens on human cells. When this occurs there is a possibility that immunocompetent clones of cells will arise which recognise the cross-reacting antigens as foreign and initiate an autoimmune attack on host tissues.

There is epidemiological evidence that a number of putative autoimmune diseases are precipitatedly infection. If the specific micro-organisms that initiate each disease could be identified then there is a possibility that the conditions could be prevented. Investigating this idea requires a combined epidemiological and laboratory-based approach together with access to a wide range of clinical material. This research programme is, therefore, ideally suited to the new Lancashire and Lakeland Medical Research Trust. It would use the unique epidemiological approach developed in the departments of geography and mathematics at Lancaster University and integrate it with the basic science of the Institute of Environmental and Biological Sciences.

In this article I will describe some of the evidence for the role of molecular mimicry in autoimmune disease and discuss how this problem could be investigated.

MOLECULAR MIMICRY

There is evidence from a number of sources that antigens on the surface of micro-organisms can resemble antigens on human cells. It has been shown that antibodies to insulin and to brain gangliosides react with Escherichia coli. Yersinia enterocolitica have surface antigens which react with antibodies to the human thyrotrophin receptor. Streptococci have surface components which cross react with HLA antigens. Antibodies to chorionic gonadotrophin react with S epidermidis, E coli and Pseudomonas maltophilia. Glycopeptides from human and rat brains share antigenic determinants with meningococcus group B and E coli. Furthermore monoclonal antibodies to nicotinic acetylcholine receptors react with proteins from E coli, Proteus vulgaris and Klebsiella pneumonia.

There is also evidence that infection by micro-organisms can trigger autoimmune reactions. Streptococcal infections can precipitate rheumatic fever, guttate psoriasis and glomerulonephritis. In each case the disease is immune mediated. In rheumatic fever and in psoriasis this is thought to be linked to molecular mimicry between streptococcal antigens and cardiac muscle and skin keratinocytes respectively. In addition immune mediated arthritis is well documented following infection by salmonella, shigella, campylobacter, yersinia and chlamydia.

EPIDEMIOLOGY

Information from epidemiological studies can provide clues to indicate whether or not particular autoimmune conditions are linked to infection.

Age Incidence

The age incidence of infectious diseases can be illustrated by considering infectious mononucleosis. The incidence of this condition rises to a peak in the teenage years and then falls progressively. The causative agent, the Epstein-Barr virus, is common and most people meet it in childhood when it causes a mild or asymptomatic infection. In fact the age incidence of first exposure is a falling exponential curve so that only a few meet the organism for the first time in the teenage years and very few thereafter. The probability of serious disease, however, rises with age at first exposure, presumably due to progressive impairment in the immune response to new antigens. The age incidence of the clinical disease infectious mononucleosis is the result of two processes, one falling with time and one rising with time. The result is a curve which rises to a peak and then falls.

In the same way if an autoimmune disease is precipitated by first exposure to a common micro-organism which everyone eventually meets, then the age incidence will rise to a peak in early or middle life. Conditions due to very common organisms will peak early, while conditions due to less common organisms will peak later. Figures 1 and 2 show that the age incidence of onset of multiple sclerosis and psoriasis show this pattern.

Social Class

The rate at which micro-organisms circulate in a community is influenced by a number of factors linked to social class and general economic circumstances. As a general rule as social conditions improve the rate of circulation of enteric organisms decreases and the average age at first exposure to any particular enteric organism increases. Since serious disease tends to increase with age at first exposure the result can be an increase in disease with improved social conditions as occurred with poliomyelitis prior to immunisation.

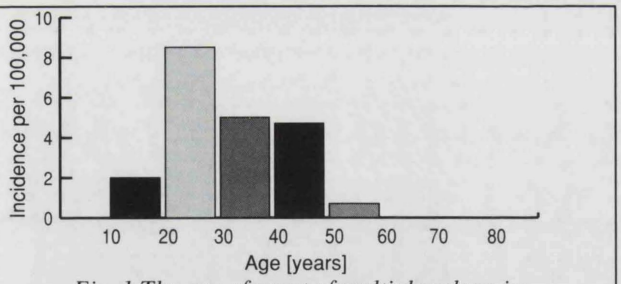

Fig. 1 The age of onset of multiple sclerosis

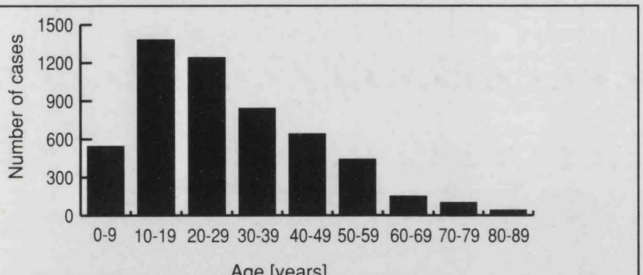

Fig. 2 The age of onset of 5544 cases of psoriasis

Conversely if a putative autoimmune disease shows an increase in incidence with improved social conditions then the possibility that the disease is caused by exposure to enteric organisms should be investigated.

Geographical Distribution

Multiple sclerosis and insulin-dependent diabetes mellitus both show a marked increase in incidence with distance from the equator. This can be explained in terms of a response to enteric micro-organisms as described in the previous section. Equatorial countries tend to have poor socio-economic conditions which lead to a rapid rate of spread of enteric organisms. The technologically advanced countries in temperate regions have a slower rate of enteric spread. The result is that the age at first exposure in temperate climates is increased as is the probability of serious disease.

Seasonal Incidence

Infection varies by season. Respiratory tract infections are more common in winter months, while enteric infections increase in frequency through the warmer summer months to peak in September. If a putative autoimmune disease shows a seasonal pattern of onset this is at least consistent with an infectious cause. Obviously if there is a long latent interval between infection and disease onset this will interfere with the seasonal pattern. It is also important to remember that infection could act as a nonspecific factor precipitating presentation without being directly causal.

It is of interest that insulin-dependent diabetes mellitus and multiple sclerosis show a seasonal variation in presentation. The number of cases rises through the summer months to peak in autumn. There is a second peak in the winter months and a low point in May. The seasonal incidence of other diseases is less well documented and is a possible area for future research. To study seasonal incidence, however, it is important to have an objective way of determining the time of onset and that is not always easy.

Epidemic Spread

Many viral infections show epidemic spread with marked variation in the incidence from year to year. If a virus which shows this pattern causes an autoimmune disease then that disease should also vary in incidence from year to year. In fact in most cases where studies have been done the year to year variation is no greater than expected by chance. This is in fact one of the most powerful arguments against the role of many viruses in autoimmune disease.

Space-Time Clusters

Infections, which show epidemic spread, cluster in time and space as they pass through a community. There are now very sophisticated mathematical techniques for analysing spatial and temporal distribution of disease and the department of mathematics at Lancaster University is at the forefront of this research. These techniques can be used to analyse the infection hypothesis of autoimmune disease.

LABORATORY STUDIES

The results of epidemiological investigations will indicate whether or not infection is likely to be important in any particular disease. In addition it should be possible to get clues as to whether the route of infection is respiratory or enteric, and whether the organism is viral or bacterial. This information can then be used to identify a range of candidate organisms for specific conditions. The next stage will be to try to identify cross-reacting antigens between the organisms and the relevant host tissue. In some cases the relevant host antigen is known; this applies to the thyrotrophin receptor in thyrotoxicosis and the acetylcholine receptor in myaesthenia gravis. In other cases autoantibodies are available as in haemolytic anaemia and the skin diseases pemphigus and pemphigoid. In other cases the information about the primary antigen is less precise but it likely that this will become available in the near future due to rapid progress in molecular biology. If antibodies to the relevant antigens are available or can be produced then they will be used to search banks of organisms for cross-reactions.

Once a putative organism has been identified clinical studies will be designed to see if infection is associated with disease onset or exacerbation and whether or not termination of carriage influences the disease process.

DISCUSSION

Epidemiological studies have produced evidence that infections are linked to autoimmune disease and there is a plausible hypothesis based on molecular mimicry which indicates that the link might be causal. However, although the epidemiological studies to date have produced valuable information, it has not yet been possible to identify the specific micro-organism which causes any one of the major autoimmune conditions. A possible reason for slow progress is that the conventional view of infection is too simple. Viral infections of the respiratory and enteric tracts lead to a profound change in the microbial flora. In the case of the respiratory tract there is overgrowth by staphylococci and enterobacteria. It is possible, for instance, that when a viral infection precipitates autoimmune disease, the autoimmune response is to cross-reacting antigens on bacteria rather than the virus. This possibility could help to explain some of the contradictions in the epidemiological data. It would make sense of the observations, for instance, that epidemics caused by different viruses can precipitate the same autoimmune disease and that different autoimmune diseases can be precipitated by the same virus.

The pathogenesis of autoimmune disease is obviously an important area of study and there are clear ideas of how to take the work forward. Lancashire and Lakeland Medical Research Trust is well placed to lead this work and it promises to be an exciting field of investigation.