PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Introduction to Multiple sclerosis? progress and problems. A Theme issue published by The Royal Society

The Royal Society

Phil. Trans. R. Soc. Lond. B 1999 **354**, 1613-1614
doi: 10.1098/rstb.1999.0505

THE ROYAL SOCIETY

Introduction

Multiple sclerosis is a remarkable disease. It was one of the first disorders of the nervous system to be described in a way that we recognize as thoroughly modern. Charcot (1868) gave a careful description of its pathological and clinical features and made a serious attempt at interpreting the symptomatology in the light of the morbid anatomical changes. Some of his physiological conjectures were remarkably prescient. And yet over 130 years later, despite considerable progress in the past decade in understanding numerous facets of the disease, a persuasive synthesis is still not possible.

A complete understanding of multiple sclerosis would require a knowledge of the cause, mechanisms of tissue damage and—since one of the outstanding features of the disease is the completeness of recovery from relapses in its early stages—mechanisms of repair. Because in the later stages severe disability is the rule, there also needs to be an understanding of the reasons for failure of the repair process and of other mechanisms of irrecoverable deficit. Major gaps in our understanding remain. Where are they?

Epidemiological evidence has long suggested that two factors are involved in causation: genetically determined susceptibility and exposure to an environmental agent. The identification of the latter has so far defied all attempts; it is widely assumed to be infective, perhaps viral in nature, but the evidence is fragmentary and unconvincing. More progress has been made towards identifying the genetic factors determining susceptibility; it is reviewed by Compston (this issue). It is clear that multiple genes are involved and a number of associations have been identified, but how the genetic factors operate and how they interact with the putative environmental agent(s) in establishing the disease is unknown.

The epidemiological evidence also suggests that there is a latent period between the establishment of the disease and its first clinical expression. The mechanisms of latency are unknown, and only one factor leading to the precipitation of clinical relapse—intercurrent viral infection—has been identified. The frequent absence of evidence of infection at the time of first clinical expression or relapse argues for the existence of additional precipitants. As to the mechanism of tissue damage, there is a consensus that it is dependent on immune-mediated inflammation. However, the detailed sequence of cellular events is not yet agreed and recent observations have raised the question as to whether there is more than one pathogenetic mechanism involved, perhaps correlating with different clinical forms of the disease. These issues are addressed by Lassmann (this issue).

An increased understanding of the dynamics of multiple sclerosis, both clinical and pathological, has come from the exploitation of magnetic resonance techniques, both imaging (MRI) and spectroscopy (MRS). These methods give a guide to pathology *in vivo* but as pointed out by Barkhof & Van Walderveen (this issue), the limited pathological specificity of these methods constrain the interpretations that can be made on the basis of results obtained with them. Nevertheless, serial application of MRI and MRS has led to the definition of the relationship between clinical events and pathological activity. In this way, the crucial involvement of inflammation in relapse and resolution of inflammation in remission have been identified. Changes at the membrane level which contribute to recovery from experimental immune-mediated inflammatory demyelination have been identified, and there is evidence that at least one of these applies in human disease. These developments are discussed by Smith & McDonald (this issue).

If repair processes in demyelinated fibres are so effective early in the course of the disease (as reference to the opening paper by McDonald & Ron in this issue shows that they manifestly are), why does disability accumulate later? Failure to maintain the local repair processes is likely to contribute, although little is at present known of their time-course and the factors influencing it. A second possibility is that axonal degeneration plays an important part. As Lassman (this issue) and Perry & Anthony (this issue) point out, the existence of axonal degeneration has been known and repeatedly confirmed over more than a century. Its role in determining disability (as discussed by Smith & McDonald, this issue) has only become clear in the past five years through the application of MRI and MRS. What determines axonal degeneration is a topic of major current interest which has potentially far-reaching implications for treatment.

The development of effective treatment for multiple sclerosis has been one of the most heartening developments of the 1990s. The value of these treatments is unfortunately limited; relapse rate using the licensed agents β-interferon and glatiramer acetate is reduced by only about one-third and slowing of the rate of progression of disability has been hard to demonstrate convincingly, although there is now reasonably good evidence for a modest effect. These and a number of other new treatments including the anti-CD 52 humanized monoclonal antibody Campath-1H, which is highly effective in suppressing disease activity, target the immune system, although in no case is the mode of action fully understood. These issues and the problem of developing new and better therapeutic strategies are discussed by Hohlfeld (this issue) and by Scolding (this issue). The considerable problems of monitoring effectiveness of treatment are discussed by Miller &

Thompson (this issue). MRI provides a robust way of detecting pathological activity, but the methods used so far have proved to be poorly predictive of future progression of disability. With the advent of even partially effective treatment it will be very difficult to carry out in future controlled clinical trials on the scale necessary to demonstrate effectiveness in such a variable chronic disease. Accordingly, there is a pressing need to develop more reliable indices of outcome.

June 1999 W. I. McDonald

Reference

Charcot, J.-M. 1868 Histologie de la sclérose en plaques. *Gaz. Hôpital* (*Paris*) **41**, 554–566.

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