More than one hundred years have gone by since Charcot gave a strikingly modern, clinical and pathological account of multiple sclerosis (MS). Indeed, as Fog points out (Chapter 2), a very great deal of subsequent writing amounts to little more than expansion of Charcot’s descriptions as detail has been filled in, and recognition of the truly protean manifestations of the disease. ‘Ideas about the cause of multiple sclerosis have long been the weathercock of medicine swinging from one fashionable and unproven theory to another, pointing most recently towards a virus infection which seems to be related to measles’ (Lancet); still more recently the small transmissible agent first described by Carp et al. has also been adopted as a contender by the same journal (Lancet)—though both Carp and Henle et al. are very far from making such claims. Burnett, remarking that ‘more than one editor interested in the changing pattern of medical science has commented on the influence of fashion in the interpretation of disease’, singles out MS as ‘an example which, at the moment, is moving from autoimmunity to slow virus infection without any really legitimate reason for the change’. Perhaps it is true today that ‘slow virus’ gives the verbal satisfaction which ‘autoimmunity’ did a decade ago. The twin ideas of ‘autoimmunity’ (rather broadly interpreted) and ‘slow’ infection remain the pivotal ideas (with various combinations) around which modern thinking about aetiopathogenesis has evolved. Genetic aspects of MS have been relatively neglected, though it would be remarkable if, practically alone amongst diseases known to medicine, ‘diathesis’ (a term which used to
conceal our ignorance of human genetic mechanisms) played no role in the evolution of the disorder.

It is of interest transcending the immediate problem of MS, to examine the causes, general and special, that have so long delayed real advance in our understanding of the disease, and to single out some for more detailed study since they continue to operate.

Untestable hypotheses (*aus der Luft gegriffen*) abound in the literature of MS, many being based on uncritical acceptance of 'soft' facts and data. Every possible category of disease process has had its advocate, and the modern rush to expound phenomena in terms of molecular biology, with its accompanying aura of 'science', has generated its own speculations. Whilst the making of hypotheses is often an essential preliminary to insight, only those which offer refutable predictions will guard against degeneration into an encumbering mythopoiesis? Above all, such exercises must be grounded on 'hard' facts and for a variety of special reasons these are particularly difficult to establish in the field of MS investigation. The situation is compounded by the tendency, by no means limited to MS (or even medicine as a whole), to confuse observation (even when accurately made) with interpretation and hypothesis. Amongst the reminders which should be prominently displayed in the research worker's laboratory is one to the effect that 'of all scientific instruments available, reasoning is perhaps the least reliable': and facing him as he enters his laboratory might be Claude Bernard's aphorism, 'Put off your imagination, as you put off your overcoat, when you enter the laboratory. But put it on again, as you put on your overcoat, when you leave.'

Some of the more important difficulties will be briefly introduced, their explanation being considered in detail in individual chapters.

**Important difficulties in MS**

**Diagnosis**

First and foremost stands the *difficulty in recognition*—in other words, *diagnosis*. The truly protean picture of the disease, especially in the early stages, has been commented upon by Fog (Chapter 2). To this must be added the problems posed by *formes frustes*—cases which after initial symptoms or signs never apparently progress (Charcot) so that the classic 'dissemination in time and space', which makes six or seven cases out of ten so simple to diagnose, is absent. Indeed McAlpine? pointed out that approximately one patient in 20 is free from fresh symptoms for 15 or more years following the first symptoms, and this initial latent phase tends to be especially long