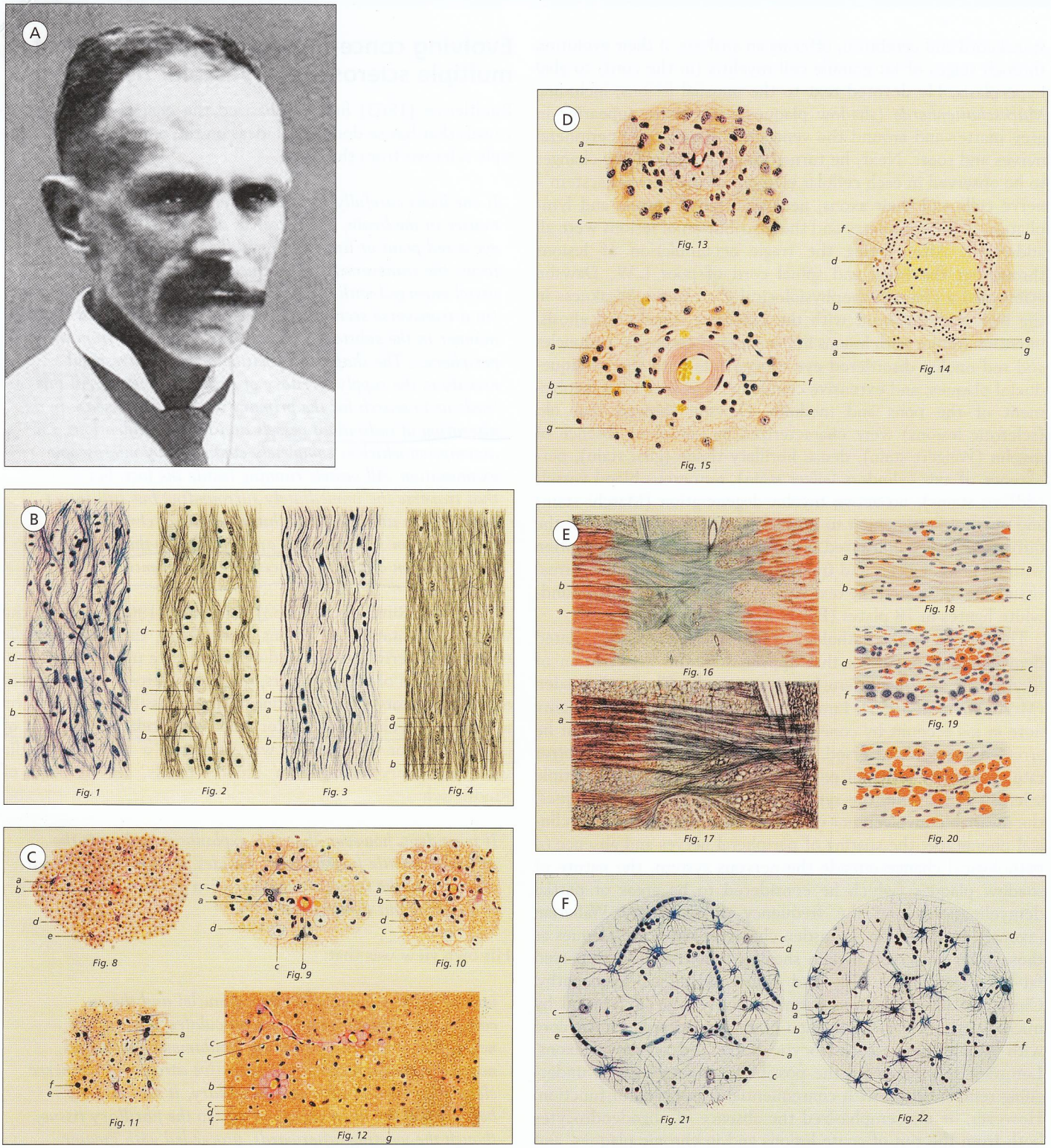

Figure 1.17 (A) James Dawson (1870–1927). (B) *Figs 1–4*: Successive stages in the evolution of a sclerotic area in the posterior columns of the cervical spinal cord. Sections cut in longitudinal direction of the nerve fibres show increasing glia fibril formation. *a*: Glia nuclei; *b*: glia fibrils; *c*: fat granule cells; *d*: persistent axis cylinders. *Figs 1 and 3*: Ford-Robertson's methyl violet stain; *Figs 2 and 4*: palladium methyl violet. (C) *Figs 8–12*: Successive stages in the evolution of a sclerotic area in the posterior columns of the cervical cord. *a*: Glia nuclei; *b*: blood vessel; *c*: fat granule cell; *d*: myelinated nerve fibre; *e*: finely granular glia tissue; *f*: naked axis cylinder; *g*: transition to normal tissue. (D) *Figs 13–15*: Sequence of changes in the blood vessels. *a*: glia nuclei; *b*: blood vessel; *c*: fat granule cell; *d*: cell containing blood pigment; *e*: lymphocyte-like cells; *f*: plasma cells; *g*: glia tissue; *h*: connective tissue cell. (E) *Figs 16 and 17*: Persistence of axis cylinders across a demyelinated area in the pons. *a*: line of transition between myelinated and demyelinated fibres; *b*: median raphe where axis cylinders intersect. *Figs 18–20*: Stages in the demyelination of an area and in the evolution of the fat granule cell. *a*: Small glial nuclei; *b*: transition forms between *a* and *b*; *c*: fat granule cell; *d*: nerve fibre; *e*: blood vessel; *f*: proliferated glia nuclei. (F) *Figs 21 and 22*: Glia changes in a completely demyelinated area in the cortex. *a*: Proliferated glia cells with protoplasm and processes differentiated into fibrils; *b*: capillaries with glia fibrils attached to their outer membrane; *c*: ganglion cells; *d*: small glia cells forming nests around the remains of ganglion cells; *e*: degenerated ganglion cells; *f*: retained axis cylinders. Note that the normal cytoarchitecture of the tissue is preserved. From Dawson (1916).

McAlpine's MULTIPLE SCLEROSIS

FOURTH EDITION

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spinal cord and cerebrum, offering an analysis of their evolution through stages of fat granule cell myelitis (in the cord) to glial hyperplasia. He devoted text to the unusual lesions, including *Markschattenherde* (shadow plaques), and those appearing in grey matter and around the ventricles, optic nerve, peripheral nerves and roots. Next, he turned to an analysis of the changes to be observed in each cellular element of the nervous system – nerve cells and their axons, neuroglia, blood vessels and lymphatics. Form, symmetry and the distribution of lesions were all addressed. After listing the tragic accumulation of lesions throughout the brain and spinal cord of poor L.W., Dawson attempted a clinicopathophysiological correlation. Weakness in the legs was consistent with the extensive spinal cord gliosis; intention tremor with lesions in the superior cerebellar peduncles and red nuclei; disordered eye movements with the periaqueductal plaques; and extensive cranial nerve palsies with involvement of the pons and medulla. Dawson showed that old (sclerotic lesions) were characterized by complete absence of myelin (Weigert stain), dense fibrillary tissue (glial stain), persistence of axis cylinders (silver stain), numerous blood vessels (diffuse stains), no active myelin degeneration (Marchi stain) and an abrupt transition to normal tissue. In acute lesions, the differences were infiltrated blood vessels, active demyelination with fat granule cells, and transitional zones shading into normal tissue. He illustrated the text with 22 colour and 434 black-and-white figures in 78 plates (Figure 1.17A–F).

The section on the pathology of multiple sclerosis and related demyelinating processes that appeared in the first edition of *McAlpine's Multiple Sclerosis* was written by Charles Lumsden (McAlpine *et al* 1955). Lumsden immediately struck a gloomy note in his account by concluding that demyelination might be arrested but never reversed. He went on to emphasize the error rate in autopsy series of patients diagnosed as having multiple sclerosis during life, the symmetry and confluence of plaques, the invariable involvement of the cerebrum irrespective of clinical phenotype, the sparing of peripheral nerves and absence of pathological change outside the nervous system, the nature of shadow plaques (which he considered to be areas of partial demyelination), and the frequency of secondary Wallerian (axonal) degeneration. Lumsden characterized acute plaques as those with preserved myelin sheaths, albeit with interspersed fat-laden microglial cells and some degree of axonopathy. Chronic plaques featured a rim of active myelin removal by microglia, an intermediate zone of gliosis and an acellular core with parallel arrays of astrocytic fibrils and preserved axons. Lumsden speculated on the possibility of intact axons undergoing remyelination with consequential restoration of function. However, he also emphasized the absence of oligodendrocytes both from the rim of acute lesions and in chronic plaques, and he considered it unlikely that surviving oligodendroglia might proliferate. Lumsden had his own way of revising books and he entirely replaced the 1955 version in 1965 and again in 1972. Now, multiple sclerosis was considered an autoimmune disease in which exposure of myelin following various biological accidents induced antimyelin antibody formation leading to plaque formation. The 1972 version contains, in addition to its revision of the pathological anatomy, a definitive account of the chemical pathology of multiple sclerosis. It is said that hard work on this edition took its toll, and Lumsden had several periods of illness prior to his early death in 1974.

Evolving concepts in the pathogenesis of multiple sclerosis: the vascular hypothesis

Rindfleisch (1863) first emphasized the change around blood vessels that has so dominated ideas on the pathogenesis of multiple sclerosis from that time:

> *If one looks carefully at freshly altered parts of the white matter in the brain, one perceives already with the naked eye a red point or line in the middle of each individual focus, the transversely or obliquely cut lumen of a small vessel engorged with blood. In the spinal cord the ... grey foci (in a transverse section) intervene in a wedge-shaped manner in the substance of the anterior columns from the periphery... The shape and position of these correspond exactly to the supply territory of each blood vessel. All this leads us to search for the primary cause of the disease in an alteration of individual vessels and their ramifications; an assumption which is completely confirmed by microscopic examination. All vessels running inside the foci, but also that traverse the immediately surrounding but still intact parenchyma are in a state characteristic of chronic inflammation... Their walls are enormously thickened by the accumulation of nuclei and cells in the adventitia.*

Following Rindfleisch (1863), Marburg (1906) stressed the vascular orientation of lesions, considering the *Körnchenzelle* to be small perivascular round cells that take up myelin debris. In the opinion of these authors, multiple sclerosis was therefore an inflammatory demyelinating disease possibly mediated by a soluble myelinotoxic factor and with relative sparing of axons. But for Charcot, it was primarily a disorder of glia with secondary changes in blood vessels. As he said of Rindfleisch:

> *It is evident, however, that this explanation only sets the difficulty a little further back. Besides, the predominant part accorded to the vessels in the evolution of the morbid process is anything but demonstrated.*

His own view was that:

> *undoubtedly, the multiplication of nuclei and the concomitant hyperplasia of the reticulated fibres of the neuroglia constitutes the initial, fundamental fact, and necessary antecedent; the degenerative atrophy of the nerve elements, is consecutive and secondary; it had already begun when the neuroglia gave way to the fibrillary tissue, though the wasting, afterwards, proceeded with greater rapidity. The hyperplasia of the vascular parieties plays merely an accessory part.*

Against this background of claim and counterclaim for the inaugural event leading to tissue injury, Dawson summarized controversies on the causation and epitomized these as the 'exogenous' or 'endogenous' schools but substituted the terms 'inflammatory' and 'developmental', respectively. He assembled teams who preferred either inflammation or developmental abnormalities as the pivotal abnormality, and listed the (mainly contemporary) onlookers whose views he took to be undecided