Panencephalitis and Measles

Since the conference held last year to discuss subacute sclerosing panencephalitis (S.S.P.E.) and its relationship to measles 1 several papers have thrown further light on this perplexing but important problem. The characteristic clinical features of the disease 1 include a slow onset over several months, progressive dementia, myoclonic jerks, pyramidal and extrapyramidal signs, an electroencephalograph with regular periodic complexes, a parietic type of colloid gold curve on testing the cerebrospinal fluid, and death usually within two years. In the brain there is perivascular inflammation, neuronal degeneration, and gliosis involving both astrocytes and microglia. Neurones may contain nuclear and cytoplasmic inclusions, while demyelination is usually slight and occurs independently of neuronal degeneration. However, not all reported cases conform entirely with this description, and they may have had different causes.

J. H. Connolly and colleagues, 2 who first described the association with measles, have reported on three characteristic patients. One showed signs mainly of a lesion in the left cerebral hemisphere during the early months, and at necropsy the changes were found to be more severe in the left hemisphere. Asymmetrical signs leading to a diagnosis of tumour had been previously described. 3 Another patient had unusually severe demyelination, possibly owing to extensive oligodendrocytic changes, with proliferation of protoplasmic astrocytes and lipid phagocytes. All had nuclear and cytoplasmic inclusions in neurones and glia, staining for R.N.A. but not D.N.A. No virus could be recovered from the cerebrospinal fluid, brain, or faces, but measles antibody (of high titre in two patients) was present in the serum and C.S.F. of all, and in one it showed a 16-fold increase over eight months of the illness. The serum: C.S.F. ratios of measles antibody were much lower than those of poliovirus antibody, which suggests that in S.S.P.E. measles antibody is synthesized in the central nervous system. Fluorescent antibody tests specifically showed measles antigen in neurones. All three patients had had measles between October 1952 and July 1953, and developed S.S.P.E. within a 6-month period of 1965. No satisfactory explanation for this clustering of a rare disease can be advanced. The authors conclude that measles virus probably enters the central nervous system during a childhood attack and in a small proportion of patients remains latent, to be later "reactivated" by an unknown mechanism to cause subacute sclerosing panencephalitis.

The virus may persist in a state analogous to that described by R. Rustigian 4: HeLa cells persistently infected with measles virus and grown in the presence of measles antibody ceased to produce detectable infectious virus, but synthesis of viral antigen and the formation of intracytoplasmic inclusions continued. Measles virus had never been isolated from the central nervous tissue in subacute sclerosing panencephalitis until recently L. Horta-Barbosa and colleagues' reported success from a brain biopsy of a typical case. Tissue cultures of the biopsy material failed to yield complete infectious virus, but specifically immunofluorescent inclusions were seen. However, when mixed cultures were grown of the biopsy tissue together with HeLa or HepII cells, cytopathic changes were seen, and measles virus (or a very closely related one) was isolated and re-isolated from the brain biopsy. This interesting technique may have important applications in the investigation of other latent virus infections.

Sir Macfarlane Burnet 5 has suggested that subacute sclerosing panencephalitis is the consequence of a persistent measles infection in a person who has developed measles-specific tolerance in his thymus-associated immunocytes (responsible for delayed-type hypersensitivity) but normal responsiveness...
in his gut-associated immunocytes (responsible for antibody). The tolerance could be due to a persistent measles infection of the thymus concurrent with the infection of the central nervous system. From a study of 80 cases of S.S.P.E. O. Kolar provided some confirmation of unresponsiveness in thymus-associated immunocytes, and reported improvement after thymectomy in one case. However, he considers that the hyperreactive gut-associated immunocytes (especially the plasma cell infiltration) also play a part, and that autoimmune hypersensitivity may contribute to the pathogenesis of the disease. The treatment he suggests is the infusion of normal lymphocytes or thymocytes, or giving antilymphocyte globulin. If these proposals could be confirmed, even thymus transplantation might be contemplated.

A further possible aetiological factor has been discovered by M. Katz and colleagues, who have described the isolation of what appears to be a slow virus from three cases diagnosed as subacute sclerosing panencephalitis. All had measles antibody. Material obtained by frontal-lobe biopsy about seven months before death (in two patients) was inoculated into the frontal lobes of ferrets, chosen because of their susceptibility to viruses including myxoviruses and some slow viruses. After an incubation period of about five months the ferrets developed ataxia and spasticity; proliferation of protoplasmic astrocytes in the cortex, perivascular cuffing of arachnoidal vessels, and minimal meningeal inflammation were observed. In a second passage the incubation period shortened to three months, and a diffuse meningo-encephalitis sparing the cerebellum and without demyelination developed. In a third passage E.E.G. abnormalities were observed three weeks after infection. The earliest histological change was proliferation of protoplasmic astrocytes. That the transmissible agent did come from the patients' tissues appears to have been established by adequate controls. Moreover, some sparing effect was demonstrated by administration of the serum from one of the patients to infected ferrets. No evidence of measles infection was found in the ferrets.

Thus it is possible that subacute sclerosing panencephalitis is a consequence of any of several infectious processes in the central nervous system. One of these appears to be a persistent non-productive infection with measles (and perhaps similar viruses), and another may be slow-virus infection. Or it may result from some synergistic relationship between a persistent measles infection and a slow-virus infection, which could be the unknown cause of reactivation of the latent measles infection or even of the immunological abnormalities. Some important questions appear to need answer.

What proportion of measles infections' "prime" their hosts with a persistent infection—particularly of the thymus—and what proportion (if any) of infections with live virus measles vaccine do likewise? Is the slow virus likely to be transmitted in vaccines and other materials such as interferon prepared in human cells? The stability of scrapie virus to formalin inactivation suggests that even inactivated vaccines containing other slow viruses could conceivably be infectious. These questions cannot be answered quickly, and the problem re-emphasizes the urgent need for an adequate system for the long-term prospective surveillance of the recipients of new vaccines. The difficulties are considerable, the cost may be substantial, and it may take a long time, but we cannot afford to delay any longer a start to confirming or refuting the unsubstantiated and possibly unnecessary anxiety that subacute sclerosing panencephalitis or other long-term effects may follow the administration of some vaccines.

Harvey Cushing: Great Pioneer

No one man ever established a specialty of medicine, but no man's name is more closely associated with brain surgery than is Harvey Cushing's, whose birthday was 100 years ago. Beginning in 1902, he devoted his whole life and his remarkable qualities and energies to a new branch of surgery and in so doing created what have proved to be its immovable foundations.

Harvey Williams Cushing was born in Cleveland, Ohio, on 8 April 1869 and graduated from the Harvard University Medical School in 1895. After four years' training with the famous William Halsted, of Baltimore, and a year in Europe, he undertook the development of a neurosurgical clinic at the Johns Hopkins Hospital, and from 1912 to 1932 carried out the same pioneer work at the Peter Bent Brigham Hospital in Boston. He died in 1939.

Cerebral surgery had begun in the 1880s as part of the wave of enthusiasm induced by the new aseptic methods and inspired by the rise of neurology as a clinical specialty as well as by experimental brain research, involving mainly the problem of cortical localization. Unfortunately, as it was not immediately realized that there was a need for new techniques and for more physiological, neurological, and pathological knowledge than was then available, the clinical results were at first disappointing. General surgeons such as von Bergmann, Horsley, Keen, Macwean, and others could not liberate themselves entirely from general surgery, but it was Cushing coming from the next generation who could take this step. He was one of the first to become a full-time brain surgeon.

It was a case of the right man with the right training being in the right place at the right time. Cushing possessed to an outstanding degree the attributes of a pioneer. He had determination, self-criticism, obsession of thoroughness, perseverance, extraordinary industry and stamina, an enterprising spirit second to none, and complete devotion to his patients. He had worked in the physiological laboratory of Kroener in Berne and briefly with Sherrington in Liverpool. He had a thorough and extensive background of general surgery, including Halsted's slow and careful techniques, which he applied to brain surgery, and he appeared at the very moment when a new and seemingly hopeful surgical advance was foundering from a lack of the qualities he brought to it. He approached the surgical treatment of disease of the nervous system with characteristic vigour and all-embracing completeness. His experimental work on problems of basic physiological importance, both normal and pathological, resulted in significant contributions to the elucidation of cerebrospinal-fluid pressure, cerebral circulation, trigeminal sensation, and of endocrinological function and disease. In pathology, both living and post mortem, he together with his colleagues made fundamental advances, especially in the study of brain tumours. He acquired a wide knowledge of neurology together with its related specialties and was in fact a superb clinical as well as surgical neurologist. Above all the patient was of central concern to him. The various surgical techniques introduced by Cushing were perhaps his greatest benefaction to the young discipline because they rapidly increased the versatility, precision, and safety of the operator.