DEGENERATIVE DISEASE AFFECTING THE NERVOUS SYSTEM [1]

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The term "degenerative disease" is one which is rather widely used in relation to the nervous system and yet one which is rarely formally and carefully defined. The term appears to be applied to disorders of the nervous system which often occur in later life and which are of uncertain cause. In the Shorter Oxford Dictionary the word degeneration is defined as "a change of structure by which an organism, or an organ, assumes the form of a lower type". However this is not quite the sense in which the word is applied in human neuropathology, where it is conventional to restrict the use of the word to those organic disorders which are of uncertain or poorly understood cause and in which there is a deterioration or regression in the level of functioning of the nervous system. The concept of degenerative disorder is applied to other organs as well as to the brain, and as disease elsewhere in the body may affect the nervous system, it seems reasonable to include within the topic of degenerative disorder affecting the nervous system those conditions in which the nervous system is involved as a result of primary degenerations in other parts of the body.

Therefore, one can divide the degenerative nervous system disorders into those which are primarily extraneural in origin and those which are primarily neural.

EXTRANEURAL DEGENERATIVE DISORDERS

The extraneural degenerative disorders can be separated into two groups — those in which the circulation of the blood or of some blood born constituent is affected and those in which the axial skeleton is affected primarily, with consequent involvement of nerve tissue.

Degenerations Affecting the Blood Circulation

The nervous system is highly dependent for its continuous functioning upon having adequate quantities of glucose and oxygen available. The brain has very little reserve of either glucose or oxygen, and both are carried to it in arterial blood. Therefore anything which impairs the arterial blood circulation of neural tissue is likely to disturb the function of the nervous system. If such disturbance persists for a sufficient time or occurs sufficiently often, permanent defects in neural function may result. The disturbance in arterial flow commonly comes about as a result of degenerative disease of the arteries. The factors responsible for such arteriosclerosis and

atheroma are far from completely understood and both disorders are usually regarded as degenerative. Narrowing of the great arteries in the neck or of the intracranial arteries may sufficiently impair cerebral blood flow to lead to a variety of consequences. An acute decrease in local brain circulation may produce the typical picture of a stroke. The impairment in circulation may be more brief but occur repetitively, producing a picture of so-called "transient ischemic attacks", or "little strokes", or impairment in flow may develop gradually and be of a sufficient degree to slowly impair brain function without there being any distinct single acute disturbance.

Furthermore, degenerative arteriosclerosis or atheroma of the coronary arteries may lead to acute myocardial infarction, with sudden inefficiency of the pumping function of the heart, thus leading to a general decrease in brain blood flow. In this circumstance, if there is also a local impairment in blood flow from a local arterial degeneration, there may well be resultant brain damage. Hypertension too may lead to areas of brain damage as a result of rupture of small cerebral vessels, and some might regard hypertension as a degenerative disorder.

Numerically, these various arterial circulatory disorders are probably the most common cause of degenerative brain disease, if one is prepared to regard them as degenerative conditions, but this is really a matter of definitions.

Diabetes mellitus can be looked on as a degeneration of the pancreatic insulin-producing islets of Langerhans. As far as the nervous system is concerned the consequent relative lack of insulin produces a state in which the available glucose in the circulating blood cannot be made available for neuronal metabolism. Thus the function of the brain is disturbed because the neurons cannot use the glucose which is being carried past them in the blood stream.

Degenerations Affecting the Spine

The other main circumstance in which an extraneural degenerative process may affect the nervous system is when there is degenerative osteoarthritis of the spine with associated intervertebral disc protrusions. These may compress emerging cervical or lumbar nerve roots and also may compress the cervical spinal cord producing a cervical myelopathy which can lead to paresis of the legs with impairment of sphincter control.

PRIMARY NEURAL DEGENERATIONS

The primary neural degenerations are a heterogenous group of conditions which tend to begin in one particular functional system within the neuraxis and to affect this system more severely than other systems, though they may spread to other systems at later stages in their evolution. It would not be practicable to go into the full ramification of the classification of primary neural degenerations in the present paper, but some of the more common types can be considered by way of illustration. It will be convenient to divide these degenerations into those which primarily affect

1. the intellect,
2. the motor system,
3. the extrapyramidal system,
4. the cerebellar system,

though it should be understood that degenerative disorders which begin in one system do tend finally to involve other functional elements and sometimes the whole nervous system in the course of their progression.

Degenerative Disorder Affecting Intellectual Function

The selective disturbances of higher intellectual function that are called "dementias" can be due to a variety of pathological conditions. Some of these are of quite unknown cause and are regarded as degenerative in that they produce a deterioration and regression in the level of brain function. Probably the most common of the dementias is Alzheimer's disease. This variety of presenile dementia begins in middle life and steadily progresses over several years to leave the sufferer intellectually impoverished and often dysphasic. At a later stage the pyramidal system may be affected and many patients end their lives in custodial care. The brain in the disorder has a rather characteristic microscopic appearance and occasional instances appear hereditary. There is a less common form of degenerative dementia known as Pick's disease which also has a rather characteristic distribution in the brain and a characteristic microscopic appearance. It also is hereditary. A further rare variety of dementia, Jacob-Creutzfelt disease, tends to run a fairly rapid course. Until quite recently, Jacob-Creutzfelt disease was considered another degeneration of unknown cause. However, quite recent experimental work has shown that this condition can be transmitted to monkeys and the disorder may prove due to "slow" virus infection.

Motor System Degenerations

The degenerations of the motor system are embraced in the term motor neuron disease. The most common variety, amyotrophic lateral sclerosis, can begin at any age though when it occurs in childhood it goes under the name Werdnig-Hoffman disease. Motor neurone disease involves a progressive degeneration of the lower and upper motor neurons resulting in weakness and wasting of muscles, sometimes with spasticity and sometimes hypotonia, depending upon the relative degrees of involvement of upper and lower motor neurons. The bulbar mechanisms become affected and the condition tends to run a progressive course to a fatal termination in two or three years. It is one of the most pathetic of neurological disorders and is quite untreatable. Sometimes only the lower motor neuron is involved in the condition, in which case the designation "progressive muscular atrophy" can be applied, but this is a relatively rare form of motor neuron disease. Probably it was over-diagnosed in the past, some instances when investigated by modern techniques proving due to chronic progressive motor polyneuritis. When motor neuron disease predominantly involves the bulbar muscles the condition may be referred to as "progressive bulbar palsy". However, it is very useful to employ the general term "motor neuron disease" for all these subvarieties.

Despite a considerable amount of research, no adequate explanation for motor neuron disease has been produced.

Extrapyramidal Degenerations

Parkinsonism is the most frequent of the extrapyramidal degenerations. Though the disorder has been known since 1817, the gross and microscopic pathology of Parkinsonism is still a matter for some argument. There is an increasing tendency to accept that lesions in the substantia nigra in the midbrain are the essential pathological abnormality though there are often widespread changes in other parts of the brain and spinal cord in Parkinsonism. Recent experience with levo-dopa and advances in neurochemistry have made it appear probable that a degeneration of unknown cause occurs in the dopamine-producing neurons of the substantia nigra and that this is responsible for at least the rigidity and akinesia of Parkinsonism, though perhaps not for the tremor. Levo-dopa provides a replacement for dopamine, being converted to the latter in the nervous system.

The cause of the common variety of Parkinsonism that is now seen is quite unknown. Sixty years ago an epidemic of encephalitis lethargica swept through the world and this was followed by many instances of a Parkinsonian-like syndrome. However this condition has now disappeared and the only common type of Parkinsonism is of uncertain cause. There seems strong evidence that arteriosclerosis rarely, if ever, causes Parkinsonism, and other aetiological varieties of Parkinsonism are quite infrequent.

Wilson's disease (hepato-lenticular degeneration) is another variety of extrapyramidal disorder. It is clearly hereditary, and tends to appear in the second and third decades of life. There are dystonic movements, and intellectual function deteriorates. There is also a disturbance in liver function. The condition appears related to a disturbance in copper metabolism and the manifestations can be improved by treatment which binds the copper in the body to chelating agents and thus allow it to be removed from the tissues and excreted.

Chorea is in a sense the "opposite" of Parkinsonism. There are involuntary movements of a quite different pattern to those of Parkinsonism, in fact an excess of associated movement rather than a deficiency, and there is a diminution in tone instead

of the increased tone of Parkinsonism. The pathology of chorea appears to be situated in the basal ganglia though its precise localisation is not completely certain. In the hereditary Huntington's chorea the main region affected is the caudate nucleus. Huntington's chorea tends to begin in the third and fourth decade of life. As well as a progressive chorea there is a progressive dementia. Although the disorder is inherited as an autosomal dominant, the chemical basis through which the genetic abnormality comes to clinical expression is quite unknown.

Cerebellar System Degenerations

There are a number of slowly progressive degenerations of the cerebellar system. The most common is Friedreich's ataxia. This disorder is hereditary and usually begins in the second decade of life and runs its course over ten to twenty years. There is a progressive clumsiness of gait and arm movement so that the sufferer is finally confined to a wheelchair and then to bed. Pathologically there is a degeneration of peripheral nerve as well as of the afferent cerebellar connections in the spinal cord, but the ascending sensory fibres in the posterior columns also degenerate so that joint position sense is lost. This further increases the overall handicap. Associated with the condition, there is a degeneration of heart muscle with a replacement fibrosis of the myocardium.

There are a number of other degenerations of the cerebellar system, some mainly involving the afferent pathways to the cerebellum and others the efferent pathways from the cerebellum. Both cerebellofugal and cerebello-petal types of disorder tend to produce the same clinical picture of a progressing cerebellar ataxia. Some of these degenerations are hereditary, for example, Menzel's type olivo-pontocerebellar atrophy, but others are sporadic, and the microscopic appearances of the hereditary and sporadic types may be identical. During the later stages of these disorders, the extrapyramidal and pyramidal systems often may be involved and sometimes the visual pathways and retinae.

The Nature of Neural Degeneration

It is interesting to consider the possible nature of the biological processes involved in these system degenerations of the neuraxis. The main clue we have as to their cause is that some are definitely hereditary. Therefore one can speculate that perhaps a hereditary or acquired disturbance in nucleic acid metabolism and formation may somehow cause certain nerve pathways to degenerate and to stop functioning much faster than others. Clearly, when these disorders are hereditary the basic genetic defect in nucleic acid metabolism has been present since birth, yet the disorder may not have appeared clinically for some thirty or forty years. Why there should be this delay is at present quite obscure but the solution to this problem might provide one of the most fascinating answers in biology. At present there is available no plausible explanation for these varied and yet selective degenerations of parts of the nervous system. Some seventy years ago concepts such as *abiotrophy* or *premature physiological senescence* were being employed to explain these conditions. Despite the advances in neurochemical knowledge that have occurred since those days we are quite unable to translate these philosophical concepts into the hard data of molecular biochemistry. Until someone can do so it seems unlikely that any rational treatment will be available for these conditions which slowly and steadily devastate the nervous systems of some of our unfortunate fellows.