JAKOB-CREUTZFELDT DISEASE.

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THE presenile psychoses have been the subject of intensive study in recent years. Both Alzheimer's and Pick's disease can now be regarded as well-defined clinico-pathological conditions. However, there occur cases with dementia developing in middle age or in early senium which do not fit into any of the established clinical types. A small group of cases characterized by dementia, extra-pyramidal symptoms and involvement of the spinal cord has been described by Jakob (1920) and Creutzfeldt (1920) independently. Similar cases have since been reported by Meyer (1929), Davison (1932), Jansen and Monrad-Krohn (1938), Davison and Rabiner (1940), and most recently by Jervis, Burdum and O'Neill (1942). McMenemy (1940), in a review of dementia in middle age, stated that the number of cases of that type reported in the literature did not exceed 14. Though all of them had the syndrome mentioned above in common, they varied considerably in respect of the leading symptoms. While in some the clinical picture was dominated by dementia associated with a variety of psychotic features, in others the extrapyramidal and in a few the spinal symptoms were predominant. Nothing definite is known about the etiology of that condition, though the hypothesis has been expressed that it may represent an atypical form of encephalitis. Josephy (1936) suggested that it might be a deficiency disease. No agreement has been reached on a suitable terminology. Jakob's original description of the condition as spastic pseudosclerosis has been found to be misleading. K. Wilson (1940) proposed to call it "cortico-striato-spinal degeneration." Davison and Rabiner (1940) speak of "diffuse encephalomyelopathy." Other authors advocated the provisional term Jakob-Creutzfeldt disease. In view of the scanty knowledge of the symptomatology and pathology of the disease, this term seems at present to be the most acceptable.

We have observed a patient of this type over some months, and it has been possible to carry out a full pathological investigation in this case. A second case will be reported briefly which one of us (E. S.) observed some years ago.

CASE 1.—Thomas Y—, aged 49, hotel manager, was admitted on 26.ii.44. Family history negative. The patient was a healthy child, and at school he was of average intelligence. He served in the Great War for four years and was discharged physically fit. He entered his father's business and was very efficient at his work. He was described as a solitary, timid and somewhat

suspicious man. There had never been any woman in his life except his mother, to whom he was greatly attached. He was healthy until 1941, when he complained about tiredness and lack of energy. His condition became gradually worse. In July, 1942, a hypochromic anaemia was diagnosed: blood examination revealed 60 per cent. Hb, R.B.C. 3,700,000. No other signs of disease were found. He received iron therapy, and after three months he was free from symptoms and remained well until the onset of the present illness. Eighteen months prior to admission it was noticed that he tended to fall asleep during the day, and that he was becoming progressively slow in speech and action. Nine months later his business accounts were found to be inaccurate. He showed impairment of memory, which gradually became worse. He was depressed, and said that people were against him because he had let his family down and was unclean. He thought that he was suffering from venereal disease and that other people knew about it. He feared that something terrible was going to happen to his mother and himself. He could not concentrate, and lost interest in everything. He used to sit for hours motionless and seldom spoke. His gait was stiff and uncertain. On one occasion he was incontinent of urine. On the day prior to admission he was very agitated and tried to kill himself.

Physical examination on admission.—A well-built man of good colour and moderate nutrition. Apart from slight oedema of the hands and feet there were no symptoms of circulatory disease. B.P. 142/106. Respiratory system: N.A.D. Alimentary system: Tongue clean, bowels constipated, liver normal in size. Blood count: R.B.C. 4,200,000; Hb. 90 per cent. Urine analysis completely negative. Renal function: Water excretion and concentration tests gave normal results. Blood W.R. and Kahn negative.

Central nervous system.—Motor system: The patient sits with hands on knees, head bent, eyes downcast, mouth slightly open and with the lower lip rimmed with saliva. He stands with knees slightly bent and shoulders drooping. Facies wooden and stolid, eyes with a far-away look. Gait: Unsteady and clumsy, with occasional stumbling. He walks slowly and takes short steps. When the hands are held forward coarse tremors occur, right more marked than left. During tests for Rombergism, head-nodding sometimes occurs. No intention tremor. There are fine fibrillary twitchings in the pectoral muscles and in the glutei and hamstrings on both sides. Motor power normal except in the lower limbs, where power is generally reduced, especially in the extensors. Both speech and movements are slow. No paralysis is present. The patient has difficulty in carrying out fine movements with the fingers, e.g. picking up a coin. Muscle tone normal in the upper extremities. Rigidity in lower limbs, but not of a cog-wheel character. Position of legs when at rest in bed is one of 10° flexion. Dysdiadochokinesis in both hands. Muscle volume: distinct symmetrical atrophy of a moderate degree is present in the muscles of the thighs and calves, and atrophy of a slight degree in the shoulder girdle and the pectoralis muscles.

The sensory system.—Hypaesthesia for touch and pain on hands and feet. Sharp was returned as blunt in 40 per cent. of cases. Temperature appreciation is impaired. Cold is well recognized on all parts of the body, but warm

is poorly appreciated in the hands and feet. Tactile discrimination is impaired on all extremities. Deep sensibility normal, except for the vibration sense which is grossly impaired on the lower limbs. There is increased tenderness on pressure of the muscles and nerves of the lower extremities. Tactile discrimination impaired on all extremities. Stereognosis: correct replies given only after delays of one and two minutes. He is unable to distinguish between milled and unmilled coins. Ataxia: patient has difficulty in walking along a straight line. "Heel to knee" test performed poorly, especially with the left leg. Rombergism is present.

The reflexes.—Corneal, pharyngeal, abdominal reflexes and plantar extensor response normal on both sides. Oppenheim and Rossolimo negative; biceps, triceps, radial reflexes normal; knee and ankle jerks absent both sides.

Cranial nerves.—Smell normal. Visual fields, acuity and fundi normal. Eyelids slightly drooping. The movements of the external ocular muscles are normal, except that there is a limited upward movement of both eyes. Convergence incomplete. Horizontal nystagmus to the right. Otherwise no abnormality of the cranial nerves.

Cerebrospinal fluid.—W.R. negative. Kahn negative. Cells, 2 per c.mm. Globulin normal. Colloidal gold test normal.

Mental condition on admission.—The patient is content to sit in his room motionless. His expression is impassive, but he is obviously very depressed. He seldom speaks of his own accord. He replies to questions slowly in a dejected and monotonous voice and often does not answer for some time. His answers are brief and always relevant. He says that he is a broken man and that there is no hope for him. He believes that his private parts are diseased and that he has syphilis. He fears that he may have infected his mother. He blames himself for having disgraced his family. He implores the doctor to shoot him. He avoids other patients, whom he is ashamed to face. He believes that people avoid him because of a smell that comes from him. At times he becomes frghtened and agitated when left by himself.

Orientation for person and space correct. Orientation in time usually good, but there have been occasions when the patient got out of bed at 5 a.m. and dressed in the belief that it was time to do so. Memory and retention are poor. The patient regularly forgets that he has been examined the day before. He forgot the lumbar puncture after 24 hours. He realizes that his memory is failing. General knowledge is fair, knowledge of current events very poor.

Progress notes.—For the first three weeks after admission the patient's condition showed no material change. In spite of his ataxia he was able to go out for short walks. Sometimes on a cold winter day he would refuse to have a fire in his room and say that he wanted to expiate his sins. Memory and retention deteriorated and he confabulated. Orientation in time became grossly defective. In the middle of March his physical condition showed signs of rapid deterioration. He was incontinent of urine. The ataxia became worse and he was unable to walk without help. He looked extremely ill. His consciousness was less clear. He could perform only the simplest tests of intelligence, and had difficulty in comprehending what he was required to do.

He reiterated that he was a sick man and that he would never leave the hospital alive. During April he went downhill rapidly. He lost a great deal of weight. He took very little food. His complexion was sallow. (The blood picture remained normal.) He was confined to bed all the time. Mood and thought contents remained unchanged. During the last four weeks before his death his consciousness became progressively clouded and he could hardly answer questions. A dysarthria of the bulbar type developed and he had difficulty in swallowing. He died with signs of bronchopneumonia. The diagnosis was Jakob-Creutzfeldt disease.

Post-mortem examination (Dr. W. Blackwood).—Bronchopneumonia in both lungs. The heart showed a moderate degree of brown atrophy, with slight arteriosclerotic changes of the coronary vessels. Otherwise the organs appeared healthy on macroscopic examination. Central nervous system, see below. The microscopic investigation showed the typical changes of early bronchopneumonia. There were some foci of old interstitial fibrosis in the heart muscle. The spleen showed acute engorgement, with hyaline thickening of the corpuscular arterioles. In the kidneys there were some fibrosed glomeruli. Suprarenals were healthy. The pituitary was of normal size, and there were no abnormalities in the glandular tissue. The posterior lobe showed some cells containing haemosiderin. Portions of the muscle which had appeared atrophic clinically were examined. The muscle bundles of the deltoid were slightly atrophic microscopically, and so were the bundles of the glutei which showed variability in calibre and hypernucleation suggestive of partial denervation.

Central nervous system.—Brain : Weight 2 lb. 4 oz. The meninges appeared normal. There was generalized symmetrical gyral atrophy, more marked in the frontal regions than in other lobes. The basal vessels were healthy. On section there was no particular abnormality, apart from slight enlargement of the lateral ventricles. Ependyma healthy.

Microscopic examination (E. Stengel).—Cerebral cortex. Sections were examined from all cortical areas and stained by HE and Nissl, for microglia and oligodendroglia and astrocytes, myelin, fat, and by silver impregnation (v. Braunmühl's method). The Nissl stain showed numerous fairly distinct foci of loss of nerve cells, chiefly in the third layer of the frontal (including pre-Rolandic), parietal and occipital areas, less numerous in the temporal lobes. The sensory areas of the cortex showed only very few of those foci. Many nerve cells showed on Nissl stain colliquation of the cytoplasm and shrinking of the nuclei. Those nerve cells were in many places surrounded by an excessive number of microglia cells and phagocytes. These changes were particularly marked in the cornu ammonis of either side. Fat stain revealed excessive lipoidosis of nerve cells in the same areas and phagocytes full of lipochrome. There was lipoid material in the glial elements and in the adventitial spaces of the small blood vessels as well as in the endothelial cells of the capillaries.

Those signs of fatty degeneration of nervous tissue were most pronounced in the third layer of the cortex, which also showed disorientation of the pyramidal cells.

There was a general increase of microglia and oligodendroglia. The glia proliferation in the cortex corresponded in degree to the loss of nerve cells. The

oligodendroglia cells showed signs of "acute swelling." The microglia was also increased in the white matter of the gyri, especially of the frontal lobes, and so were the astrocytes. Myelin stain showed numerous small areas of demyelinization up to about 1 mm. in diameter. Swollen myelinated fibres in various stages of degeneration were seen to enter some of these circular areas, which were most numerous in the external three layers of the cortex. Those foci were very scanty in the parietal and occipital sensory areas. Silver impregnation revealed the presence of moderately numerous senile plaques, especially in the depth of the sulci. Those plaques were distributed over all layers. They were small, and were not related to the much bigger areas of demyelinization. The centres of many plaques showed an amorphous substance, with a light brownish tinge on silver impregnation. No intracellular neurofibrillary tangles of the type of Alzheimer's neurofibrillary changes were seen, nor were there intracellular argentophile bodies, such as those described in Pick's disease. The blood vessels of the cortex and the leptomeninges did not show pathological changes, apart from the fatty deposits in the adventitial spaces above. No iron deposits were seen.

Centrum semiovale.—While in the white matter of the gyri the microglial elements were increased in many areas, no abnormalities were found in the centrum semiovale.

Caudate nucleus, putamen and globus pallidus.—Cell changes similar in nature to those found in the cortex were present. The large nerve cells were more severely affected than the small ones. Myelin stain showed no focal demyelinization, but there was abnormal swelling of fibres in many places. There were no pathological changes in the *optic thalamus*, but there were signs of cell degeneration in the *substantia nigra*. A considerable amount of the dark cell-pigment was found in the adventitial cells and spaces of the blood vessels, indicating destruction of pigmented nerve cells. There was also a certain amount of that pigment in the glial elements of those areas.

Midbrain and medulla.—In the posterior colliculi there were some small foci with satellitosis and neuronophagia suggestive of cell degeneration. In the medulla there were foci of nerve-cell destruction, and acute microglial activity in the nucleus of the spinal tracts of the fifth nerve on either side. The large motor cells of the cranial nerves showed signs of degeneration (chromolysis, increased lipochrome content) with proliferation of the surrounding glial cells, but there was no indication of pathological cell loss. There were no signs of demyelinization.

Cerebellum.—There were small foci of glia proliferation in the white matter surrounding the dentate nuclei on both sides, and there were foci of demyelinazation similar to those found in the cerebral cortex in the same areas. The cerebellar cortex was free from pathological changes, apart from abnormal swelling of some Purkinje cells.

Spinal cord.—The meninges were healthy macroscopically. Size and consistency of the cord were normal. Even with the naked eye areas of degeneration could be seen in the white matter. They were quite distinct in the posterior, less distinct in the lateral columns of all segments. Myelin stain showed large areas of demyelinization. The myelin sheaths in parts of the

posterior and lateral columns were either completely lacking, or showed all degrees of degeneration from swelling to extreme ballooning and the formation of large myelin balls. Fat stain showed fatty deposits in phagocytes and in all layers of the walls of the blood vessels within or adjoining the areas of demyelinization. The axis cylinders also showed various degrees of disintegration. There were areas of *status spongiosus* in the posterior and lateral columns. The reaction of the glia was obviously inadequate to fill the gaps, though there was considerable astrocytic proliferation. On the whole the picture was similar to that found in subacute degeneration of the cord. Like in the latter disease, the areas of demyelinization were, in cross section, wedge-shaped with peripheral bases. The changes were more marked in the cervical and thoracic than in the lumbar and sacral segments.

The large motor cells of the anterior horns showed very marked signs of degeneration. Many of them were completely filled with lipochrome. In others a few Nissl granula were left and only a minority of cells were normal. The damaged cells were surrounded by satellites. The number of the motor elements appeared reduced in the cervical and lumbar segments.

Peripheral nerves.—Portions of the sciatic nerves were examined microscopically. Cross sections showed a moderate degree of swelling and loss of myelin in many bundles, but there was no marked loss of fibres. Longitudinal sections confirmed those findings, and also showed granular change of the myelin substance. The mesodermal sheaths of the nerves were not affected, and there was no sign of inflammation.

Summary.—This is a case in which the first symptoms of cerebral disease appeared at the age of 46. They were lethargy and slowness of action. Progressive dementia followed, associated with severe depression. The patient died two years after the onset of symptoms. Neurologically he showed the Parkinsonian syndrome, ataxia, absence of the deep reflexes and disturbance of vibration sense in the lower extremities. There was muscular wasting in the shoulder girdle and in the large muscles of the lower limbs. Towards the end bulbar motor symptoms developed. The pathological investigation revealed degenerative nerve-cell changes in the cortex, especially in the third layer, in the corpora striata affecting mainly the large cells, in the substantia nigra and among the large motor neurons of the spinal cord and, to a lesser extent, of the medulla. The glia proliferation was moderate in degree and mostly of a secondary character. There were, in addition, small foci of glia proliferation in the midbrain and the medulla, independent of nerve-cell degeneration. Argentophile plaques were found in the cortex. There were small patches of demyelinization in all layers of the cortex as well as in the white matter of the cerebellum, and there were large areas of destruction of white matter in the spinal cord. Early myelin changes were found in the sciatic nerves. Inflammatory changes were absent throughout the nervous system.

Comment.

The clinical symptoms can be related to the degenerative changes in the nervous tissue which, though widespread, did not affect all parts of the brain

to an equal degree. Certain areas and cell types showed a higher susceptibility to the damaging agent than others. Glial reaction was poor, and there was no tendency to proliferation of fibrous astrocytes as in disseminated sclerosis. The lack of vigorous glial reaction was most clearly seen in the spinal cord. In this and other respects the spinal lesions were very similar to those of the subacute combined degeneration of the cord, though in the latter condition degeneration in the motor cells of the anterior horns is not usually seen.

The pathological findings in our case differed in some respects from those reported hitherto. No previous investigator has found senile plaques. Their presence in our case was possibly incidental. In a few cases, however, Alzheimer's neurofibrillary changes were seen, which were absent in this case. Another new feature was the involvement of the substantia nigra, which was reminiscent of that found in post-encephalitic Parkinsonism. The distribution of the cell degenerations in the cortex was somewhat different from that found by others, as in our case certain layers and areas were not markedly affected. The involvement of the peripheral nerves, as shown by examination of the sciatics, is also an unusual feature.

The pathological changes found in Jakob-Creutzfeldt disease, as compared with those of Alzheimer's and Pick's disease, are characterized by their subacute nature and by involvement of medulla, spinal cord and peripheral nerves. It can easily be understood that variations in distribution and degree of the widespread lesions may result in different clinical pictures, in which certain components of the syndrome which were less pronounced in our case may be very prominent. A good example of such a variation is the following case, which one of us (E. S.) observed together with Dr. R. N. Craig some years ago.

CASE 2.—A. S. C—, business man, aged 66, was admitted to the Arthington Nursing Home for Nervous Diseases, Torquay, on February 12, 1941. He had been mentally and physically healthy until the early months of 1939. There was no history of alcoholism. Family history negative. The first symptoms of his illness were forgetfulness and increased fatigability. In autumn, 1939, the patient had to give up work. Some months later wasting of the hand muscles was noticed. This was progressive, and from August, 1940, the patient was unable to write. At that time he first showed difficulties of articulation and swallowing. A few weeks prior to admission he became restless and depressed, and complained about being watched. On admission the patient presented the picture of an advanced organic dementia with confabulation. He was apprehensive, but did not express delusional ideas. The mood was one of depression of a moderate degree. On physical examination the cardiovascular, respiratory and urinary systems were found to be healthy. B.P. 158/80. There were no signs of a deficiency disease. The blood picture was normal. W.R. blood negative. C.S.F. completely negative. Nervous system: Pronounced Parkinsonian posture. Tremor in both hands. Marked rigidity in all extremities. Severe dysarthria of the bulbar type. Impairment of swallowing. Pharyngeal reflexes absent. Otherwise cranial nerves intact. Abdominal reflexes absent. Cremaster reflex present on the left, absent on the right side. Moderate muscular wasting with fibrillations in the shoulder

girdle and upper arms; advanced atrophy of all muscles of both forearms and hands. Biceps and triceps reflexes exaggerated both sides. Wasting of moderate degree, and fibrillations in the muscles of the calves. The atrophic muscle groups were paretic. Examination for disturbance of sensation was difficult owing to the mental state of the patient, but there seemed to be no gross disorder, apart from increased tenderness of the nerve stems in the lower extremities. No cloni. P.E.R. both sides, right more than left; Oppenheim positive both sides. Gait was paretic. During the last few weeks before his death on May 5, 1941, the patient had difficulties in breathing, suggestive of paresis of the intercostal muscles. The diagnosis was Jakob-Creutzfeldt disease.

No full post-mortem examination could be carried out. It was possible to examine the brain and spinal cord, but only macroscopically. They showed no signs of vascular disease. The meninges appeared healthy. There was diffuse cortical atrophy of moderate degree, more pronounced in the frontal and temporal lobes. Naked-eye examination of cross-sections of the spinal cord was suggestive of foci of degeneration of white matter in the lateral and to a lesser degree in the posterior columns.

In this case the lower motor neurons as well as the pyramidal tracts were more seriously involved than in Case 1, thus producing the clinical picture of amyotrophic lateral sclerosis. Similar cases have been described by Meyer (1929, 1938).

It is noteworthy that in both cases and in a number of patients described by other authors depression was an outstanding feature among the mental symptoms. The same has been found to be the case in a considerable proportion of patients with Alzheimer's disease (Stengel, 1942), from which otherwise this condition differs considerably. Jakob-Creutzfeldt disease as a rule runs a course not extending over two years.

The two cases reported in this article fail to give any direct clue to the etiology of the peculiar condition. Jakob (1921) has discussed the possibility of its being an atypical encephalitis. It has been argued that it is difficult to conceive of an encephalitic process of relatively acute course without involvement of mesodermic elements. That argument is not quite convincing in view of the fact that the progressive pathological changes seen in post-encephalitic Parkinsonism are also of a degenerative nature. The strongest argument against an encephalitic or myelo-encephalitic character of the disease is the nature of the spinal changes, which are similar to those found in deficiency anaemia. We therefore tend towards the view, first expressed by Josephy (1936), that the condition might be a deficiency disease. In Case 1 there was a history of anaemia, though not of the deficiency type. That finding is difficult to interpret, since by the time the patient was admitted to hospital the blood picture had improved. However, it can be safely assumed that there are types of deficiency disease still undefined biochemically. Certain pathological changes in Case 1, such as the degeneration of the motor nerve-cells and the foci of glia proliferation, are reminiscent of those seen in pellagra. Possibly some cases of obscure origin which have certain features in common with our two patients belong to

that group. Hemphill and Stengel (1941) described a middle-aged woman with a depressive psychosis and various cerebro-spinal symptoms running a subacute coure. The pathological changes were not unlike those in Case 1, but there was, in addition, a recent subarachnoid haemorrhage. In view of the nature of the pathological findings, the authors expressed the opinion that the condition may have been due to a deficiency disease.

In recent years considerable attention has been paid to certain features in the symptomatology and pathology of involutional, presenile and senile psychoses, which suggest a relationship to avitaminoses. The findings reported in this paper are of interest in connection with those hypotheses.

Conclusions.

Two cases of Jakob-Creutzfedt disease have been described. In both a depressive state was associated with a variety of neurological symptoms. Both patients died within two years after the onset of the disease. In the first case a full pathological investigation was carried out which added new features to the pathology of the disease. The diagnosis and etiology of the condition has been discussed, and the view has been expressed that it might be a deficiency disease.

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