Short Notes and Clinical Cases.

A CONTRIBUTION TO THE PATHOLOGY OF THE LATER MANIFESTATIONS OF ENCEPHALITIS LETHARGICA: INVESTIGATION OF A CASE.*

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INTRODUCTION.

THE object of the present investigation was two-fold; firstly, it was desired to ascertain whether an acute attack of encephalitis lethargica from which recovery took place gave rise to organic destruction of nervous elements with consequent changes in the neighbouring neuroglia; secondly, it was hoped to gain some indication whether the well-recognised progressive later manifestations of disturbance of the nervous system are to be explained by a slow progressive lesion initiated by the acute attack.

The present case was particularly suitable for the investigation since the patient had lived some eight years after a typical acute attack.

CLINICAL REPORT.

J. J., spinster, aet. 59, was admitted to the Royal Infirmary, Edinburgh, on February 12, 1921. We are indebted to Professor Edwin Bramwell for the following clinical notes.

History.—The details of the patient's illness were ascertained from her sister. Some three weeks previous to admission there had been a gradual onset of drowsiness and lassitude; the drowsiness became so pronounced that, five days later, the patient had to take to bed, and she slept almost continuously; when sufficiently stimulated she could be roused, although from this time it was necessary to feed her.

The patient continued more or less in the same state up to the time of admission to hospital; throughout, when roused, she was always able to appreciate what was said to her. About a week before admission she began to complain of occasionally seeing double and of indistinctness of vision.

On admission. The patient was extremely drowsy, but could be wakened; she was able to give intelligent answers to questions, but spoke in a slow, monotonous voice and only after a pause. It was observed that the face was immobile and devoid of expression. The right pupil was larger than the left, but both pupils reacted to light and on accommodation; the patient was unable to converge especially with the right eye, and could not look upwards beyond the horizontal plane. The abdominal reflexes were not elicited; the plantar response was flexor on both sides. No abnormal signs other than those mentioned above were detected in any system.

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Fig. 1. Preparation from the mid-brain showing great proliferation of astrocytes, some of which are large and in various stages of amitosis. (Frozen section treated by Cajal's gold chloride sublimate method).

Fig. 2. Preparation from the mid-brain. In the upper part of the section, dense gliosis is present. In the lower part, the fibrous elements are less numerous and some of the astrocytes are still in a phase of vegetative activity. (Frozen section stained by the Krystallviolet method).

Six days later (February 18, 1921) a lumbar puncture was performed. The cerebro-spinal fluid was clear, not under tension, and contained 40 cells per c.mm., the majority of them being reported as small lymphocytes.

Progress.—The patient remained in hospital for five weeks. During the first three weeks the temperature was occasionally rather above normal, but thereafter pursued a perfectly normal course. The drowsiness, the immobility of the face, and the slowness of speech passed off gradually. Before she was discharged, all movements of the eyes could be well carried out, but the right pupil remained slightly larger than the left.

Shortly after leaving hospital, she developed involuntary movements of the legs; they were intermittent, of varied intensity, of an irregular compound nature, absent during sleep, on walking, and on making other voluntary movements.

In January, 1922, one year after the acute attack, the patient was admitted to the Royal Edinburgh Hospital for Incurables; but after five months she was discharged from the Institution, since her condition had become no worse and she no longer required indoor treatment.

On leaving the Royal Hospital for Incurables, the patient went to live at Queensberry House, Edinburgh—a home for old people. She there came under the care of Professor William Russell.

For the first four years of her stay in the Home, she was able to go about the buildings and in the gardens. During this time it was observed that, when walking, she tended to trot, and held the arms in a flexed position across the trunk. Further, her face became expressionless and her condition one of apathy.

These signs of Parkinsonism gradually progressed and necessitated the patient spending more and more time in bed; after 1926 her condition was such that she was disinclined to get up. Eventually her death was due to inanition.

During the acute attack, the symptoms indicated that a definite focus of damage had occurred in and around the nuclei of the third cranial nerve, and the midbrain was selected, therefore, for investigation.

After autopsy, the portion removed was fixed for ten days in formol-ammonium bromide solution, and then frozen sections were made in a plane at right angles to the long axis of the midbrain. Sections were impregnated by Cajal's gold chloride sublimate method and by Gross-Bielschowsky's method; a third series was stained by the Kristallviolett method for neuroglial fibres.

REPORT ON THE MATERIAL EXAMINED MICROSCOPICALLY.

Throughout the midbrain, areas were present in which great proliferation of astrocytes had occurred; for the most part the cells were fibrous in type.

Many of the proliferated astrocytes had regressed and formed areas of dense gliosis. On the other hand, not only were there large astrocytes with thick processes and nuclei rich in chromatin, but the cytoplasm of some contained two nuclei; further, throughout the areas of gliosis, but especially in certain parts, some of the large vegetative astrocytes occurred in pairs and small groups. Thus the stages of amitotic division were present. (Figs. 1 and 2.)

Among the areas in which gliosis was especially pronounced were the regions of the nuclei of the third nerves, and the nuclei themselves had been encroached upon by the astrocytic proliferation.

COMMENTARY.

As a means of elucidating the nature of any disease, morbid histology has certain very definite limitations. It is of positive value in this connection only if changes in the structure of the cell are demonstrated or the anatomical relationship of the cell to its environments is shown to have been altered. Further, it can fulfil this purpose only if the vital processes which have brought about the changes can be deduced from the altered form and arrangement.

Microscopical examination of the tissues may reveal the results of acute disease. But unless the sequelæ are causing alterations in the function of the body cells at a later time, the condition is one of repair and not of disease. On the other hand, before a more or less longstanding condition can be designated a chronic disease, it must be producing an effect, either local or general, on the individual cells and tissues. This effect is naturally progressive.

We have described histological changes in the present case, and we shall argue later that they are not only consequent on an acute condition, but that they represent an instance of a chronic progressive lesion. Before doing so, however, it is necessary to consider the significance of the proliferation of interstitial cells which occurs so frequently in morbid processes. Our views on this subject have been stated briefly in a paper recently published by us (SLATER AND REYNOLDS, "A study of a case of cervical glioma," *Brain*, 1929, LII, Part 4).

Throughout the body, whenever destruction of tissue occurs, the interstitial supporting cells proliferate. In the paper referred to, we suggested that the products of lysis of the dead tissue stimulate the reproduction of the cells. The phenomenon, however, may not be the result of actual destruction, but may be consequent upon damage to the tissue of such a degree as to give rise to abnormal metabolic products of a potency sufficient to provide the stimulus for proliferation of the neighbouring cells. Again, direct damage to the interstitial cell itself may cause it to divide, provided the damage is not so severe as to destroy it. This is a natural corollary to the fact so commonly observed in tissue which is undergoing necrosis, viz., that one of the last vital acts of a dying cell is to attempt to reproduce. Even in necrosing nervous parenchymal cells—cells which in the process of specialisation have lost to all intents and purposes the power of reproduction—we have seen occasionally two nuclei; this observation can be explained only on the fact that the dying cell has attempted to reproduce itself, and is in keeping with the fundamental principle of phylogenetic survival. The reproduction of cells now being considered occurs not only in those states which are commonly designated 'disease,' but in conditions of trauma; the law enunciated is merely the statement of a fact fundamental to healing and repair.

With this conception of the basis of cell proliferation in relation to damage and destruction of tissue, we can attempt to translate the histological data in the present case into the processes of which they are the expression.

It may be taken as proved that acute encephalitis lethargica is a condition due to a 'virus.' In the present instance the virus caused damage and destruction to the tissues of the midbrain, whether parenchymal or interstitial, with consequent proliferation of the interstitial, viz. the neuroglial, cells capable of reproduction—the astrocytes.

The histological picture, however, does not show astrocytes which have proliferated merely during or immediately subsequent to the acute attack and then, having developed fibres, have passed from an active to a passive or quiescent stage. Some eight years after the acute attack, large astrocytes with thick processes are present; some of them are arranged in pairs and small groups, and some even have two nuclei in the cytoplasm. These cells are typically astrocytes in an active phase of reproduction. This means that damage or destruction is still going on and it is justifiable to presume that the process has been continuous. Moreover, this supposition is supported by the widespread distribution of the gliosis present at the time of death; judging by the scar formed after repair of traumatic lesions of the central nervous system and having regard to the types of proliferated astrocytes in the case now published, the appearance cannot be explained by the occurrence of an acutely produced lesion eight years ago followed by a period of complete quiescence with a subsequent and very recently initiated active process.

Again, a theory which advanced a recent progress beginning *de novo* could not explain adequately the nature and source of the factor responsible. It must be concluded, therefore, that in addition to the acute process of eight years ago, the present case presents a chronic and continuously progressive condition.

It remains now to consider how such an interpretation of histological facts coincides with the clinical progress of the patient.

At the time of the acute attack attention was directed to the midbrain by the occurrence of certain prominent signs. Apart from the problematical significance of drowsiness, lassitude, and want of expression, a lesion of this part of the central nervous system was shown by inability to converge or to look upwards; this was supported by the pupils being of unequal size. As we have argued, the lesion in the midbrain at that time consisted of damage to certain parenchymal structures, and most probably of destruction of some of their elements. Further, it has been suggested that damage or destruction of interstitial cells occurred. Since the patient recovered the power of ocular movements, however, the destruction and damage to the nerve cells concerned were not of such a degree as to prevent an adequate number recovering sufficiently to fulfil normal ocular functions. Consequent upon the acute lesion, proliferation of astrocytes occurred; and, fibres having been developed in their cytoplasm, they regressed, areas of dense gliosis remaining. Shortly after the acute attack, the patient developed involuntary movements of the legs; these were due undoubtedly to central irritation, but there is nothing

in the case to localise the site. Nevertheless, these symptoms were of value as indicating that a disturbance of function was continuing. Some time later, the signs and symptoms typical of Parkinsonism gradually became manifest; they progressed until ultimately the patient died of inanition.

Microscopically, not only was there found gliosis due to the lesion produced by the acute attack eight years ago, but also continuous glial proliferation had occurred up to the time of death. The continuous proliferation was due to the persistence of the virus in the tissues and was not a direct result of the damage induced by the acute attack. During the chronic stage, the effect of the toxin was much less intense than during the acute onset, but whether this was due to a numerical decrease or to a lessened pathogenicity of the virus or to both factors is unknown. A partial equilibrium between the virus and the tissues was established, but this was never complete; throughout the entire course of the disease, the infective factor predominated.

It will be seen, therefore, that the clinical course of the disease exemplified by this patient may be correlated exactly with the pathological process deduced from the histology. Both the clinical and histological phenomena are those of a slowly progressive disease following on an acute disturbance of function, with damage and destruction of parenchymal tissue.

SUMMARY.

The case was one of acute encephalitis lethargica followed by progressive Parkinsonism. The histological examination showed not only that gliosis had occurred as a result of the acute attack, but that astrocytic changes were active up to the time of death. The pathological process and the clinical course of the disease are shown to be parallel.

In conclusion, we desire to express our thanks to Professor William Russell for the opportunity given us of examining the case and for the notes on progress during the time the patient was under his care. We are indebted to the Medical Research Council for a grant towards the cost of the research and to the Carnegie Trust for financial assistance in publishing the illustrations.