THE PATHOLOGY OF POST-DIPHTHERITIC PARALYSIS.[1]

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THE observations on which this paper is based were made during a period of two years (1899–1901) in which I held the position of Assistant Medical Officer at the fever hospitals of the Metropolitan Asylums' Board.

The question of the pathology of cardiac paralysis is not here considered, partly for the sake of convenience, and partly because there is at least some probability that it is an affection independent of the nervous system.

The literature of the subject has quite recently been reviewed in two papers by Drs. Batten (1) and Rainy (2), and I shall therefore merely refer to the results of one or two recent observers.

Most important work has been done, experimentally, on guinea-pigs by Mouravieff (3). He figures well-marked changes in the nerve cells. The first alterations observable are in the cells of the spinal cord, chiefly of the anterior cornua, consisting of disintegration of the chromatic substance, peripheral chromatolysis, with abundant formation of vacuoles. Perhaps isolated cells perish, but a number, more or less considerable, re-establish themselves. During the first three or four weeks he could not find any modification in the peripheral nerves. In animals which have lived five to six weeks there is peripheral neuritis, but the spinal cells have either atrophied or re-established themselves. The explanation which he offers is that the diphtheria toxin produces considerable modification in the cells of the spinal cord, and later, as a result of these changes, the peripheral nerves undergo a degeneration, and paralysis ensues. Lesions of a similar character, but less marked, were present in the brain and medulla. The spinal ganglion cells were little altered in the first seven cases, but in the eighth there were marked changes, with degeneration of the posterior roots extending into the column of Goll. The changes in these cells recalled those in the anterior cornua, but were possibly consecutive to the neuritis.

Martin (4) found, in animals, marked nerve degeneration, but no changes in the cord or spinal ganglia. He thinks that the great argument against the central origin is the fact that sensory fibres are affected. In man, in one case during the acute stage, he found degeneration of the phrenic nerve. Batten (1)

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examined the nervous system very thoroughly in six cases of diphtheritic paralysis. He found that the nerve cells were quite normal (Nissl's method) both in the spinal cord and posterior root ganglia. There was degeneration in the cranial nerves and in the anterior and posterior spinal roots and posterior columns of the cord.

Rainy, from his experimental work, concludes that the cellular changes are most characteristic and that they are accompanied by vascular changes. The cells show moderate chromatolysis, increased acid staining of the achromatic substance, and vacuolation of the cell protoplasm. The cell alteration is probably antecedent to that of the nerves in the majority of instances. Bielschowsky and Nartowsky (5), from recent experimental work, conclude that the essential lesion is the parenchymatous degeneration of the peripheral nerves, and that any slight changes in the anterior horns of the spinal cord are secondary. This view is distinctly opposed to that of Mouravieff, and it is important to notice that the former authors observed typical palsy as early as eight to ten days after the injection of the toxin.

I now proceed to give some account of my own work on this subject. The methods used were as follow:—

The spinal cord was examined by Nissl's method and also by the Marchi stain. *In using Nissl's stain I employed a saturated solution of corrosive sublimate as* the fixative, and have found it useful to stain the sections with erythrosin after instead of before methylene-blue, as recommended by Rainy. The spinal roots and peripheral nerves were examined by the method recommended by Sherrington, namely, fixing in ½ per cent. osmic acid of small lengths (1–2 cms.) of the nerve for two to four or six hours, followed by thorough washing in running water for twenty-four hours. The pieces are then macerated in Ranvier's 30 per cent. alcohol for a week or more, teased and mounted in 50 per cent. glycerin. This is a very delicate method, and is really the only reliable one for the detection of degenerating nerve fibres. The Marchi stain was used for the muscles.

I have had the opportunity of examining the neuro-muscular system in four cases of diaphragmatic paralysis following diphtheria. I have confined myself to a study of this paralysis, because it has the advantage of being quite definite and limited, and, at the same time, of being typical; and any changes found may, I think, be fairly taken as a type of the pathology of diphtheritic paralysis in general. It is unnecessary to give any clinical details of the cases except to say that death occurred in two cases on the thirtieth day of disease, and in the other two on the thirty-sixth and fortieth days respectively.

Spinal cord.—The whole of the cord, corresponding to the third and fourth cervical roots, was examined in two cases by Nissl's method. The great majority of the cells were quite normal, but in some sections a large cell, towards the base of the posterior horn, showed powdery chromatolysis and increased acid staining of the cell body. Occasionally, also, I found a similarly altered cell in the postero-external group of the anterior cornu. With these few exceptions the nerve cells in this region of the cord were quite normal. There was a complete absence of round-cell proliferation and of hæmorrhages, but there was, perhaps, slight vascular engorgement.

In the third and fourth cases the cord was examined by Marchi's method. There appeared to be some scattered degeneration spreading in by the posterior roots towards the anterior cornua, but there was certainly no degeneration passing upwards in the posterior columns.

The posterior root ganglia were not examined.

Phrenic nerves.—Portions of both these nerves close to the muscle were examined in the manner described above. In all four cases both nerves showed marked degeneration. The myelin sheath had disappeared to a great extent from many of the fibres, being represented by patches of black staining granules at intervals. In some instances they were quite characteristic of Wallerian degeneration, but in others only one internode of the fibre showed these droplets, while neighbouring internodes appeared quite normal. This was noticed by Martin, and is probably the earliest change which has not yet resulted in a true Wallerian degeneration.

Spinal roots.—The third and fourth cervical roots were examined in two cases. The anterior showed many degenerated fibres. Degenerated fibres were present also in the posterior roots, but were distinctly less numerous than those in the anterior roots.

Diaphragm.—This muscle showed a considerable amount of fatty degeneration in scattered distribution. Normal fibres were, however, in a decided majority. This change is not sufficient to be characteristic, but would probably be more so had the patients lived longer. I have found it quite as well marked, and sometimes much more so, in various other diseases, namely, ulcerative endocarditis, typhoid fever, and pharyngeal abscess. It is of interest here to note that in a case of phthisis I found extreme fatty degeneration in the diaphragm. In such a case the degeneration probably has a similar causation to that found by Mott (6) in severe anæmia.

These results, therefore, agree in the main with those of Batten, and locate the primary and chief changes in the peripheral nerves.

With a view to testing the theory of Mouravieff, in its application to man, I have devoted much time to a study of the nervous system in cases which have died early, before paralysis set in. In man the nervous system is affected by the diphtheria toxin in a selective manner, the great proportion of paralyses occurring in the muscles supplied by certain cranial nerves and the phrenic. The hind-limbs and the trunk are much less frequently affected, and the upper limbs extremely rarely. In view of this I have confined my attention to a study of the following nerves and their nuclei — third, sixth, ninth, tenth, and eleventh cranial and the phrenic.

The patients all died from cardiac failure within about a fortnight of the onset of the disease, and it may therefore be supposed that the dose of toxin which the system received was considerable, and such that one would expect the patients to have developed paralysis had they lived long enough. In rare cases where patients have recovered from severe cardiac affection, in the early days of convalescence after diphtheria, they are extremely likely, later on, to develop severe paralysis. This has been my experience, and I mention it because it might perhaps be urged that it does not follow that because the heart muscle is severely affected in any one patient the central nervous system would also be affected. I admit that it is not a necessary consequence, but from clinical experience it is what one is led to expect.

Now, on Mouravieff's hypothesis in these cases, one ought to find definite changes in the nerve cells of the nuclei of origin of some of

these nerves which are most commonly affected in diphtheria. I have carefully examined in this way three cases, and the phrenic nerves alone in three others. The nuclei of origin were examined by Nissl's method as in previous work, namely, the oculo-motor, abducent, glosso-pharyngeal, vago-accessory, and the third and fourth cervical segments. I have been quite unable to convince myself of the presence of any definite changes in the nerve cells of these nuclei. The nucleus of the cell is well preserved, not eccentric, and the nucleolus normal. There is complete absence of vacuolation, and the chromatic granules are normal in size and arrangement. There were no definite vascular changes, and no round-cell exudation. It is specially important to notice that the vago-accessory nuclei appeared to be normal, because these nerves are paralysed more frequently than any others in the body; also because this fact may help to dispose of any idea that cardiac paralysis is due to an affection of these nuclei.

The nerves were carefully examined by the teasing method, but in no instance were any degenerated fibres found. Paralysis of the palate or of the internal rectus does occasionally occur quite early in convalescence, but it is uncommon, and I have not had an opportunity of examining the nerves in such a case. Martin found distinct degeneration of the phrenic in man as early as the fifth day, but probably this is unusual. However, it is important, because it tells against the theory of the central origin of the peripheral nerve degeneration.

So far, then, it does not appear that Mouravieff's hypothesis will apply to man. Indeed, it seems to me improbable that the changes which Mouravieff has described would disappear as degeneration in the nerve occurs, because, as Warrington (7) has shown, section of anterior and posterior roots produces definite chromatolytic changes in the cells of the anterior cornua, and therefore the degeneration of the spinal roots would tend to increase and prolong any previous change in the nerve cells. Possibly the few cells I found altered in the cervical cord, in the cases of diaphragm palsy, became so owing to the lesion in the spinal roots.

It seems difficult to understand why, if the cell alteration is sufficient eventually to produce nerve degeneration, it is not also of itself sufficient to cause paralysis, which would then appear at a much earlier period of the disease. That such early paralysis is not present is very well shown, at least in the case of diaphragm palsy, in which the onset is remarkably definite and sudden, and followed as a rule by death in three or four days. It is, I think, a significant fact that Mouravieff never found degeneration of the nerve fibres coincident with changes in the nerve cells. Again, although degeneration of the posterior root fibres is a fairly constant phenomenon, Mouravieff only once found modifications of the cells of the posterior root ganglion,

namely, in one animal, in which degeneration of the posterior roots was present.

Finally, a very weighty argument against Mouravieff's explanation may be found in the peculiar distribution of the change in the medullary sheath of the nerve fibres pointed out by Martin, and which I can fully confirm. This change is often conspicuously scattered along the length of the fibre, some internodes being quite normal. True Wallerian degeneration is found only if sufficient time has elapsed after the interruption of the axis cylinder took place, before death occurred.

On the whole, then, the balance of evidence is in favour of the following conclusions:—

1. That in the paralytic stage of diphtheria the only important change discoverable is situated in the peripheral nerves.

2. That if there are any changes in the cells during the preparalytic stage, they do not stand in a causal relation to the parenchymatous degeneration in the nerves.

3. That, therefore, the parenchymatous degeneration of the nerve fibres must be regarded as the primary lesion.

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