

Some Appearances Indicating Phagocytosis observed in the Brains of the Insane: Essay for which was awarded the Bronze Medal of the Medico-Psychological Association, 1896. By JOHN TURNER, M.B., Senior Assistant Medical Officer, Essex County Asylum.

Dr. Bevan Lewis ascribes to the Deiters cells of the brain a phagocyte function; as the scavengers of the brain they absorb and remove effete material, and also according to his view attach themselves to degenerated nerve-cells, whereby these structures are gradually through their agency absorbed and removed.

The following observations appear to indicate that other bodies besides the Deiters cells take an active part in attacking and removing the nerve-cells in the cerebrum.

The phenomenon about to be described is so obvious and so commonly met with in the brain of the insane that it would be a matter of great surprise if it had hitherto been altogether overlooked. Still, beyond the observations quoted below, I am unable to find any reference to the subject, either in standard works on insanity or in journals treating of matters relating to this disorder, and it appears of such an important nature as to warrant a detailed description to bring it more prominently before notice even if it has been previously recognised. Dr. Palmer in his "Illustrations of Normal and Defective Development of the Multipolar Cells of the Cerebral Cortex," *Journal Mental Science*, Vol. xxxiii., figures the process I am referring to (see especially Figs. 15 and 16), but merely refers to them in the text as illustrating degenerated and wasted multipolar cells. Drs. Batty Tuke and Woodhead in their article "Pathology," *Dict. Psycho. Med.*, p. 904, observe that they have obtained evidence of leucocytes taking on a phagocyte action in a case of insanity of nine months' duration with obscure motor symptoms. "The large cells of the motor area were found undergoing degeneration, and had evidently been attacked by leucocytes." . . . "The substance of the cells was in many cases invaded by one, two, or three such bodies, and were also surrounded by large numbers of the small nuclei of neuroglia." In this case Deiters cells were not found. This would appear to be a similar process to what I am about to describe, although, as no figures are given, it is difficult to make certain whether it is altogether the same. At any rate, its authors appear to regard it as an uncommon

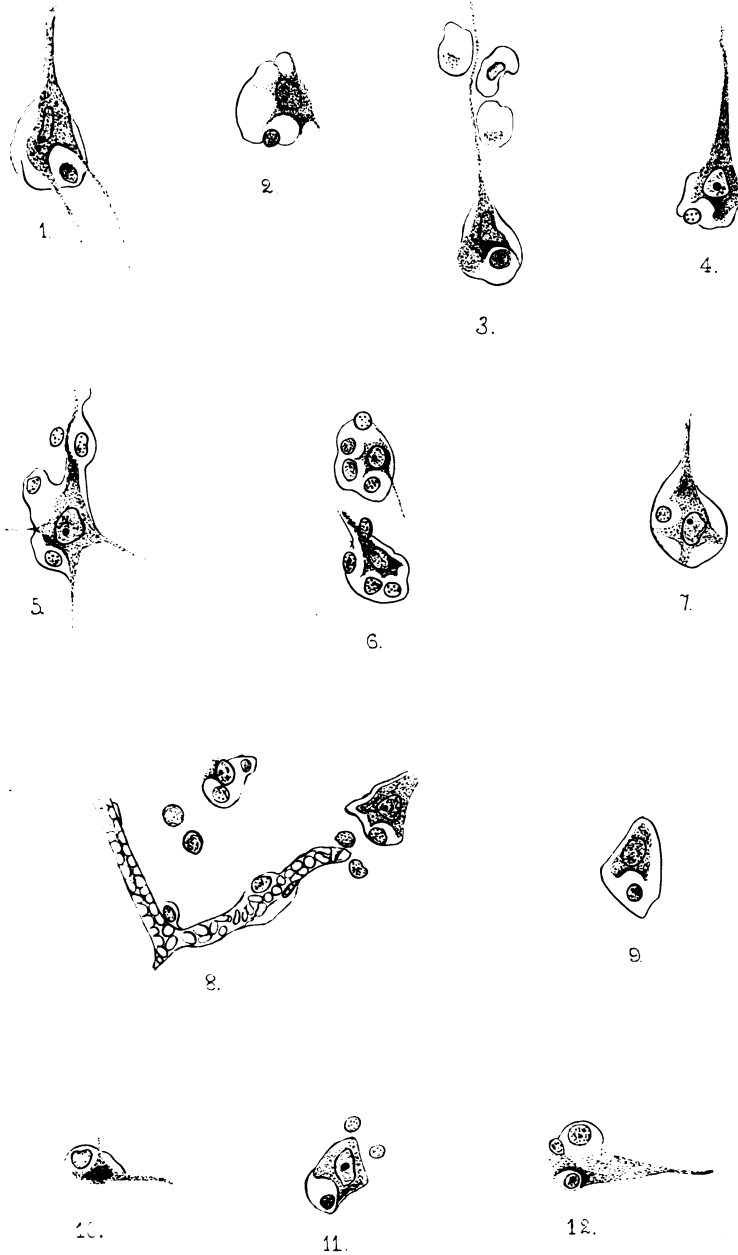
occurrence, whereas, as will be shown, the process I describe is commonly seen in many varieties of insanity, and is especially abundant in senile brains.

Lying free within the peri-cellular spaces are cells which stain (or rather outline) crimson with acid fuchsin, and contain granules also crimson. They are round, oval, or shrivelled, and measure between 4 and 9 μ . Sometimes only one is seen in a space, at others two, three, or four, and in almost every case the cytoplasm of the nerve-cell nearest to the invading cell has a portion deficient. The nerve-cell appears as though a piece had been bitten out, leaving a clean-cut semi-lunar gap. The effect is striking. We can, in favourable preparations, follow as it were all stages of the process from those nerve-cells which have only a small piece of cytoplasm eaten away (Figs. 1, 4, 3, 10) to those which consist of little more than a nucleus surrounded by a mere remnant of cytoplasm, utterly devoid of all processes (Figs. 6, 9). Even in these extreme cases the outline of the cytoplasm still corresponds in its indentations to the position of the invading cells. Sometimes we see the apex process with an invading cell lying close, and here the process appears as though being eaten through (Fig. 5). I have never seen the nucleus implicated. In the most advanced instances, where but little else is left of the nerve-cell it is apparently still intact, though often shrunken, and perhaps with no nucleolus visible.

My notes concerning this appearance extend back for five years, but until recently the condition was figured without, as I now believe, a due appreciation of the importance attaching to it. The notes refer to many varieties of insanity, viz.:—General paralysis, alcoholic insanity, and various forms of melancholia and mania. I do not infer that these are the forms of insanity in which this condition is mostly seen, or to which it may be peculiar. I mention them simply as being the cases where, so far, I have met with it to a marked extent; probably a more extended examination of morbid brains will show that the appearance is common to other forms of insanity.

The ages of my cases vary between 28 and 80, and it has been met with in those where the onset of the mental disorder was of quite recent occurrence. The cases from which the figures are taken were as follows:—

No. 1.—A female, *æt.* 52 (Figs. 1 to 4 inclusive). Although the attack of insanity was stated to be of four or



To illustrate Dr John Turner's Prize Essay.

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five years' duration, her symptoms were acute. She was in a state of active melancholia, constantly restless, extremely agitated, and profoundly miserable. After a short residence she died of cardiac failure and exhaustion of melancholia. The figures, as in all the other cases, are taken from preparations of the frontal lobe.

No. 2.—A female, *æt.* 80 (Figs. 5 to 8 inclusive). Her insanity was of over five years' duration, and her prevailing symptom that of melancholia, with restlessness. After a residence here of four or five months she died of bronchitis and senile decay. The nerve-cell destruction in her case was most marked and extensive, and seen both in section from the frontal and occipital lobes, but more in the former; here there was scarcely a single cell without one or more invading cells lying in its peri-cellular space. There were very slight evidences of proliferation of the Deiters cells; a few were noticed in the first layer, but none elsewhere. Fig. 8 shows a capillary in the neighbourhood of two nerve-cells, outside of which are several cells in all respects similar to those in the peri-cellular spaces. All the capillaries exhibited cells (wandering leucocytes) in their peri-vascular spaces, but this condition was not nearly so marked as in the next case.

No. 3.—A female, *æt.* 28 (Figs. 9 and 10). She was admitted here acutely melancholic, refusing food. She was kept in bed, where she lay moaning and groaning, was restless at night, and struggled when one attempted to examine her. After remaining in this low and exhausted state for three weeks she developed bronchitis and died. Her insanity was of recent onset, dating only five days prior to admission. She had had a slight attack of melancholia five years previously. Sections taken from both frontal and occipital regions showed a great quantity of invading cells, most of which were small, and had a denser appearance than the cells in the two prior cases; but though this was the rule, yet some of them were large, measuring $8\mu \times 6\mu$, and with only a few granules within (Fig. 10).

No. 4.—A female, *æt.* 33 (Figs. 11 and 12). This woman was a general paralytic. The disease was in a fairly advanced stage. Sections from her frontal and parietal lobes exhibited extreme proliferation and growth of Deiters cells, and also a very considerable invasion of the peri-cellular spaces by cells which were in almost all cases associated, as above described, with partially destroyed nerve-cells.

What are these cells? I think there can be very little doubt but that they are wandering leucocytes. Their size, as has been mentioned, varies between 4μ and 9μ . In the great majority of cases they are 6μ . Generally round and plump, but sometimes shrivelled, or with a kidney-shaped appearance. They outline vivid crimson with acid fuchsin, and contain granules which also stain crimson; sometimes their contents appear dense, at others only a few scattered granules are seen within. With logwood they stain deeply; with Rosin's stain, the methyl green picks them out. The capillaries in the neighbourhood of the affected nerve-cells (and I am now referring to cases uncomplicated by increase of Deiters cells or proliferation of cells in the walls of the blood-vessels as seen, *e.g.*, in general paralysis) always show a fair number of exactly similar looking bodies just outside their walls in the pericellular space and also within (see Fig. 8.) Likewise within the big vessels of the pia we see amongst the blood discs a few bodies evidently leucocytes, which have an identical appearance to the cells found in the pericellular spaces. These facts strongly suggest that the invading-cells are wandering leucocytes, more especially as we know that in normal brains they are met with in the pericellular space. Obersteiner (*The Anatomy of the Central Nervous Organs*, translated by Hill, p. 138) figures a nerve-cell and capillary with surrounding lymph space, in the pericellular portion of which are two leucocytes occupying a position at the base of the nerve-cell similar to what I have described.

Whatever explanation may be hazarded of the appearances above described, there can be no doubt that a very strong impression is left on the mind, when examining specimens which exhibit this condition, that the nerve-cells are being destroyed by the neighbouring bodies seen free in the pericellular space. Practically in all cases where they are seen a portion of the cytoplasm of the nerve-cell in their vicinity is deficient. This piece, as mentioned before, and as the figures show, has a clean-cut, scooped-out appearance, and if two or more cells are present then two or more portions of the cytoplasm in their neighbourhood are scooped out. It seems to me that we must suppose that either the invading cell exercises a solvent action on the cytoplasm of the nerve-cell in its vicinity, whereby such portion is carried away by the lymph stream, or else they themselves absorb and, as it were, feed on the nerve-cells. That is, they exhibit a phagocyte function. There are certain facts which render this last

suggestion the more probable. We know that leucocytes are capable of exercising such function, but the question arises why they should attack nerve-cells, in the vicinity of which they normally come without exercising such action. Is it because the nerve-cells are degenerated, and therefore fit objects for them to destroy? Or that for some reason or another they are endued with a depraved appetite, so to speak, and attack structures which they normally leave untouched? Or that owing to blocking up of the lymph channels they get shut into the peri-cellular spaces and so feed on the nervous elements in default of other sustenance? At present one is hardly in a position to give any decided opinion as to which of these explanations, if any, is the true one, but from other appearances noted so far in the specimens where the condition is met with, it would seem as not at all unlikely that the latter, viz., that the leucocytes are hemmed in and cannot escape, is in some cases a feasible explanation why they attack the nerve-cells. In such preparations the peri-vascular spaces are seen heavily laden with pigment, which might easily by its presence block the lymph channels, especially at the narrow parts where the peri-cellular space blends with the peri-vascular. Such a condition was extremely well marked in the case of No. 3, and was seen both in fresh preparations and in hardened specimens; some of the finer vessels were completely mapped out in pigment granules, clumps of which were deposited at each branching of the vessel. The fact that these invading cells are seen in recent cases of insanity would appear to indicate that they do not necessarily only attack degenerated nerve cells.

From the nature of the appearances described it can readily be appreciated that they are only to be demonstrated in sections so mounted that all their parts are preserved *in situ*; otherwise the little free cell would be washed away. Hardening brain in Muller's fluid, etc., produces such shrinking and distortion of the elements as to obscure the appearance. At any rate, I have not been able to perceive it in brains so prepared, although it was evident in other parts of the same organ differently treated. My procedure was as follows:—Very small (thin) pieces of brain from cadavers not more than 10 hours dead, were placed in Fol's solution and left for 24 hours at a temperature of 35 deg. to 40 deg. C., or for 48 hours at the ordinary temperature; then washed and placed into alcohol 80 %_v, finally into ab-

solute alcohol, where they remained 4-5 days. Soaked in chloroform for 6 hours and then placed in paraffin of a melting point of 50 deg. C. and left at that temperature for 16 hours. Sections cut and fixed to the slide by capillary attraction (Altmann-Gaule method). They were stained in a concentrated solution of acid fuchsin, to which was added a little aniline blue. After staining a few minutes they were rinsed in water and treated to 0.25 per cent. alkaline alcohol. This was rapidly poured off. Then again they were dipped into water and dehydrated in absolute alcohol and cleared in clove oil or xylol. Photo-micrographs are submitted herewith.*

EXPLANATION OF THE FIGURES.

- Fig. 1. Invading cell $5\mu \times 4\mu$. Nucleus of nerve-cell $10\mu \times 4\mu$. No nucleolus seen. Apex and two basal processes.
- Fig. 2. Nerve-cell extensively destroyed. No processes. Nucleus of nerve-cell $10\mu \times 8\mu$. Nucleolus $2\mu \times 2\mu$. Invading cell $6\mu \times 6\mu$.
- Fig. 3. Apical process faintly seen running between three other cell spaces. Nucleus of nerve-cell $12\mu \times 8\mu$. No nucleolus. Invading cell $6\mu \times 6\mu$.
- Fig. 4. Nerve-cell with no basal processes. Nucleus $12\mu \times 12\mu$. Nucleolus $3\mu \times 3\mu$. Invading cell $6\mu \times 6\mu$.
- Fig. 5. Shows invading cells attacking apical process. Three basal processes faintly seen. Cytoplasm of nerve-cell full of yellow pigment. Invading cells $7\mu \times 6\mu$ and $7\mu \times 5\mu$, with scanty contents.
- Fig. 6. Two nerve-cells nearly entirely destroyed, except their nuclei.
- Fig. 7. Nerve-cell with short apical and three blunted faint basal processes. Invading cell has bitten deeply into cytoplasm.
- Fig. 8. Shows a capillary with no peri-vascular space visible. The capillary is full of blood discs. Several cells similar to the invading cells are seen within, and just without its walls. Two neighbouring nerve-cells shown with invading cells.
- Figs. 9 and 10. Two nerve-cells attacked. In 9 only the body of cell is left. No processes. In 10 the invading nucleus is large, $8\mu \times 6\mu$, and with scanty contents.
- Figs. 11 and 12. Two nerve-cells from general paralytic brain. In 12 no nucleus is seen, and one of the invading cells is very large, $9\mu \times 8\mu$.

* These have been placed in the Library of the Medico-Psychological Association.—[ED.]