

THE CEREBRAL CORTICAL CELL UNDER THE INFLUENCE OF POISONOUS DOSES OF POTASSII BROMIDUM.

BY HAMILTON K. WRIGHT, M.D., C.M.

*Medical Registrar and Neuro-Pathologist, Royal Victoria Hospital,
Montreal, and*

John Lucas Walker, Exhibitioner of Cambridge University, England.

A SEARCH through medical literature has failed in bringing to light any account of the changes induced in cerebral cortical nerve-cells or their appendages, of either man or lower animals, by the action of either medicinal or poisonous doses of potassii bromidum.

Not long since I obtained the brain of a man who for three years was subject to attacks of idiopathic epilepsy of varying frequency, and who, in error, for a period of eighteen days, consumed continuous excessive doses of the above salt which indirectly, if not directly, seemed to be the cause of his death.

This appeared to be an opportunity for an investigation, and if possible, a determination of any alterations in the cerebral psychical cells, whose functions were certainly disturbed, as will be seen by the clinical history of the case.

But being aware, however, of the fact, that seldom a single isolated example of any morbid tissue metamorphosis can be taken to firmly establish it as a pathological entity, and also of the frailty of any inference drawn, or conclusions arrived at, from the observations of such a solitary instance, I have taken the precaution to control my study by examinations of the cerebra of four rabbits, which were subjected daily to large doses of potassii bromidum for a period of nearly

a month. And to make assurance doubly sure I kept two rabbits under identical environment and feeding, without, however, administering any drugs to them.

Moreover, it must be readily seen that in such a case as this, with its antecedent history of psycho-motor disturbance, adequate control and verification by experiment were absolutely necessary to avoid confounding a possible underlying patho-anatomy of the epilepsy itself, with a more recent destructive change produced by the action of the drug.

CLINICAL HISTORY.

Before proceeding to detail the observed modifications in the nerve-tissue of the various cerebra, it will be well to give the history of the patient as learned from his own account, and from the physician in charge. For this history will establish the fact that the case is one of extreme bromidism, and will militate against the assumption that the alterations are merely those of cell exhaustion which without doubt supervene in epilepsy, in consequence of the continuous explosive discharge in the psycho-motor region of the cortex cerebri.

Briefly, the history is as follows:—

The patient, a man aged 26 years, came under observation on February 11, 1897, with a history of *grand mal* of three years' standing.

During the first year the fits occurred once or twice a week, then about once a month for eighteen months, and for six months before coming under notice they attacked him not oftener than monthly. During these last months, however, there were intercalated between the major attacks several fits of *petit mal* every twenty-four hours.

No mental disability attended the onset, or followed the minor epilepsy, but after each major fit there was intense headache and a stupor lasting generally twenty-four hours.

Observation showed him to be slightly neurotic in temperament, and to be subject to frequent attacks of *petit mal* during each day. Reflex and muscular power appeared to be normal.

No major fits occurred during the time the patient was under

observation, but nevertheless he was put under bromide treatment for the minor attacks and for the headache which invariably followed them.

On the second or third day of treatment it was noticed that he became heavy and stupid, and this stupor became more and more marked until death two weeks later. About a week before the latter event, on February 23, muscular weakness supervened, and the man was almost unable to walk or handle the ordinary utensils used in eating; when he did move about it was more as an automaton than as an intelligent conscious being.

On February 27, sixteen days after the commencement of the administration of the bromide, it was observed that he had considerable difficulty in swallowing. On the 28th the difficulty became pronounced and in addition he now failed to recognise his friends; urine was passed involuntarily. After March 1 no food or liquid was taken by the mouth, as the patient had several attacks of choking that left him extremely cyanosed. Also there developed on this day a few moist râles in the lungs. He became comatose and his lower jaw relaxed. Brandy and milk were given through a stomach tube in order to sustain life. Respirations now became rapid, thirty-six per minute, and the temperature rose to 100.25°F .

On March 2 his tongue became swollen and the administration of stimulants and food had to be discontinued because of the choking produced by the passage of the gastric tube. On the afternoon of this day the temperature rose to 104.1°F ., the respirations to 48 per minute, and the pulse rate increased to 132.

Next day, March 3, bilateral bronchitis became pronounced, and before evening this had developed into a pneumonia affecting both sides. In the evening his eyes were examined and an intense bilateral optic neuritis was found to be present, and the double conjunctivitis which had set in a week before became more marked. In addition there was an abrasion of the corneal epithelium on both sides. At 5.30 p.m. of this day the pulse rose to 240 and maintained this or a higher rate until death. The temperature gradually heightened from that hour on until it reached 108.4°F ., just prior to death at 3.30 a.m. of March 4.

From the time the patient came under observation on February 11 until interference with deglutition occurred on the 29th, he took ostensibly twenty grains of potassii bromidum three times a day, but really he had consumed 160 grains three times per diem, thus making a whole ounce in twenty-four hours. The error arose through the solution of the salt being 1 in 3; and

the patient had been given an ounce of the mixture three times daily, instead of a drachm diluted to an ounce with water, as was directed by the physician in charge.

It will be seen, therefore, that the quantity of the drug taken by the patient was great, and quite sufficient to cause the onset and persistence of the motor and psychic phenomena of extreme bromidism such as occurred on, and continued from, the third day of the administration of the salt.

Careful analysis of the above record of the patient will show that, in no period of his illness was he subject to a large number of rapidly recurring convulsive outbreaks, that for the six months before the commencement of the bromide administration he had but one major fit a month, and that during the eighteen days in the hospital only *petit mal* with subsequent headache was noticed.

This history, together with the fact that competent observers are not agreed as to the presence of morbid changes in the cerebral cortical cells of those who have suffered from idiopathic epilepsy, even when most carefully examined by approved modern methods, justifies my assumption that any changes exhibited by the sensori-motor cells of the cerebrum under discussion may be regarded as certainly not attributable to the primary cause of the epileptic manifestations themselves, nor to any condition induced as a result of such manifestations. They must, therefore, be ascribed to the effect (1) of poisonous doses of potassii bromidum, or (2) to too long an exposure after death of the brain before it was immersed in a fixing medium, or (3) possibly to the action of the fixing medium.

The necropsy was performed twelve hours after death, but during this lapse of time the body was kept at a temperature of between 20° and 30° F. in the mortuary refrigerator of the laboratory, and at the time of the examination presented no sign of decomposition in any of its parts. Yet without doubt it must be allowed that some *post-mortem* alteration took place, some fine change, even though not obvious, and this will have to be considered in a final summing up of the case.

MACROSCOPIC OBSERVATION OF THE HUMAN BRAIN.

Naked eye examination of the human brain disclosed the following: slight œdematous effusion over the whole cerebral cortex, and a noticeable capillary distension in the frontal and parietal pia mater; the lateral ventricles contained the normal quantity of fluid and their ependyma was healthy. No spots of softening or induration could be felt in the cortex that would point to the possibility of the convulsions being of organic cause.

Without being cut into by any of the generally used laboratory methods farther than was just necessary to expose the lateral ventricles, and with only a partial removal of the pia-arachnoid, the entire brain was placed in a 3 per cent. solution of formaline, and this was repeatedly renewed until the tenth day, when the brain was removed and divided by a sagittal cut into right and left hemisphere, and then each half by transverse-cuts into slices about two cm. in thickness. No gross alterations of any kind were to be seen in the cortex, medullary centre, or internal ganglia, and the tissue was re-immersed for more complete fixation. At the end of another week the brain was well hardened throughout and fit for microscopical investigation.

Small pieces were then taken from the superior, middle, and inferior aspects of the pre-central and post-central convolutions of each hemisphere, corresponding roughly to the lower and upper limb and face centres respectively; and also from the frontal and occipital lobes. But as the examination of these showed no differences according to position, the situation from which the pieces were taken may be entirely disregarded.

After being thoroughly washed, the pieces were halved and a moiety of each dehydrated in alcohol, carried through celloidin, and an attempt made to stain the sections therefrom by hæmatoxylin-eosin, Nissl's, and Unna's polychrome dyes. The remaining halves were treated to a week's bath in Müller's fluid, as they were intended for examination by the silver method.

It is my experience that nerve cells and their fine constituents are inclined to stain badly with aniline dyes if the fixing medium had been only formaline. [The case under consideration is no exception to the rule, and I have, I regret to say, to confess to somewhat meagre results from their use in this case.]

Still with Nissl's fuschin method, and by the use of Unna's polychrome, changes are shown in the cells which tell of the deleterious action of some toxic agent, and which supplement the alterations made out by the silver stain used in the case. They also corroborate the demonstration of changes in the blood-vascular tissues afforded by the hæmatoxylin-eosin method.

MINUTE ANATOMICAL CHANGES.

Blood-Vascular Alterations.

The pial vessels are dilated wherever observed and are filled with corpuscles, and so also are the various sized vessels that pass from the surface into the cortex and medullary centre. Careful examination, however, discloses no gross injuries of the vessel walls, and no noteworthy increase in number, or alteration in quality of the erythrocytes or other blood-elements. Yet a fine lesion is to be observed in the vessel wall which consists of a slight swelling and inwards protrusion of the endothelial nuclei and a more marked avidity manifested by them for the various dyes.

The larger vessels are not the seat of any considerable change. But the nuclei of the endothelium are swollen and bulge well into the lumen of the canal.

In the medium sized vessels the turgescence of the endothelial nuclei is the salient and only change; if anything it is more pronounced than in the larger vessels. In some instances the nuclei project inwards so far as to nearly block the tube; but no bulging of the vessel walls on either side of them is to be observed, nor any evidence of stasis in the blood stream from the narrowing of the lumen.

In the capillaries most nuclei are turgescient and deeply stained. Occasionally a slight bulging outwards into the peri-capillary space is noticeable, corresponding to the position of the enlarged nuclei. At no point, however, do the latter impinge so far on the capillary canal as to cause stasis in the blood-stream. The peri-vascular spaces

contain a fine granular débris and often polynuclear corpuscles.

It will be seen, therefore, that the blood-vascular tissues have not been acted upon to any great extent by the bromide. The enlargement of the nuclei of the endothelium, the deep staining, the distension and engorgement of the vessels, and the filling of the peri-vascular lymph spaces with cell-detritus are the only manifestations of its action.

Pathological Histology of the Human Cerebral Cortical Cells as shown by the Aniline Stains.

The most salient alteration is a near approach to absolute homogeneousness in the protoplasm of the bodies of the cells. No lamina of the cortex is wholly exempt. As this feature of degeneration, however, appears most evident in the pyramidal strata, cells from these will stand as examples for description throughout this paper.

The amorphous character of the extra-nuclear protoplasm is made evident by both of the Nissl stains, and equally so by polychrome stain. It may be looked upon, therefore, as essentially due to changes of the cell plasm, and not as a consequence of any unknown action of the staining fluids themselves. Many cells, about one in every ten, show absolutely no chromophile particles in their body protoplasm, while others, and these in great number, contain but a few of them irregularly scattered and scarcely distinguishable from the surrounding hyaloplasm. There appears to be no constancy in the point of distribution of the chromophile particles in the cell body. In one a few grains may lie close to the nuclear ring, with other few near the apex or scattered along the basal margin, or the particles may be present in only one of these positions.

In every instance where the complexion of the cell protoplasm has undergone this transformation it is accompanied by evidences of change in the nuclei. It appears to be a rule that in some measure the one shall be attended by the other.

It is to be expected that the nuclear outline should be somewhat hazy and ill-defined when the marked alteration in the encompassing body-plasm is considered. Carefully prepared sections not unusually show almost a blending of the outer margin of the nuclear ring with the body plasm. The inner margin also is ill-defined, and may present a finely dentate contour, the long processes of which proceed inward for a short distance and merge, or end, in the deeply stained nuclear fluid. At first I thought that the dentate and rayed inner margin of the nuclear ring was due to the diffusion of the stain which sometimes occurs. But clean alcohol and aniline oil gave a similar picture, and therefore it is most likely that the condition is a morbid one. The membrane again may not be equally stained throughout, but may have sections of pale, granular material interposed between other sections deeply stained and not in any way altered from the normal.

Often nuclei are seen dislocated from the axial position which they occupy in the normal cells. Instead of lying centrally as in health the nucleus is now displaced, it may be slightly, but in no rare number of cases to the periphery of the cell. No example presented itself, however, of even a commencing extrusion of nuclei from the cells which contain them, providing that the latter are not more degenerate than already described.

The nuclear achromatin in the great majority of all cerebral cortical cells no longer deserves the name, for it has not decolourised in any of the stains. In consequence of this the general appearance of the nuclear vesicle is more homogeneous than in sound cells, and there is a decided lack of refractile brilliance in it.

Morbid changes, however, are not wholly confined to the nuclear membrane and its contained fluid. The nucleolus in most cases is turgescient and blanched, or in a fair way towards complete disintegration. The contour of health is lost, and the smooth roundness is now represented by a granular delicately crenated rim. A still more advanced stage of atrophic metamorphosis is observable in a rarer number of nucleoli. They may be swollen to nearly twice

their healthy size and present an etiolated form with a lightly but distinctly dyed margin suggestive of a membrane. The latter is generally round, but may be flattened as though erosion had taken place. On the whole this state of the nucleus is rare. More often there is an irregular staining of its structure. From the inner aspect of its margin delicate rays project, and after crossing about a third of the diameter of the swollen nucleolus they become lost in the more pale central portion.

Are these spurs made up of aggregations of minute dust particles which now overlie the nucleolus, or are they a part of the latter structure itself which has yet retained a sufficient affinity for the dye to successfully resist the action of the decolourant? In view of the fact that they show, even in the thinnest sections, and also that there is a positive alteration in the chemical properties of the rest of the nucleolus manifested by its blanched, turgescient condition, it seems likely that they are a part of the nucleolus not yet wholly implicated in the chemical change which has affected the greater part of the structure. Moreover, similar features obtain in the nucleoli of the poisoned rabbits, and these confirm the conclusion that this feature of degeneration in the human nucleoli is an actual atrophic change and not due to any fortuitous collection of nuclear dust particles.

Other nucleoli show centrifugal blunt spurs, very short, or longer and more sharply pointed which project from the surface outwards into the encompassing nuclear matrix. These are not rare; but I have in no instance been able to follow a ray to the periphery of the nuclear membrane except where a nucleolus almost abuts upon the latter, and then only from that sector of it which faces the nuclear rim. In all these cases of nucleolar metamorphosis the body of the structure is increased in any transverse diameter but is less deeply dyed than in health. In addition, the edges of the shorter spurs may be finely granular.

But the great majority of all nucleoli show no such remarkable morbid features, the change which they present being of milder degree. Most common is a swollen, blanched

condition throughout, which may, or may not be accompanied by some aberrancy in form. Yet, be the structure round, oval or flattened, its edges are invariably finely granular throughout, or show in some limited extent a very delicate crenation.

In cells whose nucleoli are in an advanced stage of metamorphosis, or are entirely absent, there are to be seen large angular particles lying in the altered achromatin of the nuclei. These are never so small as the large molecular particles of healthy nuclei. The foreign forms stain deeply and are sharply defined from the abnormally tinted protoplasm in which they are scattered. In form and avidity for stain they closely approximate the large angular particles described by Berkley in the nuclei of the cerebral cortical cells of rabbits that he poisoned by alcohol. More than six were never observed in any one nuclear sack; three or four is the usual number. Never do they approach in size or form the large corpuscular bodies seen and pictured by the above mentioned observer in his experiments with ricin and other equally virulent poisonings. I looked very carefully for these, but neither here nor in the rabbits' cerebra was I able to detect them.

In sections, purposely over-stained, an excellent exhibition is made of the not infrequent enlargement of the main apical processes of the cell bodies. This feature is usually a part of a general enlargement of the entire cell. The basal processes of such cells and their proximal branches are also implicated to some degree in the swelling of the cell body. Slight bulging and dentation is observable in the margins of the processes close to the cells from which they originate. Where enlargement of the cell bodies and their processes is extreme the pericellular spaces are either obliterated or narrowed almost beyond recognition.

Besides the above noted alterations in the cell body there is to be observed a more grave and advanced atrophy wide spread through all cortical layers. Sharply defined and regular contour now no longer obtains. A slight crenation of one side of a cell foreshadows the extreme atrophy that has occurred in another not far removed from it. The

crenation may be extreme and affect the whole outline of the cell body, or there may be more than mere crenation. The cell may be puckered or shrivelled, and its protoplasm reduced to an irregularly thin amorphous layer which closely embraces a shrunken homogeneous nucleus. Other cells are ragged in outline with alternate rough projections and deep or shallow bays with frayed margins. In the latter lies a granular *débris* which is more deeply stained than the cell protoplasm from which it has not improbably been shed. Rarely extreme examples of this are to be seen in which the nuclei are eroded in that segment which is in contact with the disintegrating sector of the cell rim.

The process of disintegration in some instances has not stopped short of almost total destruction of the cell body. In the most remarkable examples the peri-cellular space now contains in its median or lateral aspect a mass of deeply stained granular *débris*. From the edge of this a fine strand or two, very pale, or irregularly stained, may pass to the margin of the extra-cellular space. Doubtless these are the remnants of once healthy cell processes.

The above described morbid change is certainly one of advanced degree and not far removed from a final disintegration of the whole cell and its appendages. Whether or not many cells have actually split up and been removed by the lymph stream is hard to determine. I looked carefully for absolutely empty cell spaces and found none. In every one that caught my eye was a cell, normal, or in one of the grades of degeneration already mentioned.

Turning now from the proper cortical cells to those whose function is mainly one of support, it may be seen that they are implicated in a slighter degree. A few of the neuroglia nodal points have swollen to twice their normal dimensions, and are pale and granular. Only one or two deeply stained molecules are visible in such. A considerable number is shrivelled up into some aberrant form. They may be kidney, or pear-shaped, and crinkled in part, or in their entire margin. Deeply stained throughout they exhibit no interior molecules and contrast remarkably with the normal nodes in their neighbourhood.

Both types of degeneration prevail almost wholly in the grey cortex, only rarely can an altered glia-cell be observed in the subjacent medullary substance. In the deeper parts of the white matter the support cells are all regular in outline, round, and both their chromatic and achromatic substance is in a perfectly sound state. This is of course what might be expected from the known action of potassii bromidum on the central nervous system, and is certainly a strong point in favour of the change which has affected the proper cortical cells being the result of the action of the excessive doses of the salt given in mistake in this case.

Histological Appearances by Berkley's Silver-Phosphomolybdate Method.

In comprehensive and trustworthy research on the nervous system it is necessary to supplement one method by others.

Berkley has recently given us a method which is apparently adequate as a means of demonstrating the morbid changes in the protoplasmic extensions of nerve cells. Using this mode as described in the 1895 winter number of *BRAIN*, I obtained good results. Golgi's, and Cajal's methods had been tried upon some of those portions of cortex which had been hardened in Müller's fluid, but with unsatisfactory results.

But cursory examination of the proper cortical tissue successfully stained by the silver phospho-molybdate shows that a severe process has been in operation. Destruction of cell bodies and their appendages is as extensive as that shown by the aniline stains.

Breaches of continuity have happened widely in both axons and neurodendrons, and their alignment is now indicated by globular or club-shaped detritus, or else by well preserved segments. This phase in the cells is, in part, an artefact. For, unfortunately, the tissue was overhardened in Müller's fluid and thus rendered somewhat brittle. The microtome knife, therefore, broke through portions of the dendritic processes and their buds. These, however, generally

lie close to their parent cell. Yet in some instances they have disappeared altogether, probably washed away in the process of clarifying and mounting.

It is therefore not easy to determine just where the pathological process ends and the accidental changes begin. So that we must guard against interpreting purely manipulative alterations as changes caused by the poisonous action of the potassii bromidum. Therefore, I have controlled the investigation by observations on other human cerebra that had suffered exposure to the same laboratory conditions. A further difficulty is presented by our ignorance of the action of nitrate of silver on adult nerve tissue which has been altered by disease or *post-mortem* exposure.

On the whole, silver has not yet proved itself to be the ideal stain for the investigation of neuro-pathological changes.

Yet since the attempt first made by Kronthal¹ to use the chrome-silver, many other competent workers have entered the field and have overcome in some degree the difficulties met with in the use of the Golgi method when applied to the investigation of suspected morbid alterations in adult cerebra.

Greppin,² in 1893, Colela,² and Golgi⁴ himself in 1894, and later in the same year Klippel,⁵ Azoulay⁶ and Andriezen,⁷ gave us results obtained by them. All of them also offered them with more or less apology for the possible imperfection of the chrome-silver method.

In 1895, Monti⁸ of Pavia, in an experimental research into the effects on canine cortical cells of artificial embolism, achieved happier results.

But it was not until Berkley,⁹ of Baltimore, carried out by his improved Golgi method, his series of investigations on artificially induced lesions in the cerebral cortical, and other brain cells of rabbits, that we had a trustworthy demonstration of degeneration of cell appendages by the silver method.

By the use of his modification of the silver method, I find the following departures from the normal which were foreshadowed by the Nissl and polychrome stains.

In all cortical laminæ are cells which are in some stage of degeneration. No stratum appears to have escaped, and the atrophied cells in any one layer agree so closely in number with those in any other, that any difference may be passed over. The change is likewise similar in all, although it seems that the pyramidal cells are most deeply implicated. Because of this and the individual importance of the pyramidal cells attention will in the main be confined to them.

Fig. 1 is a good example of the least degree of change observable in the cortical cells. The cell body is irregular in outline, slightly enlarged when compared with the healthy pyramidal cells, and presents in some part of its rim, blunt cusps which alternate with deep or shallow concavities.

If the primal ascending dendron is followed to its visible termination, several ampullous or varicose swellings of varying size are met with, separated from each other by longer or shorter stretches, not different in form from health except that a great many lateral buds have been shed, thus leaving the stem bared for short distances. The thrown off buds, however, lie on the surface of the section not far removed from the bared margin. Their dislodgement is without doubt manipulative. Quite different from this, is the denudation presented by the before-mentioned varicosities; these are clearly defined in outline and absolutely budless. The tissue in their neighbourhood, except rarely, contains no signs of shed gemmulæ and these are probably a few of those already mentioned as thrown off, but in this case more widely separated from, the healthy portion of the process.

On the basal processes also varicosities are to be seen, but they are small, and like those on the ascending protoplasmic process, are sharp in outline and shorn of the lateral projections which obtain on the unaltered part of the extensions. One may be seen on each secondary branch and ranges in size from a small and scarcely recognisable to a readily obvious swelling. None of them, however, reach the dimensions of the swellings on the apical projection and its branches.

On the latter parts the varicosities follow each other in

more or less rapid succession, elliptical, round or oval, and all of about the same transverse diameter. The visible tips of the off-shoots from the main stem may end in an oval

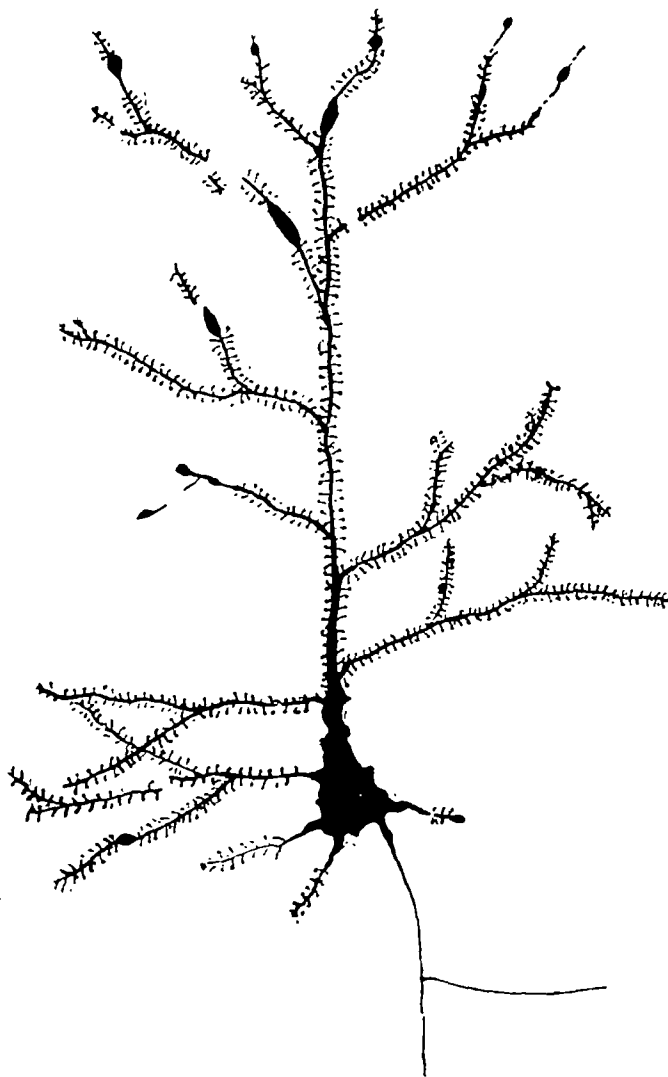


FIG. 1.

Cell body and extensions from the chief pyramidal layer of the human brain. Body covered with projections. Swellings on the dendrons. The break in continuity is artificial.

or sack-like enlargement of great relative magnitude, but generally, however, they are smaller than those observed on the main apical process.

Where branches are given off from the secondary apical processes, and at their splitting point into tertiary ramifications, enlargements are also to be seen; but these are generally forked in shape, thus conforming to the bifurcation of the stem, and in most instances have retained the mossiness of the healthy part of the stem. It is hardly likely, therefore, that these swellings are similar in origin to the first-mentioned, which are denuded of buds.

The axis cylinders of the cells not more deeply implicated than those described are intact so far as they can be traced. Unfortunately, this is not for any great distance, because in most sections they are broken off and carried away.

Cells in the state described above are on the whole not great in number compared with those showing advanced deterioration.

Fig. 3 shows to what an extreme condition many of the cells have been brought by the action of the poison. The cell bodies are irregular in their outline, not infrequently deeply excavated in some one aspect, and showing more ragged cusps than less involved cells. Where processes exist (and the most persistent are the apical), they are swollen, and coarse close to the cell, and farther out are the seat of bulbous enlargements. In this stage of atrophy, however, the latter are larger and more numerous on the basal extensions than on similar parts of the previously mentioned cells. A pathological fragmentation has occurred here, and the globular or granular remains of the smaller pieces yet remain to indicate that the processes were sundered by a morbid rather than manipulative process.

In such cells the various processes are swollen close to the cell body, and after a short course into the sustentacular tissue they end in an oval or round bare swelling. But the ending may not be so abrupt. A gradual dwindling is obvious as the course of the protoplasmic process is followed outward and the ultimate termination may be sharp. Beyond many of such terminations are small, or larger,



FIG. 2.



FIG. 2.



FIG. 3.



FIG. 4.

Extremely degenerated pyramidal cells from the human brain. Excavation, wasting, and disintegration of the bodies is seen. Also budless swellings on the protoplasmic extensions and thinning and disappearance of the distal parts of the latter.

sharply defined oval, round or rod-shaped masses. They may be shed portions of the degenerated processes which now serve as a contact body for a silver deposit, or they may be simply a precipitate of the latter agent itself, having no structural basis, although the sections as a whole are remarkably free from "blobs."

The primal apical process at, and for some distance above, the cell from which it takes origin is ragged in outline and on one or other side displays a single jagged excrescence or a series of excrescences. Farther up the stem may be in no wise unsound for a short distance; yet sooner or later varicose enlargements are met with bereft of buds and altogether similar in aspect to those already described.

Only rarely in examples of degeneration to the degree portrayed in fig. 3 can an apical dendron be traced to any great distance from its cell. A pointed or globular ending is usual in the upper layers of the external pyramidal lamina. Beyond this, *débris* marks the alignment of the process. A globular, sharply defined mass, an attenuated black or more lightly stained line or two, or a moniliform thread with scarcely recognisable lateral projections yet remain of the once healthy extension. The secondary branches are in most cases reduced to mere stumps, with here and there along their short course thinned truncated remains of tertiary twigs.

The axon of cells so far involved is yet almost intact. But a swelling of it is to be observed close to the base of the cell from which it takes its departure, quite twice the size of the similar part of the process of the healthy cells. No doubt it portends the absolute loss of the axis cylinder which has occurred in fig. 4 and other cells about to be described.

A still more extreme stage of degeneration is that pictured in fig. 2. The cell body may be roughened in outline and shrunk to one-half or one-third its normal dimensions. It is surmounted by a withered ragged-edged process whose secondary branches have disappeared *in toto*. Such an apical process is of short length and gradually dwindles from its base, and finally ends in an attenuated

termination, beyond which lie a few black or deep brown dots and dashes not unlike a "Morse Code;" the probable remains of the once sound structure. Basal prolongations have disappeared almost entirely. Some evidence of the axis cylinder is yet visible, however, in the swollen stump coming off from what was in health the base of a cell; but beyond this the structure is not observable.

The possibility of *post-mortem* alteration is best considered at this stage.

EFFECT OF POST-MORTEM CHANGES.

Pieces of human cerebrum were exposed to conditions as nearly as possible of the same nature as the diseased brain, and then used as control.

Such control tissue showed with aniline dyes a slight over-staining of the achromatin of both the body and nucleus of the cells, but no loss in number of stichochromic particles in the former, or the larger molecules from the latter. The dust grains of the nuclei were also obscured or lost to view in the unusual colouration of the nuclear matrix. The nucleoli, however, were well stained, smooth, round, and sharply defined, and presented none of the aberrant forms and appearances described. No angular particles were visible in the nuclear vesicle, nor was the vesicle itself dislocated except rarely, and its outline was sharp and circular, or oval. Occasionally a cell appeared to be enlarged but never ragged in outline, or with its margin undergoing a process of disintegration. Shrinking or plication was not visible in any of the cells.

When stained by the silver phospho-molybdate method axons were found to retain their position, but were occasionally enlarged close to the cell if the cell itself seemed enlarged. Such enlargement was also noted to be a feature of a few basal and apical protoplasmic extensions. But the withering of cell bodies such as seen in fig. 2, or the dwindled extensions of figs. 2, 3, and 4, were not observable. Nor in any instance were there present the varicosities shown in figs. 1 and 3, except (rarely) at the forkings of the secondary

and tertiary branches. Lateral gemmulæ were present and well stained in most instances, but whole stretches of many processes both apical and basal were stripped of them; yet they were to be seen scattered through the section, and may therefore be looked upon as accidentally disengaged from the parts to which they belong. This observation is further strengthened by the fact that, in sections purposely cut thick so that processes might be seen between the upper and lower planes without actually appearing on the surface of the section, the lateral gemmulæ were found to be in position, although on account of the thickness of the sections they did not show with the same sharp definition of the thinner sections.

Of considerable importance also is the fact that in every instance observed by both aniline and silver stains the nodal points of support cells and their extensions are healthy. None of the aberrant shrunken forms mentioned in connection with the morbid brain are to be observed.

It seems likely, therefore, that the more marked deformities presented by the cerebral cortical cells in this case are due primarily to the deleterious action of the extreme doses of the bromide. The altered histo-chemistry of the nuclear fluid whereby the dust grains are lost to view may be the result of the *post-mortem* exposure which the encephelon underwent; and so also the occasional enlargement of certain cells and the beginnings of their processes. But the disintegration of the cell margin, the loss of figure, and change in staining quality presented by the nucleoli, the appearance of the foreign angular particles within the nuclear sack, must be regarded as degenerative.

The bulbous enlargements of various sizes, the disappearance from them of the rectangular buds, the shrinking of processes in cells more deeply implicated, and the ragged edges and excavations of cells, together with the withering and distortion of the latter and the disappearance of their axons, can only be looked upon as the work of a violent poison which operated during life. This conclusion is supported by the action of the same poison on the cortical cells of the rabbits as I will now proceed to show.

EXPERIMENTS AND OBSERVATIONS UPON RABBITS.

Four rabbits were used in these experiments which were treated in the following manner:—Rabbit No. 1 received by means of subcutaneous injection 36 grams of potassium bromide in twenty-two days; rabbit No. 2, 40 grams in twenty-four days; rabbits Nos. 3 and 4, 36 grams in twenty-two days.¹ Following upon the first injections the animals became drowsy and inactive, refused all food, and remained in the corners of their cages for a few hours. When disturbed their movements were slow, automatic, and were quickly followed by quiescence and renewed somnolency. At first they recovered full power of mentality and movement, and were lively in action and appetite, in the intervals between the subsidence of the effects of the drug and its next administration. But after the eighth or ninth day, the drowsiness and depression of motility became gradually prolonged, and the animals passed into a state of stupor and began to lose flesh. Fifteen days saw greatly increased depression of both mental and motor functions, and the sensory faculty became so benumbed that the animals no longer protested against the prick of the syringe. The effects of the injection here began to blend one with the other, and the phases of recovery observed at first were not again noticed. From now on the animals scarcely moved unless disturbed, and action following stimulation was purely automatic. The fore legs soon became paralysed, but the hind limbs still retained some power. Reflexes were de-

¹ At first I experienced considerable difficulty in administering the bromide of potassium to the rabbits on account of its extremely irritant action at the point of injection into the subcutaneous tissues. As I proposed to get the psycho-motor cells affected as early as possible with poisonous quantities of the salt, it was necessary in order to accomplish this, that large daily doses be given. When the extremely irritant action of a concentrated solution of potassium bromidum is called to mind, it may be readily imagined that the animals proved rebellious to 1 or 2 grams injected under the skin at one point, and that inflammation in the neighbouring tissues speedily supervened. Such indeed was the case, but this was escaped from by diluting my solution from the 1—8 strength of the first injections, to 1—9, and then injecting 12 cc. at three different places at the same time once a day. With this change of plan, irritation and inflammation at the point of injection were reduced to a minimum, and after the first ten days no pain seemed to be experienced by the animals, either as a result of the puncture, or of displacement of the tissues which occurred to make room for the fluid.

pressed excepting the conjunctival. There appeared to be no great desire for, nor was there any movement towards, food; yet this would be taken slowly but without relish if placed within easy reach. About the twentieth day stupor of high degree supervened, and two days later it was followed by deep coma, accompanied by complete neglect of food, loss of sphincter control, and absence of all mental and motor manifestations. All four animals presented a picture of total inertia, bar an infrequent and weak prolonged respiration, or an occasional twitching of the nose and ocular muscles.

As now death seemed inevitable if the drug was pushed any further, a halt was made and a chance given to the animals to recover. But during forty-eight hours, the inertia continued, and it seemed that a necessary quantity of the bromide salt had been given to produce a maximum and fatal effect.

To insure a perfect preservation of the finest and most delicate constituents of the cerebral cortical cells and their appendages, the animals were bled to death, and their cerebra placed in either alcohol or Müller's fluid. But a few minutes elapsed between the bleeding and the immersion of the organs in the fixing media.

Chloroform, ether, and other drugs, were purposely avoided in order to evade any possible complication.

As brains Nos. 1 and 2 were intended for examination by the silver method they were placed in Müller's fluid. The control for these was carried through the same fixing solution.

Brains Nos. 3 and 4 were fixed by graded alcohol. The control for these was treated in the same courses of alcohol. At the end of two weeks the organs were passed through celloidin, cut, and stained by Nissl's polychrome and hæmatoxylin-eosin methods.

CHANGES IN THE RABBIT'S BRAIN AS SHEWN BY NISSL'S AND THE POLYCHROME METHODS.

The control brains in none of over three hundred sections show departure from the normal, but this is not so in the cells of the poisoned rabbits.

Some stage of degeneration is so universal that I gave up trying to arrive at the proportion of diseased cells to those yet in health, and therefore reversed the calculation to an estimate of the ratio of sound bodies to those showing atrophy. About three times in every field, as shown by Reichert 1-18 objective, a cell approximating to those of the control cortex could be observed. The average number of cells that appear clearly in any single plane of a field is about fifteen. So that the proportion of normal cells to those in some stages of atrophy is about one to five. This is a rough calculation only, but it will indicate in some measure how widespread has been the action of the bromide, and also that probably no single type of proper cortical cells escaped the effect of the drug.

Cell bodies, their processes, in fact all the constituents of the cells may be involved together, or only one or other.

But a minute description of the atrophy is called for, because of its likeness in many features to that in the human cortical cells, and also for the reason that it places beyond cavil the observations made upon the human brain by Berkley.

Cells in an incipient stage of degeneration are not so numerous as in the cortex of the human cerebrum. But though proportionately not so numerous they are yet present, and indicate what is probably in the cell body, at any rate, the beginning of the poisonous action of the drug. Such cell bodies may be quite regular in outline but more often a slight crenation is noticeable on one or other side of the cell, or the entire margin may be markedly dentate. In the latter case there is a slight colouration of the ordinarily clear hyaloplasm, and therefore an obscuration of the stichochromic granules. But I cannot say definitely that any of the latter have disappeared; compared with those in an absolutely healthy cell in the same section or in the control tissue, they do not seem diminished in number.

The nuclei of such cells have not escaped. Whenever the cell body is affected, no matter in how slight a degree, nuclei show some departure from health. Their membranes are delicately wrinkled in some one sector, and perhaps

plicated but well defined in the remaining portions; or the whole membrane may be crinkled, and at the same time deeply plicated at some one point, and irregularly stained.

The internal constituents of the nuclear vesicle have undergone a change, but of slight degree, in these slightly affected cells. The achromatin is blurred and has lost its high degree of refractility. Fine nuclear dust is obscured by the over-colouration of its matrix, and the larger molecules are reduced in number. Only rarely can more than two or three particles be observed in the sack. Nucleoli are deeply stained throughout but are no longer round and clearly defined. Their edges are now delicately granular either in one or more short segments or throughout.

Cell bodies more altered than those described above are very common. In fact they form the great majority of all unsound cortical cells. The outer edge of a cell may be markedly wrinkled throughout and in some cases show a deep plication which has bent the nuclear sack inwards at the point of impingement. The cell margin also is deeply stained, but the remainder of the hyaloplasm may in such a case be clear or only delicately tinted. Not always, however, is the over-staining of the edge of the cell uniform throughout; its periphery may show in parts a finely granular refractile substance which has escaped the persistent action of the reagent and which probably foreshadows the ultimate breaking down of the whole cell. The hyaloplasm not yet absorbed is clear but almost devoid of chromatin granules.

The nuclear ring is crenated or deeply plicated. In many instances it is not discernible in its entire circumference. The beaded appearance of slightly involved cells no longer prevails. Now, comparatively large portions of the membrane are finely granular and etiolated and have interposed between them deeply stained smaller portions, or badly defined globules. In some instances the greater part of the nuclear margin is scarcely distinguishable but seems to be disintegrated and about to coalesce with its matrix and the yet remaining hyaloplasm.

The nuclear fluid is altered in quality; it is not highly

refractile, it does not stain deeply, but faintly, and finer dust particles have either absolutely, or in great measure disappeared, but there is on the other hand an increase in the size and number of the larger molecules in many nuclei. Eight or nine is not an unusual number and they range in size from twice to three times the size of normal nuclear molecules as seen in control specimens. In shape they are never round, but angular. They are similar to the large foreign particles recorded in connection with the altered nuclei of the human cerebral cells.

The nucleoli may be oval, eccentrically situated and intensely stained at one or both ends, the intervening part being pale and finely granular. On the other hand they may be faintly stained and swollen to twice or thrice their normal dimensions, and with delicately granular margins of the same degree of colouration as their bodies. The latter feature seemed to be due not to an aggregation of nuclear dust, but rather to a complete granular transformation of the nucleolus itself. In such a case a nucleolus, could it be seen in its entirety, would present a punctate surface, but in cross section it presents only a delicately granular margin. Prevalent, but less common than the above described state, is a nucleolus stained so that it resembles a crescent. One aspect may be coloured as a sharply defined crescent, but never so deeply as a healthy nucleolus. The remainder of the structure is in such a case scarcely obvious because it is pale and ill-defined.

This state of the nucleoli appears to be the precursor of the foreign angular particles that I find both in the human and rabbit cells, and which were first described by Berkley. First of all there seems to be a swelling and spongy change of the nucleolus, hand in hand with this an alteration in the chemical property of the structure whereby it stains aberrantly, and finally a disintegration into several particles which now separate and lie in the nuclear matrix as the foreign molecules.

When describing the state of the nucleoli in the human cortical cells it was pointed out that occasionally they were enlarged and arrayed in short club-shaped or pointed spurs.

On the whole such a state was rare. But in the cells of the lower animals the condition is met with often.

A still more extreme stage of degeneration of the whole of the cell body is not infrequent. In about every twenty, or twenty-five cells one is to be seen in a degree of degeneration not far removed from total destruction. All components are embraced in the wasting. A thin deeply stained, or irregularly stained, plicated membrane is all that is left of the body plasm and this encompasses an intensely dyed and puckered nuclear sack. The membrane appears to be formed of altered hyaloplasm. In many cases it is granular and pale in parts, or may have broken down into a loose *débris* which now spreads outward into the pericellular space. The crenated margin of this membrane may stretch across the angles of a plicated nucleus, thus forming tiny bays in which rests a minute quantity of clear hyaloplasm. Or the latter may not be wholly amorphous, but contain a granule or two similar to, but larger than, the stichochromic particles of the sound cell.

In yet other instances the altered cell plasm, very deeply stained, may closely embrace the shrunken deeply stained nuclear vesicle and be almost indistinguishable from the latter. The form of the whole cell may be long and ellipsoid, oval or round. No dust grains are visible in the nuclear fluid of such cells but the whole achromatin is intensely stained and may contain the large angular particles that obtain in cells already described. When they are found they are of even deeper hue than the matrix in which they lie.

It will be noticed that there has been no mention here of swollen or enlarged cells similar to those found in the human cerebral cortex. I looked carefully for them but saw none. The atrophy of cells in the rabbits' brains has been widespread and extreme, but it appears from its inception to its most extreme degree to be one of shrinking, and chemical and molecular rearrangement. It is doubtful, therefore, whether the enlargement of the numerous cells in the human case is an actual phase of degeneration induced by the action of over-doses of the bromide salt.

In many ways, however, the atrophy observed in the lower animals agrees with that seen in the human cortical cells. The altered reaction to dyes of both body and nuclear plasm, the disappearance of stichochromic granules from the former, and of dust grains and larger molecules from the latter, the appearance of the foreign angular particles in the nuclear vesicles in both, and the aberrant staining and form of the nucleoli of each are changes of a like kind, and point to an irritation of the cells by a similar agent. So also do the more extensive alterations in the cells:—the marked shrinking of both body and nuclear sack, their ragged edges, and their partial breaking down and absorption.

True, there are divergencies in the type of degeneration in the two species of cells possibly explained by the differences existing between the human and animal cells. In the rabbit eccentricity of nuclei is scarcely ever recognised, while such prevails widely in the human cortical cell.

Here as well as in the human cortex many nodal points of the support tissue are unsound. Scattered indiscriminately through the cortex are many cells with markedly wrinkled outlines and amorphous deeply stained bodies. These present no constant form, but may be deeply notched on one or two opposite sides or irregularly kidney-shaped. On the other hand, a smaller number are large, much larger than any in the control sections, pale, and their granules scarcely stained. It is a noticeable fact that here as in the human case, below the innermost cortical layer few affected support nuclei are to be seen.

BLOOD-VASCULAR CHANGES IN THE RABBIT CEREBRA AS SHOWN BY THE ANILINES.

Contrary to the conditions in the human pia-mater I found on exposure of the rabbit cerebra that there was no injection or oedema. The brain surface was anæmic and dry. It is quite possible that the mode of death of the animals accounts for these conditions; for they were bled to death.

Microscopic examination of the vessel walls shows the swollen endothelium, and bulging nuclei, which in some instances project and come in contact with the opposite wall. But the capillaries appear collapsed and are almost devoid of corpuscular elements. The median sized and larger vessels are also nearly empty but their endothelial nuclei are swollen, bulging, and deeply stained. Their size and affinity for dye is far in excess of those of normal endothelium. The peri-vascular spaces are in most instances full of a fine granular detritus. But on the whole the disturbance in the blood vascular system of the pia and cortex is slight and not so noticeable as in the human brain.

HISTOLOGICAL CHANGES IN THE RABBIT CEREBRA AS SHOWN BY BERKLEY'S SILVER PHOSPHO-MOLYBDATE STAIN.

As before, the pyramidal cell will be the chief subject of study. And I may say at the outset to avoid repetition that this cell has to all appearances borne the brunt of the action of the potassii bromidum. It is more often and more extremely affected than those of other form and position, but in those others nevertheless the kind of atrophy is exactly similar to that in the principal psychical cell.

By comparing camera lucida sketches Nos. 5, 6, 7 and 8, with those from the human cortex no great or essential discrepancy may be detected between them. In fact, so closely do they resemble each other that they are almost interchangeable and one might be used to illustrate the other.

Cells not deeply affected by the poison are visible in greater number than in the human case; but this may be apparent rather than real. For in no section of the latter are there so many cells shown as in the case of the animals. Yet the lesion is virtually the same. We find a slightened roughened body such as in fig. 5, or one that wholly normal shows on its processes bulbous swellings altogether similar.



FIG. 5.

Early degeneration of a pyramidal cell and its dendrons in the cortex of the rabbit.

to those observed in the case of the man. In every instance observed the swellings are devoid of buds, and, therefore, contrast remarkably with the apparently normal rest of the dendrons. Here the artificial disengagement of the lateral projections which has occurred widely in the human cortical cells has not taken place, for by more careful management the tissue was not allowed to over-harden.



FIG. 6.

Pyramidal cell of the rabbit, showing excavation of the body, and wasting of secondary and tertiary branches of protoplasmic extensions. In this, the extremity of the ascending process has wasted.

Fig. 5 shows truthfully the condition of many of the pyramidal cells. As in the human case the primary ascending process and its first and second twigs are more noticeably implicated than are the basal and their branches. Many cells are visible (fig. 6) in which the apical process

has dwindled, and the off-shoots are altogether wasted or scarcely recognisable on account of their great attenuation. But either where the processes still exist, or where they have disappeared, we find the characteristic varicosities marking their alignment. These are in many cases plentiful in number and various in size and form.

Along the emaciated protoplasmic filaments (fig. 7), there appears to be a scarcity of, or wasting of lateral gemmulæ; and there are but a few detached ones to be observed in the adjacent tissue. Where sections were purposely cut thick, and with the use of strong illumination, it was determined that even in protoplasmic processes in the depth of the section, the rectangular buds were decidedly small in number, and it was not unusual to see an entire absence of three or four from one side of the stem, while the other side was apparently healthy. They could not have been disengaged by the microtome knife. It is possible of course that owing to some delicate chemical change they have not stained. Yet the cell bodies and the extensions themselves, even when attenuated were deeply blackened, and in perfectly normal cells in any of the sections no lateral buds were detached. It seems possible therefore that the absence of the lateral buds is one phase, and probably an early one in the process that has caused the bulbous swelling, the wasting and absorption of the dendrons and the shrinking or distortion of the cell bodies.

Such a conclusion is borne out by the appearance of cells as portrayed in figs. 7 and 8. For in these the attenuation of protoplasmic prolongations is associated with a thinning out, and finally, in some instances, complete atrophy of the lateral buds. It is needless to point out that in the case of the swellings on the dendrons no matter of what size there is a complete absence of gemmulæ. And it need scarcely again be argued that this phase is degenerative rather than artificial.

Figs. 7 and 8 explain themselves. In them are seen shrinking and atrophy of the cell bodies. Excavation and roughening of the margins is often observable. The primal apical and basal processes are withered and shortened, and



FIG. 7.



FIG. 8.

More extreme wasting of rabbit pyramidal cells. The bodies are shrunken, and many basal processes reduced to stumps. The axis cylinder has also wasted.

bear upon them bulbous swellings of various sizes. Portions of the distal part of the extensions are visible in many instances as dots and dashes.

Still more extreme degeneration is not uncommon. All the processes of the cell may have perished from the poisonous action of the potassii bromidum. In such a case the cell body is reduced in size, distorted, and roughened in its margin, is not far from final disintegration and disappearance. How many have actually been absorbed it would be as unwise to speculate upon here as in the human case. But it may be concluded that some have absolutely disappeared considering the low ebb to which many have been brought. This may have taken place, and yet its influence on the economy of the cortex be of little importance. For it is not to be believed that the absolute removal of a small number of cells would be productive of so great a psycho-motor disturbance as the slight affection and therefore disturbance of function of a great many.

The axis cylinder in the experimental cases is worthy of consideration, and permits of more complete observation than in the somewhat over-hardened human cortex, because of its not having been accidentally detached. In cells such as pictured in fig. 5, the axis cylinder processes are sound from their point of departure from the cell body to where they become lost to view in the medullary centre of the hemisphere. Their collaterals are likewise normal so far as they can be traced.

But in instances of degeneration such as portrayed in fig. 6, and in all types of more advanced atrophy, the axis cylinder shows degeneration either early or advanced. Seldom are swellings to be seen similar to those upon the dendrons. In all cases where they occur they are small, rarely exceeding twice the diameter of the structure they affect. Close to the cell body, the calibre is increased far in excess of the normal, and occasionally a corkscrew distortion occurs; but it appears to be a late rather than early phase of atrophy. It is never recognised unless the distal portion of the axis cylinder is deeply implicated or has absolutely disappeared.

The distal portion of the axis cylinder is always most

markedly attenuated, and is the first to show signs of solution of continuity. It would thus appear that degeneration of the axial prolongation begins with attenuation more extensive in the distal visible portion and its collateral than in the proximal part of its course; that this progresses to a solution of the distal segments, finally creeping upwards. This seems to be so in such cells as in fig. 6, in which there is the first positive involvement of the neuroaxon.

But in cells the bodies of which are intact as far as may be judged by the silver method the axial prolongation is sound in all its traceable length. But if distal degeneration occurs first, as seems to occur from observations upon atrophic axis cylinders, there is no gainsaying that even in the case of cell bodies which are apparently sound, and yet whose dendrons are withered and varicose, the ultimate ramifications of the axons may be in an incipient stage of atrophy.

No instance of cell degeneration has presented itself in which the body of the cell alone has suffered. If this is in the least affected its dendrons are also involved. The latter may be thin in all their length, the seat of budless swellings, and show signs of a break in continuity, and absorption of their distal observable extremities. On the other hand, I have not failed to see many apparently normal cell bodies whose dendrites are nevertheless the seat of a few small bulbous swellings and slight attenuation. All through the cortex it may be seen that the farthest removed portion of a protoplasmic extension is the first to betray the action of the bromide salt and to become absorbed. Swellings may obtain in any part of its length, but atrophic solution of continuity never occurs close to the cell body without there having been first of all a thinning and absorption of a great stretch of the terminal end of the process. Death is from without inwards in every case. But it is hardly probable that the cell bodies remain unaffected for any great length of time, for marked implication of the protoplasmic extensions, and especially of the primary ascending one and its branches, is associated with a rough edged, shrunken or excavated cell body. Great atrophic involvement of cell

bodies is associated with attenuation and absorption of the neuroaxon. It is difficult to decide, however, whether the affection of the ascending process is really primary, or only primarily obvious. There is to be kept in mind the possibility that a slight, unrecognisable implication of the cell bodies may have first occurred and thus rendered all the ramifying processes defenceless against the poisonous action of the salt.

Another point worthy of note is that there appears to be no relation whatever between the degree of atrophy in either proper or support tissue and the position or size of the blood vessels. Those cells which lie close to a blood vessel of any size are not more involved than others relatively far distant. The salt evidently finds every part of the cortex equally accessible, although its greatest degenerative effect is beyond doubt upon terminations of all nerve cells and more especially those of the chief pyramidal layer.

CONCLUSION.

There has occurred then beyond doubt a change in the proper cortical cells and their appendages, and to a slighter degree in the support and vascular tissue in both the man and rabbits as a result of the action of pronouncedly toxic doses of potassii bromidum. In the case of the man there is reasonable room for doubt as to whether the whole of the abnormal changes presented by the nerve cells is entirely due to the influence of the salt. But after making all possible allowances for fortuitous complications, there yet remains a series of changes in them which cannot be attributed to a cause other than the suspected one; and this is substantiated by control observations, and by experiments upon the action of the same cause on the cortical cells of rabbits.

If under the same environment and dosage of bromide for the same length of time, there had been a radical or even noticeable difference in the kind of atrophy in the nerve cells and their appendages of any one of the cerebra,

it would have opposed such a conclusion and rendered the experiment of little value as a control for the human cortex. Moreover, the severity and extent of the cortical change in both the man and animals is no more or less than what was to be expected in view of the psycho-motor phenomena which they manifested during the period they were under the active influence of the drug. And this leads to the question of the mode of action of potassii bromidum when administered as a narcotic.

It is not disputed that bromide of potash when given in single excessive doses modifies in a marked manner the function of the central nervous system; that on the chief portion of this, the cortex cerebri, it is certainly depressant, interfering with the elaboration of thought processes and lowering the activity of the motor cells.

The *ante-mortem* phenomena, watched in the case of the man under conditions where there could be no possible bias, and in the case of the rabbits with a full knowledge of the force at work, corroborate fully the above opinion. The microscopical appearances both in the accidental and experimental cases of poisoning place beyond doubt the fact that toxic doses of the salt repeated at short intervals are capable of actually destroying the proper tissue of the important surface grey matter, upon which in physiological doses it operates not more than as an inhibitor.

Such being the case, the important question arises as to the manner of its action in the cerebral cortical area, whether it affects the bodies of the cells first, and thus the whole of each neurone, or whether it affects the bodies after a primary action on their delicate protoplasmic extensions.

It has been stated that in the cases of toxic degeneration under discussion many cells are observable in both classes of cerebra with normal bodies, but showing signs of atrophy (*i.e.*, bulbous swelling and attenuation), in the distal extremities of both basal and apical stalks and their branches; that on the other hand never can an even mildly affected cell body be seen bearing absolutely sound dendrons; and that in all examples where the latter are affected the atrophy in them is proportionately greater as they are followed to their ultimate visible ramifications.

Obviously, therefore, the visible degeneration began in that part of the cell spread farthest removed from the cell body.

Taking it for granted that that part of the cell structure which shows greatest disturbance from the action of any hurtful agent is the part upon which such an agent chiefly acts, it seems likely that potassii bromidum as a poison, operates principally upon the protoplasmic processes of the cells rather than upon the bodies themselves. I regret that I did not graduate the dosage of the salt in the experimental cases, for by so doing I might have determined the incipient point of the atrophy; this must be left for future observation.

But it seems justifiable to conclude that the drug in its mild action operates upon the ultimate termination of the protoplasmic extensions, and that therein lies its power of inhibiting intellectual and motor processes; first, by creating an undetermined chemical change in the delicate unprotected terminal knobs of the protoplasmic extensions and of their gemmulæ, which renders them obtuse to impressions brought to them by fibres from the periphery and from other parts of the encephalon. This does not necessarily imply an alteration in the degree of contiguity of the amyelinic knobs of either incoming or receiving cell extensions, but only a "psychical numbness," as it were, analogous to the physical numbness which occurs in the end-organs in the surface of the body under the effects of special agents. A widening of the normal breach between the terminations of the dendrons and gemmulæ is probably a later manifestation of the action of the drug, and may be due to its secondarily affecting the cell body, thus causing a general retraction of all ramifications of each individual neurone which Cajal claims is one of their attributes. The continued action of the drug on the dendrons in such a state would soon lead to the changes described in these specimens.

BIBLIOGRAPHY.

- (1) *Neurol. Centralblatt*, 1887.
- (2) *Arch. f. Psych.*, Bd. 24, 1893.
- (3) "Sulle fine alterazione della corteccia cerebrale in alcune malattie mentale," *Roma*, 1894.

- (4) *Berlin Klin. Woch.*, No. 14, 1894.
- (5) *Arch. de Neurologie*, 1894.
- (6) *Ibid.*
- (7) *BRAIN*, 1894.
- (8) *Bollet. della Soc. Med.-chir. di Pavia*, 1895.
- (9) *Johns Hopkins Hospital Reports*, vol. vi., 1897.

NOTE.—To Prof. J. Geo. Adami I am indebted for many useful hints in this work.

Towards the expense of this research a grant was made by the British Medical Association on the recommendation of the Scientific Grants Committee of the Association.