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FURTHER EXPERIMENTAL WORK ON BACTERIALLY-PRODUCED NERVOUS TISSUE LESIONS.*

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It has been demonstrated in a previous communication¹ that in lymphogenous infection of a peripheral nerve the lesion produced is interstitial in character; all the fixed tissues in contact with the infected lymph show a reaction which is of an acute nature at the site of infection focus, but becomes proportionately of a subacute and less active character in the portions of nerve more remote from the site of infection. The reaction is characterised by inflammatory phenomena, varying from a leucocytic and lymphocytic type to one in which plasma-cells are the predominant feature.

In the present series of experiments, in which bacteria have been introduced into the general circulation, it will be seen that the resultant lesion in the nervous structures is degenerative or destructive, and that it involves definite anatomical sites in the brain.

METHODS.

The entire brain was fixed in formol-saline 10 per cent., embedded *in toto* in paraffin, cut in serial section, and stained by the toluidin blue, Heidenhain's iron-haematoxylin, and Van Gieson's methods.

In the description of the nerve-cell lesions the term 'chromatolysis' will not be used, as the cells in the fornix, cornu Ammonis, and cerebral cortex have a small cell-body, and the chromophile material, normally, is of the finely powdered or amorphous variety. The term 'chromatolysis' or fragmentation of the chromophile material is therefore not applicable.

Coagulation-necrosis of the cell-body with homogeneous atrophy of the nucleus is, on the other hand, a very definite change, and easily recognisable by the intense affinity of the altered nerve-cells for stains, and their distortion and shrinkage. These appearances are indicative of active interference with cell nutrition, which is followed by necrosis and death.

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It is proposed therefore to adopt as a criterion of the lesion caused by the bacterial infection, the presence of the necrotic areas which were found in the fornix and cornu Ammonis.

The changes in the neuroglia have been, so far, observed in one experiment only. In order to preserve the complete anatomical continuity of the ganglionic laminæ in the brain, and as it was impossible to anticipate in which area of the cell laminæ a lesion might occur, the frontal pole was in each case chosen for special fixation of the neuroglial elements. Only in one instance was a necrotic area found to be included in this portion. The glial reaction will be studied more systematically therefore in another series of experiments.

DETAILS OF EXPERIMENTS.

RABBIT 1.

In the *fornix* of the *left* side there was a definite area of coagulation-necrosis affecting the nerve-cells of this structure in its *upper* portion. The necrosed area was situated at a point immediately inferior to that at which fornix becomes continuous with frontal cortex, and was sharply defined from the adjoining healthy portion by its definite staining reaction. In the necrosed area the nerve-cells, with their nuclei, were very deeply stained, altered in outline, and shrunken, thus showing a combination of coagulation-necrosis of the cell-body with homogeneous atrophy of the nucleus. The nerve elements of the contiguous portion of the frontal cortex were, for a short distance, similarly affected.

On the *opposite side* of the brain (*right*), but at the inferior end of the fornix where it is continued into the uncus of the temporal lobe, there was an area of coagulation-necrosis similar in appearance to, and as sharply defined from the normal as, that in the superior portion of the opposite fornix. The necrotic change also involved the cells of the uncus at the tip of the temporal lobe, and could be followed over it along the pyriform lobe as far as the rhinal fissure, and for a very short distance beyond. The remaining portions of the fornix were normal save for a few minute areas of oedema scattered amongst the cells.

There was another area of necrosis in the *right fornix*, in addition to that above mentioned, situated in the zone occupied by the second quarter of the fornix nearest to the frontal cortex. The necrotic area showed the typical characteristics of coagulation-necrosis with homogeneous atrophy of the nucleus described above, and appeared as a definite blue-black band of necrosed cells which was slightly but appreciably narrowed in depth and divided by a sharply cut line of demarcation from the normal cells on either side, in which the clear nuclei formed a striking contrast with those in the morbid cells.

There were many minute areas of oedema throughout the fornix, and this morbid condition attained its maximum at the left superior and the right inferior extremity, causing a considerable degree of distortion of the tissue with fragmentation of the neurons which could be followed through many sections of the series. Just behind this level the nerve-cells in the fornix were normal except in that portion immediately in connection with the uncus. In this, and in the superficial layers of the pyriform lobe, there were many necrosed cells.

The *cornu Ammonis* showed morbid changes in both its outer or *granular* layer, and its inner or *pyramidal* layer.

There were many small discrete foci of *oedema* in both cell-layers, causing a definite destruction and almost total disappearance of the nerve-cells at the points affected. Many of the cell-bodies and nuclei of the *outer granular* layer stained much more deeply than normal and showed no detail of structure, an appearance indicative of coagulation-necrosis of the cell-body and homogeneous atrophy of the nucleus. All areas of this layer however were not equally affected,

In the inner layer of small pyriform cells there was the same necrotic change. The cell-body and the nuclei stood out in bold relief as small deeply stained structures which, in many instances, were distorted. The necrotic change did not affect this lamina uniformly but in a somewhat segmental manner, though not in so rigid a fashion as in the fornix.

At the *posterior extremity* of the fornix the nerve-cells on both sides were perfectly normal. The nucleus was clear and the scanty surrounding protoplasm showed no abnormal reaction. There were, however, numerous small areas of oedema scattered throughout its entire length.

In the *posterior extremity* of the *cornu Ammonis* the majority of the nerve-cells showed the hyperchromatism of homogeneous atrophy of the nucleus, and throughout the granular layer were many small areas of oedema.

RABBIT A.

The *fornix* was practically normal from its upper extremity in the superior cortex of the brain to its lower connection with the uncus of the temporal lobe; nor was there any cell change in the pyriform lobe. The cell-layer of the fornix was seen as an unbroken line of clear nuclei surrounded by a narrow zone of faintly stained cytoplasm, and its continuation below with the superficial cell-layer of the pyriform lobe as far as the rhinal fissure was normal also. The only morbid change present in the above structure was oedema, which showed as minute and irregularly scattered areas.

In the *cornu Ammonis* of the left side there were a few scattered degenerated cells in the inner or pyriform cell-layer at the upper pole, and likewise in the same layer at the inferior end. In both these regions of the opposite side the cell-layers were normal.

RABBIT B.

There was a high degree of general oedema of the brain which necessitated prolonged **staining**. **The fornix had suffered severely**, the oedema not only interfering with the staining reaction of the cells generally but destroying them in **small patches**. The areas in which destruction had actually occurred were more numerous and larger in the upper portion of the fornix, and had caused a definite circumscribed loss of nervous tissue especially in that region of the fornix which is continuous with the upper cerebral cortex. In the centre of these oedematous areas no definite tissue existed—merely debris—while the periphery consisted of compressed, distorted, faintly stained cells. No further points could be brought out here by iron-haematoxylin staining.

The *cornu Ammonis* was very oedematous also, and this had caused minute and larger areas of destruction in both cell-laminae. The cells of both layers stained faintly by toluidin blue, thus resembling the reaction found in the fornix; but iron-haematoxylin staining brought out many scattered cells of a *small type** in the outer granular layers which stained heavily, especially in the superior half of this lamina. These necrotic granular cells were most numerous in the upper segment of the layer involving both margins for some distance, and the upper and lateral curve. The middle portion was affected to a lesser degree, while the inferior pole was practically normal. The necrotic zone occupied about one-third of the layer, its segmental character suggesting ischaemia as the mechanism of production. There were small discrete areas of oedema scattered throughout the necrotic zone which had led to a local loss of tissue. In the inner pyramidal layer there were a few scattered necrotic cells, and many small areas of oedema.

RABBIT C.

The brain tissue from this experiment was very oedematous throughout, rendering staining by aniline dyes a matter of considerable difficulty. In addition to this general

*Small diamond-shaped cells between the larger more vesicular-looking cells.

œdema there were many minute scattered areas of greater intensity which had caused minute circumscribed areas of destruction in the fornix, and in both granular and pyramidal layers of the cornu Ammonis.

In many of the œdematous areas either no nervous tissue could be defined, or the elements had been distorted and displaced. This applied to both the fornix and the cornu Ammonis. Where the elements were stainable by toluidin blue and had retained their form, both cytoplasm and nucleus were only faintly discernible and showed practically no detail of structure.

In the upper and mesial portion of the *cornu Ammonis* a few cells of the inner pyramidal layer were not quite so pale as the others, but their structure was very indefinite.

With the iron-hæmatoxylin stain many of the nerve-cell nuclei in the *fornix* stained a little more deeply and diffusely than normal, while the cytoplasm showed a similar change, giving to the cell a uniform grey black appearance in which the nucleolus alone stood out distinctly. In the outer or granular layer of the cornu Ammonis the nerve-cell nuclei, with very few exceptions, showed a marked affinity for iron-hæmatoxylin, and to such a degree that all detail of structure was masked by the diffuseness of the staining reaction. Owing to the œdematous condition of the tissue Van Gieson's stain proved of no value.

RABBIT D.

In this experiment the nerve-cell lesion was localised to definite sites in the fornix and cornu Ammonis, and was of a necrotic nature. The cells in the affected areas were distorted, shrunken, and showed a marked affinity for both toluidin blue and iron-hæmatoxylin, and formed a sharp contrast with the normal.

The *fornix* was affected on both sides, and at the same point, i.e., in the lateral curvature, midway between the upper and lower cortical regions. Above and below the necrotic area the fornix was normal, with the exception of a few cells at its inferior prolongation into the temporal lobe.

In sections taken at a more posterior level, towards the occipital pole, it was found that the areas of necrosis gradually disappeared. Each diminished in size though still preserving its definitely necrotic character; and it was observed that the lesion on the right side was more extensive than that on the left.

The *cornu Ammonis* on the left side showed little morbid change. The granular layer was quite healthy, but there were some scattered necrosed cells in the superior portion of the pyramidal layer. On the right side, a few of the cells in the granular layer were necrotic, but in the pyramidal layer there were three necrotic areas, two in the superior portion, and one at the inferior extremity, each separated by a small interval in which the nerve cells stained normally.

RABBIT I.

The *fornix* on the *right side* was quite normal, the entire structure showing as a continuous band of clear vesicular nuclei. The adjacent portions of the cortex, frontal on the upper surface and lower in the temporal lobe into which the fornix is continued, were normal also.

On the *left side* there was a small area of necrosis in the fornix situated at a point a little distance from its superior ending in the frontal cortex, and just opposite the superior pole of the cornu Ammonis.

This necrotic area was small, and occupied about one-fifth of the field under low power magnification (objective 16 mm. ocular no. 1) and was thrown into sharp relief by the normal clear vesicular cells on either side of it. All the remaining portion of the fornix was perfectly normal. The nerve-cells in the necrotic area were shrunken, deeply stained, and had lost all detail of structure.

In the *cornu Ammonis* there was a distinct difference in the staining reaction of the two sides. The pyriform layer on the right side was normal, but on the left side in the upper portion of this layer there were many necrotic nerve-cells situated at a point in the same

transverse plane as the necrotic area in the left fornix noted above. The remainder of the cells in this pyriform layer were normal.

The granular layer of both sides showed many cells of the small diamond-shaped type which stained intensely, and contrasted markedly with the larger and clearer nuclei of the vesicular-cell type normally found in this nerve-cell lamina.

RABBIT K.

There was a local lesion in the *fornix* of the *right side* involving its upper portion. It was sharply defined inferiorly from that portion of the fornix which sweeps towards the lateral aspect of the brain, but not quite so definitely on its internal aspect where the fornix cells join the mesial surface of the frontal cortex.

The cells in the necrotic area stained very deeply and both nucleus and cell-body were shrunken and distorted. In the outer portion of the necrotic area almost every cell was affected, forming a deeply stained and shrunken solid line; but more mesially the necrotic process had not affected all the cells of the fornix band, normal and necrosed elements lying side by side in a scattered discrete manner as far as the frontal cortex.

Immediately below this necrotic zone the fornix was quite normal for a definite segment of its course, but at a point mid-way between the upper and lower surface of the brain there was another necrotic area as sharply defined as the above. Here the degree of coagulation-necrosis of the nerve-cells was not quite so advanced as in the necrotic zone at a higher level; and the lesion did not involve the most inferior portion of the fornix where it approaches and is continued into the uncus of the temporal lobe. This latter zone was free from necrotic change.

In the fornix of the left side the cells were quite normal except for a few scattered necrosed nerve-cells at its inferior extremity and in the cortex of the uncus.

In the *cornu Ammonis* of the left side and in its inferior portion, the nerve-cells of the pyramidal layer were in the initial stages of coagulation-necrosis. Both nucleus and cytoplasm showed an increased affinity for the stain, and were diffusely coloured. On the right side there was a considerable number of scattered necrosed cells in the upper and more central portion of the pyramidal layer and in its middle segment.

If we contrast the two sides we find that in the right there are two definite clear-cut areas of 'mass' coagulation-necrosis which contrast sharply with the normal portions on either side of them, and with the normal fornix of the opposite side. The upper area of necrosis is of an earlier date, or of a more intense nature, than that of the lower, as shown by the deeper staining of its cells and their shrinkage. This shrinkage not only affects the individual cells but has narrowed the cell-band 'en masse' for a short distance.

SUMMARY OF EXPERIMENTAL RESULTS.

RABBIT 1.

Fornix—left: an area of coagulation-necrosis in the *upper* portion.

Fornix—right: an area of coagulation-necrosis in its *inferior* portion, continuous with necrosis of nerve-cells in the *uncus* of the *temporal lobe* extending to *rhinal fissure*.

A *third area* of coagulation-necrosis on the *right side* at a *point near the frontal cortex*. Minute areas of oedema causing cell destruction also present in both fornices.

Cornu Ammonis: in the outer granular layer, areas of oedema (minute): also coagulation-necrosis of nerve-cells in *both outer granular and inner pyriform layer*.

RABBIT A.

A slight degree of *œdema* of the *fornix*.

In the *cornu Ammonis* of the *left side* a few *necrotic cells* in the *pyriform layer*: on the *right side* both cell-layers of *cornu Ammonis* are normal.

RABBIT B.

A high degree of *œdema* with destruction of nervous tissue and a marked decrease in affinity for toluidin blue.

The *fornix* suffers severely from *œdema*, especially in its *upper portion*.

Cornu Ammonis very *œdematous* also, with nerve-cell destruction in both cell-laminæ.

With iron-hæmatoxylin, the nerve-cells of the *granular layer* in the *superior part* of the *cornu Ammonis* stain heavily. The *inferior portion* is *practically normal*. Many small areas of *œdema* amongst the cells of the *pyramidal layer*.

RABBIT C.

A high degree of *œdema*.

Small foci of destruction in both layers of the *cornu Ammonis*: staining reaction feeble with toluidin blue.

Cells of *granular layer* of *cornu Ammonis* show a marked affinity for iron-hæmatoxylin.

RABBIT D.

Fornix of each side shows a well defined *necrotic area* situated in the *lateral curve* of the *fornix*.

In the *cornu Ammonis* scattered necrosed cells in the inner *pyramidal layer* of the *left side*: *outer granular layer* healthy.

In the *right cornu Ammonis* the *granular layer* is *practically healthy*: the *inner pyramidal layer* shows three areas of *necrosis* separated from each other by a small interval of healthy tissue. The study of serial sections shows that the *necrotic area* in the *fornix* of the *left side* extends further posteriorly than that on the *right*.

RABBIT I.

Right fornix normal. In the *left fornix* a small *necrotic area* near its superior ending in the cortex.

Otherwise the brain shows no morbid change.

RABBIT K.

In the *upper portion* of the *right fornix* an area of *coagulation-necrosis* sharply defined from the normal below it. Immediately below this normal portion another *necrotic area*, as sharply defined as the above. The inferior portion of this *fornix* is *normal*.

In the *cornu Ammonis* of the *left side* the nerve-cells of the inferior portion of the *pyramidal layer* show the *early stage of coagulation-necrosis*.

The *cornu Ammonis* of the *right side* is *practically normal*. There are some scattered necrosed cells in the *central portion of the pyramidal layer*.

Coagulation-necrosis in rabbits I, D, J, K. In those there were necrotic areas sharply defined from the normal.

In *rabbits A, B, and C*, there was a *high degree of œdema*.

Definite *necrotic* areas therefore have been found in *four* of the seven brains examined ; in the other *three* there was a high degree of *œdema*, in spite of which, however, there is evidence of coagulation-necrosis in the heavy staining of the nerve-cells with the iron-hæmatoxylin method. It is reasonable to suppose that the presence of *œdema* has to a considerable extent interfered with the staining reaction in the last three cases, and masked the characteristic appearances of the necrotic change. Finally, it is worthy of note that there was no hæmorrhage at the site, or in the neighbourhood, of the necrotic foci in any of the experiments.

DISCUSSION.

In the cerebral cortex there are no gross lesions similar to the ischæmic softenings in the cornu Ammonis and fornix, but the nerve-cells exhibit varying degrees of coagulation-necrosis. A description of this morbid change has been already given, and the cortical cells show precisely the same morbid features and staining reactions so characteristic of this type of affection.

The coagulation-necrosis is not distributed in a uniform manner throughout the cortex. In the superior and lateral areas of the pallium the morbid change varies in degree from point to point, contiguous territories showing slight variations in intensity ; and all the cortical cell-laminæ are not involved in the necrotic change. For our present description we may divide the cortex from without inwards into : (1) molecular zone ; (2) external granular zone ; (3) pyramidal layer ; (4) internal granular zone ; (5) ganglionic layer ; (6) multiform layer. All these zones are not always distinct or present ; certain variations in cell lamination occur in different portions of the cortical field, but the layers as given above serve our present purpose.

The whole depth of the grey matter does not exhibit coagulation-necrosis of the nerve-cells. The morbid change includes all the outer layers as far inwards as the ganglionic lamina ; it is rare to find morbid nerve-cells in the deepest or multiform layer. In the outer layers the degenerated nerve-cells may be very numerous, or in fewer numbers, according as one passes from one point to another ; and granule and pyramidal cells are affected indiscriminately.

It is of importance to note that the above areas, viz., the cortex, fornix, and cornu Ammonis, are the seat of morbid changes, and that they are supplied by cortical vessels derived from the pia-arachnoid. We know that the central portion of the cornu Ammonis—the lamina involuta—is penetrated by folia of the pia-arachnoid accompanied by vessels. The affected areas therefore all possess one important point in common, viz., their blood-vessels are derived from the pial system, a fact which may explain the participation of the above-mentioned subcortical nuclei in the morbid process.

The morphological character of the lesions in the brain points very clearly to a disturbance of the circulation and therefore of nutrition. This, in the cerebral cortex, affects a wide area and finds its expression in the necrosis of nerve-cells in all strata, unaccompanied however by any local ischaemia indicative of complete vessel blockage. Evidence of a much more severe local nutritional disturbance is very obvious in the ganglionic and molecular layers of the cornu Ammonis and in the fornix.

A concise statement in reference to this subject will be found in an article on hæmorrhagic encephalitis by Bignami and Nazari², in which many important points are mentioned having a direct bearing upon this research. These authors have found that the lesions in the white and grey matter in hæmorrhagic encephalitis differ very materially, and their views regarding the cerebral circulation are based upon this. A sharp distinction is drawn between *miliary hæmorrhages*, which are characterized by their ring-like form round a necrotic focus and by their situation in the white matter, and the *hæmorrhagic infiltration* which follows thrombosis of the cerebral sinuses or meningeal veins. The hæmorrhage in this latter condition is extensive, affects the grey cortex, and decreases from without inwards. There are no necrotic foci surrounded by a ring of hæmorrhage such as occur in the white matter. According to the opinion of the authors both conditions are caused by a local disturbance of the circulation and not by an inflammatory process. In the one case the thrombosis of the cerebral veins induces hæmorrhage in the cortex from stasis; in the other, blockage of a precapillary arteriole results in a circumscribed necrosis in the white matter followed by hæmorrhage into the immediately surrounding parts from the collateral vessels, the pathogenetic mechanism here being precisely the same as in infarction of other organs. If a similar lesion is not produced in the grey matter, through occlusion of the arterioles, it seems more than likely that there is some difference between the circulation in the cortex and that of the medullary substance. These observations incline the above-mentioned authors to the view that, although the precapillary arterioles in the white matter are physiologically terminal, those in the grey cortex are not. In the white matter occlusion of an arteriole is followed by infarction; since the latter does not occur in the grey matter, evidently we must admit the possibility of an arterial anastomosis which is functionally adequate.

Many questions regarding the cerebral circulation are still only partially solved or remain obscure, but we are now in possession of certain facts which bear on the subject before us. All are agreed that the cortical arteries do not communicate with the basal arteries. Duret³ regards the cortical arteries as terminal, but Cordiat and Féré³ do not agree with this, although they grant that the anastomosis is not sufficient to permit of re-establishment of the circulation when obstructed by thrombus or embolus. Heubner³ supports the view that numerous anastomoses occur amongst the pial arteries, but adds that

after their branches have penetrated the cortex anastomosis ceases. On this latter point he is supported by Duret and Beevor, who hold that the cortical arteries are terminal ; but, in spite of these definite statements, it would appear that the whole question is worthy of further study, since it has been shown that the myocardial arteries are not completely terminal in the anatomical sense, as has hitherto been held.

Of great importance in the field of pathogenesis is a knowledge of the relationship between the short cortical and the long subcortical arterioles. Both are derived from pial arteries. The short are purely cortical, while the long pass straight down into the white matter, where each supplies a very narrow territory owing to the small number of branches given off. Cortical arteries divide at once and very frequently, forming a fine capillary network which is richest in the deepest cortical lamina. Further, it would appear that the short cortical arterioles anastomose in the depth of the grey matter with the long or medullary branches. The important point to be specially noted, however, is that the cortical vascular network is far richer than that of the white matter.

Whatever our present knowledge may be, from the anatomical side, of the ultimate distribution and connections of the cerebral vascular system, we seem to be justified in assuming from morbid lesions that there is a difference in the two systems which subserve the grey and white matter respectively. The evidence of this is seen in the histological difference between the *cortical* and *subcortical* lesions. The former are diffuse and consist in necrosis of the nerve-cell units ; the latter—in the cornu Ammonis and the fornix—involve a circumscribed locality and are typical of infarction. As the arterioles which supply the cortex and the adjacent subcortical zone have a common origin—the pial arteries—the difference in type of the resultant lesions must depend upon the anatomical arrangements of fine capillary branches. The definite restriction of the subcortical lesion with its pathohistological elements can only be interpreted as ischaemic in origin, and secondary to blockage of a terminal artery. But the pathogenic mechanism of the diffuse coagulation-necrosis of the cortical nerve-cells presents a more complex problem and is very far from clear. From the character of this lesion we can say definitely that no infarction has occurred, and therefore the presumption might be advanced that cortical arterioles are not terminal. The individual nerve units alone have suffered, and in a manner which points to interference with their nutrition ; but the histological picture is far from what one associates with an ischaemia, and rather suggests a stasis due to blockage of veins, a deficiency of nutriment from narrowing of the lumen of arterioles and capillaries, or both combined, as is most probable. It is only some anatomical factor within the cortex itself which could explain this different type of lesion, and for the present one would be inclined to ascribe importance to the richness of the looped cortical vascular network, which may counterbalance the effects of interference with the vascular

supply. This seems to be the most reasonable view to take of a question which is still controversial, and stands in need of further investigation.

Von Braunmühl⁴, in a paper which deals with the alterations in the brain in acute excitement, describes the changes in the nerve-cells and neuroglia especially; as he remarks, these structures stand in such close relationship to the circulation, that they react at once to its disturbance. He has found that some regions may be hyperæmic, others anæmic—the capillaries in the hyperæmic areas being unusually wide and packed with corpuscles. There is a widespread stasis and prestasis, accompanied by fine capillary hæmorrhages. The nerve-cells are pale, and protoplasmic processes necrotic and granular.

The lesion, he considers, is due to a spastic ischæmia, followed by paralysis of the capillaries which accounts for their congestion. In the pyramidal layer of the cornu Ammonis coagulation-necrosis of the nerve-cells, and homogeneous atrophy of the nucleus, were present. In the ischæmic areas of the cortex, the same nerve-cell and nuclear changes were observed, accompanied by a secondary glial proliferation in the regions in which the dendrites and axons of the nerve cells had been destroyed. There was marked hyperæmia in the middle half of the cortex, but none above nor below this level.

The author considers that the above necrobiotic changes are induced by disturbances of the circulation, and adds that, in the absence of organic vessel changes, one should ascribe the necrosis to stasis of the circulation in some cases, in others to prestasis and diapedesis, and in a third group to ischæmias with more or less tissue-necrosis, all attributable to functional disturbance of the circulation. He adds that it is known that in acute excitement where there is a marked tendency to collapse, the central regulating mechanism of the vascular system is involved reflexly, causing irritation and preliminary narrowing of the vascular lumen, followed by, after some duration of time and further action of the irritant, a condition in which the vessels relax. The factors which bring this about are extraordinarily labile, and come into play, preferably, in connection with the vascular terminals. Their occurrence is facilitated the more frequent and more abrupt are the special demands on the circulation and its regulating mechanism. The author states very definitely, that in severe, long-continued, and fatal conditions of excitement of the most diverse origin, the whole vascular system, and especially the terminals, are injured; that vasomotor oscillations occur which induce circulatory oscillations in the central nervous system, and therefore parenchymatous changes; and that these occur perhaps with more regularity, the more acute and prolonged is the circulatory disturbance.

Von Braunmühl in another paper⁵ ("Über Gehirnveränderungen bei puerperaler Eklampsie und ihre Entstehung durch Kreislaufstörungen"), returns to the argument. He emphasises the vascular factor, and especially the morphological changes in the vessels, as important in the causation of brain lesions, but points out that functional disturbances of the vascular system are

equally important. He draws attention to Neubürger's observation of ischaemic lesions in the cornu Ammonis and ascribes them to functional disturbance. He refers to the observation of Spielmeyer that this functional spasm plays an important part in the genesis of epilepsy, in which morphological changes are found in the cornu Ammonis and cerebellum. According to Neubürger and Metz, this functional factor comes into play in general paralysis, the poison acting upon the vessels of the central nervous system. A similar view is held by Wilders.

The central nervous system in Braunmühl's two cases of puerperal eclampsia affords ample evidence of ischaemic cell changes. In the first case the cortical nerve-cell bodies were necrotic and shrunken with homogeneous atrophy of the nucleus. In some cells this necrotic change was of slight degree, in others much more advanced. No definite change affected the neuroglia. The adventitia and endothelium of the smaller arteries and capillaries contained altered fat, especially near the necrotic areas. This naturally would be the degenerated products of myelin sheaths in the neighbourhood. Many of the vessel nuclei showed karyorrhexis. The changes in the cornu Ammonis were prominent. What the author terms 'ischaemic cell changes' were present in the pyramidal layer. The cell body was homogeneous, and the nucleus deeply stained. (Edema of the white matter was present. The cerebellum showed changes similar to those in the cerebrum, and no inflammatory phenomena were present.

In the second case, the features of an ischaemic lesion were even more prominent. The cortical nerve-cells were shrunken, angular, deeply stained, and their protoplasmic processes much more obvious than normally. Pericellular incrustations covered the cell-body, and throughout the tissue were small droplets of degenerated myelin. Similar changes affected the cells of the cornu Ammonis. Throughout the brain there were more or less distinct changes in the nerve-cells, especially in the nucleus dentatus.

The author, in his discussion on the nature of the pathological alteration in the nerve-cells, concludes that it falls into the category of 'ischaemic' or 'homogenising' cell disease, on account of the homogeneous and vacuolated appearance of the cytoplasm, and the intensely stained, badly defined, and structureless nucleus. Similar necrotic lesions in the cerebral cortex have been observed by Spatz and Neubürger, in whooping-cough, to occur in relationship with vessels. Some of those lesions were diffuse, others of a more focal nature.

It is noteworthy that the parenchymatous lesions attained a much higher degree in the cornu Ammonis than elsewhere. The nerve-cell processes stained with unusual intensity, and there were droplets of myelin along their course. In one case of acute eclampsia of short duration, the early signs of ischaemic cell change were found in Sommer's sector of the cornu Ammonis, while the remainder of the brain showed nothing unusual worthy of note. The cells of Purkinje in the cerebellum appeared normal, but those of the nucleus dentatus showed the 'homogeneous—ischaemic' change. There were no obvious

lesions of the vessels beyond wide dilatation of the capillaries with swelling of their endothelium. There were only a few necrotic areas.

Von Braunmühl concludes in his review that the nerve-cell changes are characteristic of ischæmia, and draws attention to the absence of any mesenchymal or glial proliferation. He admits however that this is an unusual appearance in necrosis, as it is common for the least injured glia to react. In this connection one would suggest that the poison which has produced coagulation-neurosis of the nerve-cells may have at the same time so injured the neuroglia in the neighbourhood that its potentiality for proliferation has been destroyed. With regard to the genesis of the lesions the author is strongly inclined to the opinion that such parenchymatous lesions are related to vascular disturbance, and, in the absence of thrombotic or other lesion, that this disturbance is of a functional nature.

In this connection the observations of Neubürger, in his work on angiospastic (non-embolic) infarction of the kidney, are extremely interesting. This, and gangrene of the extremities, he believes to be caused by functional vascular disturbance. Two other authors who support this view are Kuczinsky and Dosquet, who regard the presence of fibrin and few leucocytes in the lumen of the vessel as a sign of active intra-vitam vascular spasm.

Von Braunmühl inclines strongly to the view that the lesion is an ischæmic one, caused by a more or less active and wide-spread angiospasm of the cerebral vessels, followed by death of the nervous structures. He very rightly emphasises the importance of separating the diffuse from the focal lesions. In the cortex, the latter may affect a portion of the laminæ in such a way that diffuse changes alternate with focal, and he notes that where the glia has undergone proliferation there is evidence of neuronophage activity. In Sommer's sector of the cornu Ammonis, in which the pyramidal cells of this layer are rather loosely arranged, they are reduced to mere shadows, but high power magnification reveals that many of them still show signs of necrosis. Here the Hortega type of glial cells are hypertrophied, secondarily no doubt to destruction of the nerve-cells.

Von Braunmühl's view, briefly stated, is that the lesions in the brain are brought about by a primary spastic ischæmia, followed by paralysis and congestion of the capillaries. The nerve-cells of the pyramidal layer in the cornu Ammonis become necrosed, and the nucleus atrophies. There is a secondary proliferation and hypertrophy of the glia in the necrotic areas of the cortex in which the nerve-cells have lost their axons and protoplasmic processes. Here the necrotic lesions are of a diffuse type. In the pyramidal layer of the cornu Ammonis, however, where the necrotic change of the nerve-cells is of a high degree, the glial cells have been so injured by the noxious agent that their potentiality for proliferation has been destroyed. Under such circumstances only the least injured elements have retained their power of reaction. He adds that the homogeneous appearance of the nerve-cells is typical of an ischæmic lesion. This view is also held by Greenfield⁶, according to whom the appear-

ances of coagulation-necrosis of a tissue are most definite, and the necrosed elements stain in a characteristic manner on account of their increased affinity for the dye. Each unit becomes transformed into a homogeneous mass of an increased consistence, and this occurs especially in regions where lymph is readily absorbed. In the initial stages of necrosis the cells are swollen and intensely stained; later, the colour fades. All the above appearances can in Greenfield's opinion be brought about by toxins.

There are other interesting points to be noted in regard to those lesions. Greenfield⁶ has observed that in blockage of some cerebral arteries by embolism or thrombosis the collateral hyperæmia is rarely marked, and that hæmorrhage is rare. Further, the area of cortical softening is much smaller than that supplied by the obstructed artery, if the vessels are healthy. Even in total obstruction of one middle cerebral artery the softening may be limited to the parts supplied by its most central branches, the convolutions adjacent to the affected area obtaining sufficient collateral supply from other arteries.

In regard to the part played by the sympathetic nervous system in inflammation, he points out how dilatation of the vessels occurs even when all connection with the cerebrospinal vasomotor centres has been severed. He infers from this that the injurious influence of the irritant must be exerted therefore either directly on the vessel wall, or by the intervention of a local vasomotor apparatus.

Müller⁷ has demonstrated the presence of such a vasomotor apparatus in connection with the vessels of the pia-arachnoid, and those of the choroid plexus; and it would appear from his work that the nerve-supply of the vessels in the above-mentioned areas is very rich. In this connection it is therefore of interest to note that the vascular supply of the fornix and cornu Ammonis is carried inwards by a fold of the pia-arachnoid, the lamina involuta, which gives off vessels to both the above nerve-cell laminae; and that it is precisely in those two situations that the well-defined ischæmic lesions occurred in the experiments on which this communication is based.

SUMMARY.

In conclusion one would briefly recapitulate the various factors which contribute to the formation of the lesions, and which are fully dealt with in the discussion.

These are the production of definite ischæmic lesions, or acute oedema, both of which lead to localised destruction of the nerve-cell layers and adjoining tissue. In simple coagulation-necrosis without oedema the lesion is necessarily less extensive and more restricted to the cell laminae.

The localisation of the lesions ascribed to the fornix and cornu Ammonis may justify one in arguing that the vessels in those situations are terminal. In the cortex, where the lesions are less prominent and more diffuse in character, one may conclude that the absence of definite ischæmic lesions is due to the richness of the looped system of capillary supply.

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- (These two papers give the references to the articles by Neubürger, Spielmeyer, Wilder *et al.*, mentioned in the text.)
- ⁶ GREENFIELD, W. S., *Chapters in Pathology*, Edinburgh, 1905.
 - ⁷ MÜLLER, L., *Die Lebensnerven*, Berlin, 1924.

EXPLANATION OF FIGURES.

- FIG. 1.—Photograph of rabbit's brain to show : (a) Cornu Ammonis consisting of two layers, an outer of granular cells and an inner of pyriform cells ; (b) fornix connecting the upper brain cortex with the lower where it is continuous with the cortex of the temporal lobe : note the rhinal fissure which marks the lateral extremity of the pyriform lobe.
- FIG. 2.—Higher power view of cornu Ammonis, to show the lamina involuta surrounding it, containing a prolongation of the pia-arachnoid and vessels.
- FIG. 3.—Shows the lamina involuta at the lower extremity of the cornu Ammonis.
- FIG. 4.—(a) The fornix, in which there is a small area of coagulation-necrosis of the nerve-cells ; (b) the granular layer of the cornu Ammonis.
- FIG. 5.—A small area of coagulation-necrosis of the nerve-cells in the lateral portion of the fornix.
- FIG. 6.—A higher power view of fig. 5. Shows the deep black staining of the nerve-cells with iron-haematoxylin : the normal cells stain grey.
- FIG. 7.—Note the area of coagulation-necrosis in the fornix at the right and left sides of the photograph.
- FIG. 8.—Coagulation-necrosis of nerve-cells of fornix at its lower extremity where it joins the uncus of the temporal lobe. "X" is an area of oedema.
- FIG. 9.—Medium power photograph of fornix showing coagulation-necrosis of nerve-cells ; the deeply stained and structureless necrosed cells contrast markedly with the normal in which the nucleus is clearly visible. Necrosed area at left side of photograph.
- FIG. 10.—Shows the same appearances as in fig. 9. The nuclei of the normal cells are clear, whereas the cells in the necrosed portion stain deeply. The sharp demarcation of the necrotic zone is well demonstrated. Note the vessels in the lamina involuta, lying between the fornix and cornu Ammonis.
- FIGS. 11 and 12.—Magnified views of fig. 10, to show the striking contrast between the clear normal cells, with their pale vesicular nuclei, and the deeply stained shrunken necrosed neurones. In Fig. 11 the lamina involuta, with its vessels, is shown.
- FIG. 13.—Note the coagulation-necrosis of the fornix cells at its lower end, where it joins the temporal lobe, and is continued to the uncus. "X" is an area of oedema.
- FIGS. 14, 15, 16.—Examples of glial reaction in the necrotic areas. Figs. 14 and 15 are taken from the upper, fig. 16 from the lower extremity of the fornix.

PLATE I.

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

PLATE II.

FIG. 5.

FIG. 6.

FIG. 7.

FIG. 8.

PLATE III.

FIG. 9.

FIG. 10.

FIG. 11.

FIG. 12.

PLATE IV.

FIG. 13.

FIG. 14.

FIG. 15.

FIG. 16.