NOTES ON THE CHROMOPHILIC MATERIAL IN
THE MOTOR CELLS OF BRAIN AND CORD,
NORMAL (ANIMAL) AND PATHOLOGICAL
(HUMAN), AND ON THE REACTION (ACID OR
ALKALINE) OF THE CORTEX AND CEREBRO-
SPINAL FLUID.

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I.

SINCE the publication in BRAIN (Winter, 1897) of a method of examining fresh cells, I have, at the suggestion of Dr. Mott, used a solution of methylene blue in normal salt.

With this the anterior cornual cells of the cow, pig, rat, rabbit and rook have been examined, as before described, as soon after killing as the cord could be extracted. In every case, even when no other medium (Farrant's solution) has been employed, and the stained little piece merely pressed out in its own moisture under a cover glass, the chromophilic elements have been distinctly visible in their usual form and arrangement.

And as regards human cortex no difference can be detected whether one uses a solution of methylene blue in water or in normal salt; and this refers to material which, in some cases, was examined only a few hours after death (from one to four or five hours).

These observations are in opposition to Held's view, that the form the chromophilic elements (Nissl bodies) assume is artificially produced by fixing reagents, but do not affect his further supposition that the acidity of the cortex set up after death, may precipitate the granules of

the hyaloplasm in the form of Nissl bodies. Van Lenhossek has seen in spinal ganglia cells brought under the microscope directly after death without any addition of reagents, the grains of the cell protoplasm.¹

But although it may be shown that the Nissl bodies exist in quite fresh cells after death, there remains the possibility that they are precipitated as such by an acid reaction in the cortex, due to *post-mortem* changes. Held asserts that the Nissl bodies are insoluble in weak and concentrated mineral acids, but easily soluble in weak and concentrated alkalies, and he contends that during life the alkaline nature of the nerve cell fluid holds these bodies in solution, but that after death an acid reaction is set up by which a precipitation of granules takes place in the form of Nissl bodies.

There is a fact furnished by pathology and which will be further referred to later on, also opposed to this theory of Held's, and that is, that in certain morbid conditions, the bulky chromophilic spindles and blocks usually met with in healthy cells, dwindle away until they become the finest imaginable threads before disappearing altogether. The observation previously made that chromophilic material is met with in the fore-horn cells of animals freshly killed, does not prove anything decisively against the idea that the Nissl bodies are precipitated as granules from a fluid hyaloplasm that has become acid, because, however shortly after killing we test the nervous substance, we obtain both an acid and an alkaline reaction by using different indicators. This I have done with animals immediately after killing, and with human beings as short a time as seventy minutes after death, and the results of these experiments are given below.

Halliburton² states that he has never failed to find an alkaline reaction in fresh brain, cord or nerve, becoming, however, as a rule, rapidly acid after death. Langendorff (quoted by Halliburton) experimenting with frogs, rabbits

¹ Quoted by Goldschieder and Flatau. *Norm. und Path. anat. der Nervenzellen*, p. 14.

² Text book of Chem. Physiol. and Pathol., p. 515.

and guinea-pigs, finds the central nervous system to be alkaline during life, rapidly becoming acid after exposure or death.

Heidenhain and Gschleidlen state that the grey matter of the brain is acid even during life, probably due, they think, to lactic acid. J. Moleschott and A. Battistini, using phenolphthalein, found that the brain and spinal cord were acid, the grey more than the white.

With the exception of the last, no mention is made in Halliburton of the indicator used.

I have tested the reaction of the cortex and cerebro-spinal fluid in thirty-seven bodies of insane patients varying from one to forty-four hours after death, and using phenolphthalein, litmus, and methyl orange as indicators, and the grey matter (generally of spinal cord) of five animals (rook, rat, rabbit, pig, cow).

The results are always the same for the human cortex and cerebro-spinal fluid.

Phenolphthalein.—In all cases (twenty-seven human, and five animals) the grey matter discharged the pink colour from an alkaline (KHO) solution of the indicator.

The cerebro-spinal fluid of the human brains also *invariably* gave an acid reaction.

Litmus.—The paper was used ; and when care was taken to avoid contaminating it by the cerebro-spinal fluid, the results were likewise constant.

In twenty-eight human brains the cortex was always acid.

Of the five animals, the rook's grey matter, tested one hour and forty minutes after killing, gave an acid. In the other four, tested as soon as the cord (or brain) could be extracted after killing, an amphoteric reaction was obtained, but the alkaline seemed the stronger, for when the blue paper was applied it turned faintly red ; but this colour was evanescent, and faded after removal of the paper, but with red paper a permanent and decided blue was obtained.

With the cerebro-spinal fluid tested in thirty human brains, varying from seventy minutes to forty-four hours after death, there was also an amphoteric reaction in twenty-nine of the cases, for the blue paper was faintly tinged red, but

the colour quickly faded, whilst the red paper was somewhat slowly turned of a decided and permanent blue. In one case, five and a half hours after death, only an acid reaction was obtained.

Methyl orange.—This indicator, although it is not sensitive to most organic acids, reacts to lactic acid, yet, curiously enough, it only gives an alkaline reaction with cerebro-spinal fluid which after death contains this acid.

I have never obtained any reactions with yellow (alkaline) solutions, but with ten human brains and one cow's, the former varying from two and a half to twenty hours after death, a decided alkaline reaction always resulted.

With the cerebro-spinal fluid of sixteen cases also an alkaline reaction resulted in every one.

It will be seen from the foregoing that in one particular only does the reaction of the cortex differ from that of the cerebro-spinal fluid, in that the former is acid to litmus, the latter alkaline. Naturally the cerebro-spinal fluid, which permeates the cortex in all directions, will to a large extent determine its reaction; but the immediate and decided reddening of blue litmus paper shows that the grey matter contains substances not present in the cerebro-spinal fluid, or, if present, not in sufficient amount to influence its behaviour to litmus.

Lactic acid was tested for by carbol. ferric chloride (4 per cent. carbolic acid 10 c.c., water 20 c.c., liq. ferri perchlor. B.P. one drop) in sixteen cases.

A roughly quantitative estimation was attempted by always using 5 c.c. of the purple solution and counting the number of drops required to turn it completely yellow. This varied from seven to thirty, and, generally speaking, the number of drops was smaller the longer time which had elapsed after death when the fluid was tested, but not invariably. In three cases where the cerebro-spinal fluid taken from bodies seventy minutes, two and a half and twelve hours after death respectively was tested at the time of the autopsy and then allowed to stand for forty-eight hours, no very marked difference was found in the amount of lactic acid at these two different times, but if any reliance

is to be placed on the quantitative method employed, it indicated a slight diminution in the amount of lactic acid on standing.

Now, although lactic acid is found in the cerebro-spinal fluid as shortly as seventy minutes after death, it does not appear to be present in the fluid during life, nor to be formed in it after removal during life.

I have not directly tested for it under these circumstances, but from the fact that a sample removed by lumbar puncture in the case of a male general paralytic gave an *alkaline* reaction to phenolphthalein (which is sensitive to organic acids), I think it is highly probable that in this case lactic acid was not present. This same fluid, after standing forty-four and a half hours, still gave a distinctly alkaline reaction to phenolphthalein.

The above-mentioned observation tends to show that the lactic acid formed in the cerebro-spinal fluid after death is a *post-mortem* product, and that it is formed by chemical change taking place (*post-mortem*) in the brain; from whence it is carried to the fluid which bathes all parts of the brain.

I would note here that although with a freshly-killed cow a lactic acid reaction was slowly obtained from a piece of cortex in carbol. ferric chloride, yet this can quite readily be accounted for on the assumption that the protoplasm was killed by the reagent and produced the lactic acid in consequence there and then.

The results of these observations show that in human brains and animal both acid and alkaline substances are present in the cortex and cerebro-spinal fluid.

Certain German observers have already stated that such was the case, for Liebreich and Langendorff, using fresh pieces of cortex, found that they turned litmus blue, whilst Liebkühn and Edinger, using an infusion of alizarin, got an acid reaction.

SUMMARY.

(1) Chromophilic material in the form of Nissl bodies is met with in animals immediately after killing and in human

beings at least seventy minutes after death, when the nervous substance has merely been coloured by a solution of methylene blue in normal salt without any further addition of reagents.

(2) The fact that in some forms of diseased nerve cells the Nissl bodies show a gradual attenuation so that they dwindle down from bulky spindles and blocks to the finest imaginable threads, is opposed to the idea that they are produced by a precipitation after death.

(3) The reaction of the cortex varies with different indicators, showing that it contains both acid and alkaline substances.

(4) Its variations are constant, whether tested two hours or forty-four hours after death, and are as follows:—acid to phenolphthalein and litmus, alkaline to methyl orange.

(5) With animals killed and immediately tested, the grey matter gave similar reactions with phenolphthalein and methyl orange, but was alkaline to litmus.

(6) The reactions of the cerebro-spinal fluid differ from the cortex, in that with litmus an alkaline reaction is obtained. Otherwise they are the same. These results do not differ, whether the fluid is tested seventy minutes or forty-four hours after death.

(7) Lactic acid is present always in cerebro-spinal fluid after death, and appears to increase with the length of the interval which has elapsed between the time of death and the time of testing.

II.

Goldscheider and Flatau,¹ by subjecting rabbits to a high temperature in a thermostat, succeeded in producing a condition of pyrexia in these animals associated with a change in the fore-horn motor cells of the spinal cord. These changes were as follows:—

The cells appeared larger than normal, and stained (by Nissl's method) of a pale blue colour, opaque and homo-

¹ *Normale und path. Anat. der Nervenzellen.*

geneous; a finely granular condition could be discerned in relation with an ill-defined network of threads. Here and there were dark specks, probably the remains of Nissl bodies.

The nucleus was either not visible or indistinct, it stained homogeneously, and was sprinkled with the finest granules, and was not sharply outlined, and generally, as in the normal condition it was paler than the cell body.

The nucleolus was generally irregular, jagged, and darkly stained.

The dendrites were very pale and swollen, and presented slight varicosities; they showed no spindles, but only ill-defined granules.

As a result of numerous experiments, they came to the conclusion that a well-marked change of the above description was found as soon as the animal's temperature (which ranges normally from 101° to 102.7° F.) rose above 109.4° , and that if one allows the rise of temperature to last about three hours from 107.3° to 107.6° , then the first signs of alteration were visible on the periphery of individual cells.

Further, that a restitution from this condition occurred if the animal was allowed to recover; that it began after twenty-five and a half hours and was complete in sixty-eight hours.

Moxter, experimenting in somewhat different ways with artificially raised temperature in rabbits, obtained practically the same results as Goldscheider and Flatau, and he concluded that—

(1) A change in the forehorn cells is found after twenty-two and a half hours under the influence of a temperature between 104.9° and 106.7° .

(2) After several days' intermittent temperature between 100.4° and 106.3° no changes were found.

(3) Twenty-three hours, with a temperature varying from 102.5° to 105.2° , no changes were found, not even where the heightened temperature was several times renewed.

(4) That even in rabbits with lower temperatures than

those produced in the experiments an almost complete chromatolysis was met with, if the lower temperature was allowed to act sufficiently long.

Goldscheider and Flatau quote two cases where with pyrexia similar changes were found in the fore-horn cells of the cord. In the first—a man suffering from tetanus, whose temperature for the four days prior to death ranged from 98.6° to 101.1° , rising on the evening of death to 103.8° . The changes were found in all heights of the cord, in the cells both of fore and hind-horn, in the middle zone, and in Clarke's column. In the second—a girl with scarlet fever whose temperature for the last twelve hours varied between 104.9° and 105.6° —the cells of the cervical region were more affected than those of the lumbar.

Dejerine (quoted by Goldscheider and Flatau) found also in a case of pneumonia a decided chromatolysis of the nerve-cells of the spinal cord, which he considers similar to those seen in artificial pyrexia in rabbits.

Lugaro¹ asserts that experimental pyrexia causes complete disintegration of the chromatic part of the protoplasm of cortical and other nerve-cells without producing any other very marked change.

In a paper read before the Med. Psych. Soc. in May, 1898, I mentioned five cases of insanity in which I found changes in the motor cortex evidently very similar to those described (and figured) by Goldscheider and Flatau. At that time I was unaware of these experiments, yet the idea that they might have been caused by pyrexia had entered my mind, but had been dismissed because in other cases I had examined, where as high or higher temperatures had existed for some time before death, no such changes were found, and also because similar changes were occasionally met with in cases in which at least several days prior to death the temperature had not been raised.

Yet another reason against the view that these alterations were due solely to pyrexia was that in several cases where the altered cells were found in the cortex those of the fore-

¹ Quoted by Robertson and Orr. *Jour. Mental Science*, October, 1898, p. 740.

horn, cervical spinal cord, and hypoglossal nuclei showed a fairly normal arrangement and amount of chromophilic material.

Whilst I think that such reasons forbid us to regard pyrexia as the essential cause of the changes I described, it seems highly probable, considering how often pyrexia is associated with them, that such a condition will lead to alterations in the metabolism capable under favourable circumstances of producing these changes in the nerve-cells.

It is my intention here to consider in more detail the condition previously described, and to bring forward other examples since met with, because this condition seems to be of a very interesting nature, and also because others¹ have assumed that it was merely the accompaniment of pyrexia.

I do not for one moment wish it to be considered that it is peculiar to insanity—such is not the case; amongst the number now brought together is a case of typhoid fever in a female, whose brain showed the changed cells, and although she was not of normal intellect, her mental condition was such as to render it in the highest degree unlikely that the changes found in her nerve-cells were due to insanity, but that they were consequent on the typhoid fever.

Before proceeding to a description of the so-called pyrexial cell, a list is appended of cases in which there was a high temperature up to death and in which no trace of a single cell having any likeness to those in question was to be seen either in freshly squeezed-out films or in sections. A larger number of cases might have been brought together very easily, but I have restricted myself to those in which the temperature was ascertained to be high till at least a few hours before death so as to exclude the possible objection that restitution changes had taken place, and also to such cases in which beyond a certain amount of chromatolysis no very obvious alterations were noted in the cells when examined by the fresh method.

¹ Robertson and Orr. *Jour. of Mental Science*, October, 1898.

TABLE I.

No.	Sex.	Form of Insanity.	Age.	Cause of death.	Temperature in axilla (F.).
1	F.	Demented ..	33	Pneumonia	For two days prior to death varied between 101.2° and 102.8°, gradually rose till it reached 106° ten minutes before death
2	F.	Always weak-minded; maniacal	62	Abscess and necrosis of bone	For five days before death was always above 101°. (Highest = 103.8°.) On the morning of her death = 102°
3	F.	Chronic mania ..	48	Erysipelas ..	On the day before death it was 102° in the morning, 104° in evening. Not taken previously
4	F.	Puerperal mania	29	Pleurisy and Pneumonia	For the last few days as follows:—E., 106°; M., 103.8°; E., 105.2°; M., 103.6°; E., 105°; M., 103°.
5	F.	Acute mania ..	24	Pneumonia and Phthisis	For the last few days as follows:—M., 100°; 101.4°; 101.2°; 101.6°; E., 101.6°; 102°; 102.5°; 105°
6	M.	Idiot	7	Pneumonia and status epilepticus	The day before death as follows:—M., 105°; E., 103°. The next day it was 102.8° at 4 p.m., and he died at 9.25 p.m.
7	F.	Weak-minded; epileptic	27	Phthisis ..	For the last three days as follows:—M., 100°; 100.4°; 103.6°. E., 104.2°; 104.6°; 103°; falling to 101.6° at time of death.

If pyrexia alone could account for the change in cells under discussion, it is quite inexplicable why in such a case as No. 4, where for four days prior to death the temperature had stood at from 5° to 8° above normal, no such change was found.

Portions from the top of the ascending frontal of each of these cases were examined both in the fresh condition and after hardening.

(4) In the fresh cells merely coloured with methylene blue no very marked departure from the normal as regards the arrangement and quantity of chromophilic material could be determined.

In some the centre had a somewhat paler and washed-out appearance, whilst others showed granular degeneration of the Nissl bodies, but such were in a decided minority.

The cell bodies were generally irregularly angular, with many processes and not so large as in the so-called pyrexial cell, and the dendrites appeared normal in all respects, never showing the dull, pale blue uniform staining nor the very marked fragility found in such cells.

There were no special features which need be noted in regard to the nucleus. In some cases the nucleolus was large ($12\ \mu$) and pale, in others of normal size and dark. In others it had quite disappeared.

(B) In the portions of the ascending frontal which were fixed either in alcohol or sublimate, infiltrated with paraffin, and stained either with methylene blue, thionin or toluidine blue, there was a great uniformity in the appearance of the cells as regards the condition of the Nissl bodies (see figs. 1, 2, and 5).

Whilst many presented a fairly normal appearance, in the majority a very marked chromatolysis was found in all but one (No. 5) of the cases. Its characters were as follows:—

The apex, dendrites, and periphery of cell body always contained large, darkly-stained spindles, threads, or blocks.

The interior of the cell body is occupied by a paler and more uniformly stained substance, which resolves itself into a collection of pale and darker granules when highly magnified.

What I wish to draw attention to is the fact that although there is a considerable disappearance of chromophilic material in the cell, that which remains has not the appearance seen in the so-called pyrexial cell. There is no attenuation of the Nissl bodies; those which remain are as bulky and as deeply stained as usual. The condition of chromatolysis met with is quite unlike that obtained either in the partial disappearance of the Nissl bodies with pyrexia or their partial restitution with the subsidence of the pyrexia.

Except in one case (No. 7) there was no appearance of any undue shrinking of the cells, and their ground substance is nearly colourless.

The apex and dendrites are stout and have a regular outline presenting no varicosities. The nucleus is round or oval, generally with a distinct limiting boundary line, and more or less filled with a pale, amorphous material.

The nucleolus is generally darkly stained and regular in outline and varies from 4 to 6 μ in diameter. Often pale spaces or even vacuoles are seen in it.

Besides the ascending frontal in case No. 1 the frontal and occipital cortex regions were also examined, and in case No. 7 the cervical and lumbar enlargements of the cord and the hypoglossal nuclei. In the former case the pyramidal cells of the frontal region tallied with those of the ascending frontal, and a photograph of one of them is given in BRAIN (see Winter number, 1897, p. 450, fig. 1), which shows the large amount of chromophilic material and its arrangement. Similarly the giant-cells of the occipital cortex showed no marked deviations from the normal.

In case No. 7 both fresh and hardened specimens of cord were examined.

In fresh preparations of the hypoglossal nuclei the cells showed a perfectly normal appearance in the arrangement, &c., of the Nissl bodies. In the lumbar enlargement the motor cells of the fore-horn were fragile; the body of the cell was occupied by a mass of rather large granules of chromatin (granular degeneration). The dendrites appeared normal.

In sections.—Many of the fore-horn cells of the cervical enlargement presented considerable chromatolysis, characterised by the same features as mentioned in describing the ascending frontal cells, others appeared normal. In the lumbar enlargement a similar appearance of cells was seen as in the fresh preparations, the cell is filled with masses of chromatin rather smaller than usual and not rod-shaped (crumbling of chromophilic material). At the boundary the masses are larger and of a square contour. The dendrites appear normal.

Turning now to the cases which showed a similar condition of cells to that found in rabbits' cords after experimental pyrexia, the following table contains a list of these, and gives the form of insanity and the cause of death, &c.

TABLE II.

No.	Sex.	Age.	Form of Insanity.	Cause of death.	Remarks.
1	M.	40	Acute general paralysis	Pneumonia ..	Recently had a seizure before his death. Temperature not stated
2	M.	49	General paralysis	Seizure ..	His temperature rose to 105° F. before death
3	F.	35	Weak - minded from epilepsy	Status epilepticus; pneumonia	Temp. for last three days: M., 100°; 100·4°; 101°. E., 101·4°; 100·4°. Died 9.20 p.m.
4	F.	25	Acute puerperal mania	Peritonitis ..	Temp. at 6 p.m. of day of admission was 100·4°; next morning, 100·2°; 7 p.m., 103·4°; 9.15 p.m., 104·6°; 11.45 p.m., died
5	F.	49	General paralysis	Seizure ..	Temp. on morning of death = 103°
6	F.	58	Dementia and epileptic	Status epilepticus	Two days before death, evening temp., 99·4°; next morning, 98·4°; at 6 p.m., 106·6°. Died 7.30 a.m. next day
7	F.	24	Acute delirious mania	—	Temp. not raised for several days prior to death
8	M.	39	General paralysis (chronic lead poisoning)	General paralysis	Temp. not stated
9	F.	44	Weak-minded and fatuous; result of chronic alcoholism	Typhoid fever	Temp. high
10	F.	48	Chronic mania ..	Pneumonia and pericarditis	Had a temp. ranging between 102° and 104° for nine days prior to death
11	F.	40	Dementia ..	Cerebral tumour (gliosarcoma)	Temp. always sub-normal.

Although in most there was a raised temperature immediately prior to death, yet there are two exceptions to this rule (Nos. 7 and 11), and in one other case (No. 3) it can scarcely be supposed that the temperature reached was sufficient, on Goldscheider and Flatau's showing, to have caused the changes in the cells which were met with.

Portions of brain, as in the last series, were taken from the top of the ascending frontal and examined both in a fresh state and after hardening.

(A) Fresh films stained in methylene blue.

Although the following description refers more particularly to the giant-cells of the cortex, yet it also applies to the other pyramidal cells. The cells appear large and blown out; they have to a large extent lost their multi-angular shape and have a more rounded contour. The cell body and apex stains of a dull, uniform blue, but with high magnification a finely granular condition is seen. Very often towards and in the apex are seen thin threads stained of a darker blue, which are the attenuated remains of Nissl bodies (fig. 7).

Although generally not much pigment is present, sometimes there is a large amount of it.

The dendrites, which are fairly numerous and fairly bulky, stain throughout of the same dull blue tint as the cell body. They are extremely fragile. The nucleus, when visible, is most often a pale, ill-defined zone around the nucleolus.

The nucleolus is generally central, and is very rarely displaced to the side of the cell. It is always round or oval, but varies considerably in size (from 5 to 12 μ) and depth of staining. To a large extent the latter is in inverse proportion to its size; the larger it gets the paler it becomes, until in some cells it is quite invisible.

In cases 2, 7, 9, and 10 it is in almost all cells very pale and large (11 μ), with a blurred outline. In some cells it is only just visible, in others quite invisible.

In cases 3, 5, and 6 it is generally small (5 to 6 μ), very dark—indeed, almost black—and stands out prominently from the pale background of the cell body.

In the other cases there is a more general mixture of the

two kinds described, so that it is difficult to say whether the large pale or the small dark nucleolus predominates.

The large pale nucleolus in sections from hardened tissue shows often as pale multi-loculated bodies not much larger than usual, the probability being that by dehydration they have shrunk.

Vacuolation or irregular staining of the nucleolus is not seen in fresh preparations before fixing.

With the exception of the differences noted in the nucleoli there is a great likeness between the cells of all the cases. My description will apply to the great majority of the cells seen, but some are met with which are very pale and appear as ghost-like forms of the others. In some of these pale cells a nucleus is seen staining of much the same depth as the cell body, with a definite but fine border.

(B) On examining sections which have been subjected to fixing agents (alcohol or sublimate) the cells no longer present in the different cases quite such an uniform character, but the difference is mainly in the shape and depth of staining.

The giant-cells are generally large and rounded, filling out the entire pericellular space, but with some cells there appears to have been considerable shrinking, and this space is large.

The dendrites are manifestly thinner than in healthy cells, and probably less numerous, and not infrequently show varicose dilatations.

Sections stained in thionin or toluidin blue present a very characteristic appearance, owing to the universal but pale violet-tinted staining of the cell and its processes. The whole of the protoplasm staining of the same depth. It appears impossible with these stains to get a deep colour in the cells. High magnification of the apparently uniform cell body shows a delicately granular background, with larger and darker granules sprinkled about. In many cells remains of Nissl bodies can be detected in the apex and about the periphery. These are in the form of delicate threads (figs. 3, 4, 10, and 11).

This gradual attenuation of the Nissl bodies, until the

originally big spindles or rods have dwindled away to fine threads, is a point worthy of note in reference to the question as to the origin of these bodies by precipitation, and cannot easily be accounted for by Held's theory.

In the sections a large cell is occasionally seen which has absorbed the stain deeply, and appears blotchy, showing little or no detail, but these are in most cases very few and far between.

The nucleus presents no peculiarities from those described before ; we see an ill-defined granular mass arranged more or less in the form of an irregular mesh work, and described as such by German observers, but which it seems more likely is merely the representation of a coagulated albuminous mass, which during life and before fixing occupied this body as a fluid or semi-fluid material.

The nucleolus varies somewhat, corresponding probably to the variations noted in the films. It often, although darkly stained, shows a number of pale or colourless spots (fig. 4). In other cases it is pale and with a multiloculated appearance.

There is not the extreme difference in size met with in the fresh preparations, probably because the large pale nucleoli noted in the latter are more fluid in nature and have contracted more when subjected to dehydrating agents.

In cases 7, 10, and 11, besides the ascending frontal, other parts of the nervous system were examined, viz., the cervical cord in No. 7 and cervical cord and hypoglossal nuclei in Nos. 10 and 11.

In these parts, both in fresh and hardened preparations, the chromophilic material appeared generally in normal amount and arrangement, but in some few cells chromatolysis of the character previously noted was seen.

There can be no question that as far as morphological appearances go the cells of all the cases, with the exception perhaps of one (No. 7), represent a similar pathological condition, and as regards this one there are certain facts which render it probable that it belongs to the same category, but probably in a more advanced state of disease.

In fresh preparations its cells appeared identical with

those of the other cases, and in certain parts of the sections, always at the base of a convolution, some were seen which were not shrunken and appeared identical to those seen in sections from the other cases, also in nearly all the sections from these latter certain cells were met with which stained densely and appeared shrunken, and, in fact, had very much the appearance of the majority seen in No. 7.

Case No. 7 appears of sufficient interest to warrant a brief description. It was that of a well-developed, strong girl, aged 21, who, previously to her mental affection, had always had good health. She was admitted here suffering from acute delirious mania of only a few days' duration, and whilst in this state had jumped out of a bedroom window and badly bruised herself, but beyond the bruises did not appear to have sustained any serious injury to her system.

She was violently excited for the first few days after admission, and then showed signs of collapse with intervals of restlessness, when she would toss her arms about and move her head. A large bleb formed on her right heel, her tongue, which at first had been heavily furred but moist, became dry, brown, and cracked, and she died seven days after admission. Her temperature and pulse was as follows :—August 2, 5.30 p.m., 101.4°; pulse 123. August 4, 4 p.m., 97.8°. August 5, 6.45 p.m., 99.8°; pulse 142. August 6, 9 a.m., 98.6°; pulse 123; 7 p.m., 99.2°. August 7, 7.30 a.m., 98.6°; pulse 124; 7 p.m., 98.6°. August 8, 8.30 a.m., 98.6°; 6 p.m., 98.4°. August 9, 8.30 a.m., 98.4°; 7.30 p.m., 98.2°. She died at 6.20 a.m. on the 10th. The autopsy was held four and a half hours after death.

On the external surface of the dura mater was a thin, soft, dark clot, 40 × 30 mm.; it lay over the middle portion of the right second frontal convolution. The veins of the arachnoid were much engorged. There was excess of pale, reddish fluid in the lateral ventricles. No other morbid appearances noted in the head except perhaps some shrinking of the convolutions at the vertex, and the cortex was dark in colour on section. The encephalon weighed 1,218 grammes. The heart was small (245 grammes), and there were some atheromatous patches on the aorta near the valves. The

liver was pale. In other respects the thoracic and abdominal viscera appeared healthy. Portions of the ascending frontal at the top on both sides were examined fresh, other pieces from the same region were fixed in 10 per cent. formal. followed by absolute alcohol. Pieces of the liver and kidneys were put into Müller, and when examined microscopically the latter, except for very slight fatty degeneration in the superficial parts of the cortex, appeared fairly normal, but the liver showed very general and marked fine, fatty degeneration at the centre of the lobules.

In the brain the fresh films showed the giant-cells of the motor cortex, quite indistinguishable from those already described in general appearance and with the same extremely fragile dendrites. Fig. 7 shows one of them. There is evidence of remains of Nissl bodies in the form of fine threads in the apex.

The nucleolus is large, pale, and indistinct. The dendrites stain of a pale, dull blue, and all over alike.

The only difference noted in the cells was that some were pale and ghost-like, others darker and more dense.

In the sections the nerve-cells of the second layer appeared normal, but in all the deeper layers they were much altered. The pyramidal cells staining uniformly throughout of a somewhat paler colour than usual and with absolutely no chromophilic material, presented identically the same appearance as the pyramidal cells seen in the other cases of Table II.

The greater number of the large nerve-cells (giants) were much shrunken, darkly stained, and somewhat distorted, with a wide pericellular space around them. The staining of the cell body was so dense and diffuse that all detail was obscured (see figs. 6 and 8).

The nucleus was generally central and round or oval, but sometimes irregularly encroached upon by the protoplasm of the cell body. Nucleolus, round and dark. The dendrites, few in number, were dark and thin and devoid of chromophilic material, showing in places varicose dilatations along their course. The apex was very irregular in contour and in the way it stained, being very dark in some places, pale in others.

Others of the big nerve-cells were less darkly stained, and appeared as though consisting of fibres arranged as an irregular meshwork, whilst the apex had a rough, unravell'd aspect (fig. 9). And lastly, as before mentioned, a few cells characteristic of the other cases of Table II. were seen.

The blood-vessels were tortuous and showed masses of pigment, staining of a green colour, lying in the adventitia and perivascular spaces. In some of the larger vessels in the pia there was an aggregation of numbers of polymorphonuclear leucocytes filling up their lumen, whilst others were wholly or partially blocked up by a homogeneous hyaline material which stained of a greenish blue.

No appearance of any neuroglia proliferation.

The upper part of the cervical cord was also examined. The fore-horn cells were shrunken and deeply stained; the majority show the usual arrangement and quantity of Nissl bodies, whilst others with their dendrites are throughout stained darkly.

Now, unless we suppose that the fall, which probably was the cause of the small hæmorrhage on the dura, also produced such disturbance in the cerebral hemispheres as to give rise to the condition of cells found—a supposition not very probable—then we must take it that the pathological appearances noted were directly associated with the insanity.

What relation did the one bear to the other?

I would suggest from the following considerations :—

- (1) The acute nature of the mania and its rapidly fatal result,
- (2) The absence of naked eye lesions to account for such a termination,
- (3) The changes in the nerve-cells, and
- (4) The highly suggestive fact of the fatty degeneration of the liver in so young a girl.

That a wide-spread toxic influence was at work and that the chain of events was somewhat as follows :—

- (1) Mental disturbance.
- (2) Perverted metabolism resulting in the setting free of toxins in the system.

(3) Action of these on already disordered nervous system.

This also is the hypothesis that I would advance to account for the changes in the cells of the other nine cases.

A glance at the cause of death in Table II. will at least show that the circumstances under which we come across such cells are highly suggestive of poisoning, and to give an instance illustrating this we can almost count upon meeting with them in the brains of general paralytics who have died in seizures.

But whether this explanation is accepted or not, I think that sufficient reasons have been brought forward to show that the changes under consideration are not due directly or solely to pyrexia.

SUMMARY (PART II.).

Nerve-cells are met with in the human cortex, which are similar in appearance to the fore-horn cells found in the cords of rabbits after experimental pyrexia, but that pyrexia alone cannot account for their condition is shown by the following facts:—

(a) The frequent occurrence of pyrexia lasting until death in cases where such cells are not found, either in brain, hypoglossal nuclei, or cord.

(b) The occurrence of these cells in the cortex of cases which had shown no pyrexia, or in which the pyrexia had been too slight to account for them.

(c) And finally, the fact that in certain cases, while these cells were found in the cortex they were not met with in the hypoglossal nuclei or in the cervical cord, the nerve-cells in these places showing the presence of Nissl bodies in a fairly normal condition.

NOTE.

Since the above was written I have examined the brain from a man, age 34, suffering from acute mania, who died of diphtheria. His temperature two days before he died was 102° F., and although I have no record of it before that time, there can be no reasonable doubt that it was high for some

days previously, as when it was first taken the disease was in an advanced stage and his neck glands much involved. The day following it had risen considerably, and shortly before his death was 104° F.

Portions of the ascending frontal convolutions of both sides were examined fresh and after fixing in sublimate.

As regards the fresh method, although some eight or nine films were prepared and numbers of large nerve-cells seen in all, not one showed any appearance of the so-called pyrexial cell.

A very considerable number was stained of a dark, bright blue and had a normal stichochrome arrangement of their chromophilic elements throughout the entire cell; the dendrites were bulky and unstained, except for distinct threads of chromophilic material.

The majority, whilst presenting a similar appearance to the above in apex, dendrites, and periphery of cell body, showed in the interior a condition of granular degeneration of the Nissl bodies.

In some the granules are big and close set (dark cells), in others smaller and further apart (pale cells).

A perfectly analagous appearance of big cells was seen in the sections; and, in respect to the smaller pyramidal cells, although the chromophilic material may have been diminished, yet they failed entirely to show the quite characteristic appearances described before in the cases associated with the so-called pyrexial cells.

In many of the big cells in the films the nucleolus was pale, ill-defined, and more or less increased in size, in others it was quite invisible; but in the sections all of those seen were dark, sharply defined, and not above their usual size.

That there is some relation between certain fevers and states of insanity has long been recognised, and it is interesting to note that manifest changes of the nerve-cells can be detected in two of those fevers after attacks of which improvement or recovery of mental condition has occurred. I refer to the typhoid fever case recorded above and to a case of scarlet fever mentioned by Goldscheider and Flatau. In this case, however, only the changed condition of the

motor cells of the spinal cord is referred to, and apparently the brain was not examined.

As far as I know no such improvement has been noted in cases of insanity after attacks of diphtheria, which does not appear to affect the central nerve-cells so profoundly or in which at least there is not the very palpable alteration such as are seen with typhoid and scarlet fever.

DESCRIPTION OF THE FIGURES.

All were photographed with $\frac{1}{2}$ oil immersion (Beck), No. 2 eye-piece (=24x), with the exception of No. 7, which is with $\frac{1}{4}$ in. This last is from a fresh preparation, the others from sections.

FIG. 1.

Shows a fairly normal arrangement of Nissl bodies in the form of blocks and granules; the axis cylinder is also seen, and one stout dendrite with chromophilic threads in it (Case 5, Table I.).

FIG. 2.

Two cells from same case with normal arrangement of Nissl bodies. At the lower left hand part of the right cell is the axis cylinder eminence. Some pigment at the lower end of left cell.

FIG. 3.

Two cells from Case 10, Table II. Both stain diffusely and rather deeply, and show coarser granules on a finer granular background. In the upper cell a few attenuated threads of chromalin are seen in the apex. Small vacuoles in nucleolus.

FIG. 4.

Paler cell from same case with pigment at lower end. The attenuated chromophilic threads are well shown. Nucleolus vacuolated.

FIG. 5.

Cell from Case 3, Table I. Pigment in lower end. Bulky chromophilic spindles in upper part. Nucleolus vacuolated. A stout dendrite shown, unstained except for the chromophilic threads.

FIG. 6.

A darkly stained cell from Case 7, Table II., showing no chromophilic material. Apex and dendrites darkly stained throughout; the latter thin, and with varicose dilatation.

FIG. 7.

Same case. A fresh cell with a small patch of pigment at lower right end. Faint remains of chromophilic material seen in apex. Dendrites stain uniformly and are devoid of chromophilic material. Nucleolus ill-defined.

FIG. 8.

Same case. Darkly stained cell, showing a very ragged and irregularly contoured apex.

FIG. 9.

Same case. Pale cell with rough, irregular mesh work appearance of body and apex.

FIGS. 10, 11, 12.

Cells from a case of typhoid fever, Case 9, Table II.

Fig. 10 is a rather darkly stained cell with thin threads of chromophilic material shown in the apex and processes. Nucleolus is vacuolated. Fig. 11 also shows fine threads in apex and upper two-thirds of body; the lower third is occupied by pigment. Fig. 12 is a very pale cell, uniformly stained, except for one or two little masses of chromophilic material. Nucleolus is vacuolated.

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 5.

FIG. 6.

FIG. 7.

FIG. 8.

FIG. 9.

FIG. 10.

FIG. 11.

FIG. 12.