ON VACUOLATION OF THE NERVE CELL OF THE HUMAN CEREBRAL CORTEX.

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(PLATE XXIV.)

INTRODUCTION.

THE occurrence in certain mental diseases of vacuolation of the nerve cell of the cortex cerebri and the anatomical appearances presented thereby, as seen in sections cut while the brain is still fresh and stained with aniline dyes, after the method originated by Bevan Lewis, seems first to have received notice in this country at the hands of Whitwell,[1] who contributed an excellent account of the change, as it occurs in the nucleus of the nerve cell, to *Brain* in 1889. A more lucid and masterly description of this process is from the pen of Bevan Lewis;[2] but since, with the exception of these writers (so far as one can gather on looking through the literature), the subject has obtained but scant notice. It has occurred to many incredulous minds that the condition in general is a more or less pure artefact (a contention which, we are happy to say has been satisfactorily refuted by Bevan Lewis), and further, much doubt still exists concerning the pathology of this condition. A paper, therefore, dealing more particularly with its pathology cannot be looked upon as superfluous.

Any asylum pathologist, who has carefully examined a series of fresh brains by the above-mentioned method, must have noticed that this cerebral change is present in diseases other than those referred to by previous writers on the matter, or, at least, have been struck with the frequency with which he has come across the change. Such, at any rate, has been my experience, and with the end in view of ascertaining whether there was any common factor in the original diseases, either physical or mental, which were the causes of death, and which might account for the vacuolation, or even give a clue to its pathology, I have collected and tabulated the various cases in which I have found this

[1] "Nuclear Vacuolation in Nerve Cells of Cortex Cerebri," *Brain*, 1889, p. 520.
[2] "Text-Book of Mental Diseases," London, 1889.

change. My endeavours in this direction have not been fruitless, for it has been determined in each case in which vacuolation has been present that the original disease has been one of those which, it is now generally recognised, prove fatal mainly by toxæmia. In all those conditions mentioned in the literature in which vacuolation has been found, the presence of a virus circulating in the blood, either of organic or inorganic nature, or a toxin of microbic origin cannot be excluded, I venture, therefore, to assume *that vacuolation of the nerve cells of the cortex cerebri is in all cases induced by such a toxæmic condition.*

Before proceeding to detail the arguments and evidence in favour of such a thesis, I will briefly recapitulate the more important points in the anatomical features of vacuolation.

Survey of Anatomical Appearances.

It is found that the vacuoles may form either (1) in the nucleus, or (2) in the surrounding granular protoplasm of the cell body, or in both together. Vacuolation of the nucleus alone is more frequently observed in the superficial layers of the cortex, particularly the second layer, and the outermost cells of the third or small pyramidal layer, while vacuolation of the surrounding protoplasm is more common in the more deeply situated and larger cells.

1. *Vacuolation of the nucleus.*—Considering then, in the first place, the change as it occurs in the nucleus, the initial visible alteration is a slight uniform swelling of the whole of the nucleus, which is accompanied by an alteration in its normal reaction to the staining material; this is indicated by parts of the nuclear body appearing much fainter than others, and at the same time to a great extent becoming dispossessed of their characteristic coarse reticular granulation. Subsequent to these alterations one or more minute, circular, clearly refractive, oily droplets form, either in the nucleolus or in the other altered portion of the nucleus; such droplets multiply, enlarge, and may coalesce, until finally the whole nucleus is converted into one large cavity filled with lustrous, oily material. At a later stage the nuclear envelope bursts, allowing the contents to escape, and a well-defined non-lustrous vacuole is left. Frequently, however, the individual fatty collections burst without coalescing, and in that case the nucleus may come to be represented by from two to ten or more such circular vacuoles, separated from one another by delicate sepiments. Concurrent with this vacuolation of the nucleus, granulation of the surrounding protoplasm almost invariably occurs.

2. *Vacuolation of the surrounding protoplasm.*—Vacuolation of the investing protoplasm is more frequently observed in the more deeply situated and larger cells, namely, the large pyramidal and multipolar cells. The process of formation is similar to that seen in the nucleus. It commences with an alteration in the normal staining reaction of the

protoplasm, and is followed by the appearance of minute oily droplets, which, after enlarging by coalescence, burst and lead to the formation of the vacuole. In the cells in which this protoplasmic vacuolation occurs, the adjoining protoplasm is almost always seen to be in a condition of granular degeneration; the nucleus is frequently pressed upon and pushed to one side or towards the apex or base of the cell body; pigmentary degeneration often coexists; the normal number of cell processes is not uncommonly diminished; and in the altered outline of the cell one can often distinguish the rent through which the oily material which formerly filled the vacuole has escaped.

A remarkable point concerning both the nuclear and protoplasmic vacuoles is, that they are not tinted, so far as I know, by any of the ordinary staining reagents. How long they maintain their circular or oval shape it is difficult to tell, but that complete disintegration of the cell eventually occurs is certain.

Accompanying Vascular Changes.

No writers in their description of the anatomical appearances of the cortex, in cases in which vacuolation is present, have made any special reference to accompanying vascular changes, and have certainly never associated any vascular change with the vacuolation.

There is now one change, the existence of which I have observed with the greatest constancy and regularity in the cases which I have examined, namely, fatty degeneration of the fusiform muscle nuclei and of the non-striped muscle fibres of the small vessels supplying the cortex and distributed throughout it. This fatty change is, as usual, indicated by the presence within these fibres or nuclei of one or more clear, round, highly-refractive bodies, and is easily demonstrated by the fresh method (Plate XXIV. Fig. 1). In phthisis and pneumonia, in which two conditions, as I shall again mention, the existence of cell vacuolation may almost invariably be determined, I have singularly constantly discovered this associated vascular change; I have also observed it in nine out of the ten cases of epilepsy examined, and its presence in phosphorus poisoning and subjects of alcoholism is well known. The degree of the fatty degeneration appears, on the whole, to vary with the extent of the vacuolation process, but in cases of phthisis pulmonalis, in which the vacuolated cells have not been particularly numerous, I have still found the fatty change in the vessels fairly well marked.

I am inclined to look upon the coexistence of such a degenerative alteration of the vessel wall, with vacuolation of the nerve cells, as a point of the greatest importance, and one, as I shall presently attempt to prove, which lends strong support to my theory of the pathogeny of vacuolation.

Diseases in which Vacuolation of the Cortical Nerve Cell occurs.

The following are the diseases in which the occurrence of this alteration has been described:—

1. In epilepsy; and in this disease, according to Bevan Lewis, it is more especially limited to the nuclei of the cells of the second layer.

2. In diseases produced by the absorption of metallic poisons, such as phosphorus and arsenic.

3. In chronic alcoholic insanity. In this affection Bevan Lewis has described the occurrence of vacuolation in the large cells of the fifth layer.

4. Cases of dementia (Whitwell), and cases of senile cerebral atrophy.

5. In chronic pulmonary affections.

During the past year I have made a long series of investigations into the condition of the brain in persons dying of pulmonary affections, and may mention that it is mainly these observations which have induced me to formulate the theory touching the causation of vacuolation which is now presented.

The current opinion is that it is only in those pulmonary affections which are chronic that vacuolation occurs, and that in those conditions it is solely and simply due to deficient oxidation. My observations, however, certainly negative or put into the background the importance of chronicity and deficient oxidation pure and simple, and have led me to believe that vacuolation of the nerve cell of the cerebral cortex occurs rather in those lung diseases, such as phthisis pulmonalis and lobar pneumonia. These diseases are dependent upon a micro-organismal infection and growth for their production, and that in these diseases the toxæmia generated by that microbic growth is the prime pathogenic factor in producing the vacuolation.

For the purpose of determining these points the unhardened brains of 47 patients dying of various forms of pulmonary phthisis, and 13 cases of acute lobar pneumonia have been examined. Taking, in the first place, the cases of phthisis, there was found in 44 out of the 47 brains examined distinct evidence of vacuolation of varying extent. Contrary to what has hitherto been held in the case of chronic lung affections, it was observed in these instances that the vacuolation was by no means confined in its distribution to the more deeply situated and larger cells (the large pyramidal, multipolar, and spindle elements), but that it was as frequently to be observed in the nuclei of the cells of the second layer and the superficial members of the small pyramidal layer; indeed, in many instances, it was only in these two superficial layers that the change could be detected, and in almost all the cases examined it was possible by diligent searching to demonstrate examples of the change in this situation (Plate XXIV. Fig. 2).

Secondly, with regard to acute lobar pneumonia: In the brains of 13

patients dying of this disease, vacuolation was found 10 times, and in some of these cases in which, be it noted, the lungs were found in a state of grey hepatisation, the change reached extreme limits, numerous vacuolated cells appearing in the field of the microscope in all layers and in sections from any region of the cortex.

In all these cases epilepsy, alcoholic poisoning, and the other already mentioned conditions in which vacuolation has been described, with the exception of dementia, were certainly excluded; and it may be remarked, with reference to Whitwell's statement of the occurrence of vacuolation in dementia, and in justice to that writer, that it is impossible for us to tell from his paper whether the dementia was not complicated by some other physical disorder which might induce the change. That such a complication existed is not unlikely, as, so far as my experience goes, I have not found that vacuolation is a prominent feature in cases of simple dementia.

6. The other conditions in which I have observed vacuolation with the associated vascular change are all examples of acute infective fevers. They are — typhoid fever (2 cases), dysenteric diarrhœa (3 cases), erysipelas (4 cases), pyæmia (2 cases), and septic endocarditis (1 case).

Pathology.

It will be noted as a most striking fact that in all the conditions which have just been mentioned in which vacuolation of the cortical nerve cell has been found to occur, with the doubtful exception of dementia, epilepsy, and senile cerebral atrophy, there is a toxic agent acting as a fundamental factor in the causation of the disease, a poison either of a metallic nature, as in the case of arsenic and phosphorus poisoning, or non-metallic, as in the case of alcoholic insanity, or lastly, a toxin generated by the presence within the body of numerous micro-organisms, such as the toxin of the tubercle bacillus in *phthisis pulmonalis*, the pneumotoxin generated by the Fränkel-Weichselbaum diplococcus, and the encapsuled bacillus of Friedländer in acute lobar pneumonia, and the typhotoxin of the Eberth-Gaffky bacillus in typhoid fever. Even in epilepsy, in which disease vacuolation was first observed by Bevan Lewis to be such an important feature, it is now impossible for us to exclude the presence of a toxæmic agent. The experimental researches which Voison and Peron[1] have recently made in France, and D'Abundo[2] in Italy, have led to the identical conclusion, namely, that there is a virus of some nature circulating in the blood of individuals affected with idiopathic epilepsy, a virus sufficiently powerful to destroy bacteria, and to injuriously affect rabbits and guinea-pigs when injected into them.

[1] *Archives de Neurologie*, September 1892 and January 1893. "The Toxicity of the Urine of Epileptics. Epitome," *Brit. Med. Journ.* July 8, 1893.

[2] "Sull'azione battericidæ tossica del sangue degli alienati," *Riv. Sper. di Freniati*, 1892, vol. xviii. pp. 292–329.

Marie,[1] going a step further, looks upon idiopathic epilepsy as a disease of infective origin, and both he and Lannois[2] place faith in the treatment of the disease by the injection of microbic products, in order to annul the effects of the assumed epileptic toxin, a treatment presumably based on the fact known to Hippocrates, and more recently drawn attention to by Séglas,[3] Queriaud,[4] Féré,[5] etc., that the convulsive attacks of epilepsy are frequently ameliorated, or even suspended, by the onset of an attack of an acute infective fever. Even if we disregarded this array of evidence we must still take into account the presence of an undoubted poison in the blood, in the shape of uric acid, which substance Haig,[6] basing his assertion on careful clinical observations, considers an assured cause of epileptic convulsions. With regard to the second exception, senile cerebral atrophy, is it not just that we should, in old persons, put some weight upon the fact of the presence of certain injurious agents which must necessarily be circulating in the blood, substances produced by the breakdown and decay of the healthy tissues, and sufficient to induce or expedite many of the morbid changes peculiar to senility, or, as Oppenheim[7] shows, to set up in some cases a polyneuritis presenting many of the characters of other forms of toxic multiple neuritis. With reference to the remaining exception, dementia, I have already stated that the literature on the subject, and my own observations, afford no sufficient data for assuming that vacuolation is prone to occur in pure uncomplicated cases.

With so much positive and direct evidence, is one, therefore, not justified in concluding that, in the case of the highly organised cortical nerve cell, so intrinsically dependent upon a pure and untainted supply of blood for its healthy maintenance, such a harassing factor as toxæmia must not only play a most important pathogenic *rôle*, but actually induces the remarkable vacuolatory change in all these conditions.

I am perfectly well aware that in presenting the theory, that in all cases a like agent is at work, I come into direct conflict with Bevan Lewis' view, that in epilepsy the change in the second layer is dependent upon "an intrinsic morbid factor in the cell itself," and has nothing whatever to do with vitiated blood, etc., but this view is one which, ever since its publication, has puzzled the minds of many neuropathologists, and is extremely difficult for me to accept.

[1] "Infections et épilepsie," *Semaine médicale*, July 13, 1892.

[2] "Traitement de la chorée et de l'épilepsie par des produits microbiens," *Soc. des Sc. Méd. de Lyon*, October 5, and *Lyon méd.* October 23, 1892, "Epilepsie et fièvre typhoide," *Revue de médecine*. Paris, June 1893.

[3] "De l'influence des maladies intercurrentes sur la marche de l'épilepsie," *Thèse de Paris*, 1881.

[4] "De l'épilepsie idiopathique: ses modifications sous l'influence des maladies intercurrentes et son traitement," *Thèse de Bordeaux*, 1884.

[5] "Note sur l'influence des maladies infectieuses sur la marche de l'épilepsie," *Soc. de Biol.* June 4, 1892.

[6] "Uric Acid in Diseases of the Nervous System," *Brain*, 1891, pp. 63–98.

[7] "Multiple Senile Neuritis," *Berlin. klin. Woch.* June 19 1893.

Bevan Lewis acknowledges in his work, that it is not unusual to find vacuolatory changes in other cell layers in addition to the second; this is a point of some importance, and one with which I entirely agree, as, after minutely examining the cortex in ten cases of epilepsy, I can definitely state that I have never failed to find some vacuolation in other layers, and in some cases it was just as strongly marked a feature in the deeper layers as in the second; this point is further confirmed by Wynne,[1] but that writer goes further in asserting that the preponderance of the vacuolation is always in the deepest layers. With this view I cannot acquiesce, as I certainly have seen cases in which the second layer has been very extensively and almost exclusively involved. This singling out of the second layer is undeniably a curious anatomical fact, but it is not peculiar to epilepsy, for in some cases of phthisis and pneumonia I have noticed that no other layer, with the exception of isolated cells here and there, has been affected in addition to this individual second layer, though admissibly the second layer has not been so gravely diseased as in the cases of epilepsy described by Bevan Lewis. Even if it be granted that the vacuolation of the second layer in epilepsy were due to an intrinsic morbid factor in the cells themselves, how, then, is the vacuolation which in many cases occurs in other layers to be accounted for? The same thesis in the case of the deeper cells is obviously out of the question. Now, in phthisis and pneumonia, diseases in which there is unquestionable evidence of toxins circulating in the blood, it is assuredly more rational to refer the production of the vacuolation to such an agent than to assume that the vacuolation is due to "an intrinsic morbid factor in the cell itself," and since in epilepsy, as I have pointed out, there is now positive evidence of the presence within the vascular system of some injurious agent, be it uric acid or an unknown toxin, it is fair to assume that that agent is exercising a similar effect upon the cortical cells in that disease. A fact that greatly favours this inference is, that in almost all the cases of epilepsy and phthisis, and other toxic diseases which I have examined, precisely similar fatty changes are to be observed in the non-striped muscle elements of the small cortical vessels. This is a change exactly analogous, as already mentioned, to that occurring in alcoholism, typhoid fever, and phosphorus poisoning, and since in these diseases there is a well-founded presumption, to the effect that the fatty change is induced by the direct virulent effect of the poisonous substance circulating in the blood upon the vessel wall, it is almost certain that a like potent agent is operating in both phthisis and epilepsy in producing the vascular change referred to. Great likelihood is thereby given to the view that in epilepsy, as well as in *phthisis pulmonalis*, and the many other conditions mentioned, the vacuolation of the nerve cells is also due to the toxæmia.

[1] "The Morbid Anatomy of Epilepsy," *Lancet*, August 19, 1893.

Again, referring to the special liability to vacuolation which the second layer cells seem to possess, I think that they are for two reasons predisposed to the change, reasons which further negative the likelihood of the existence of "an intrinsic morbid factor in the cell." One is, that though these cells are near the surface, yet their vascular supply is not so free as is that of the pyramidal and more deeply-situated cells, for the branches of the cortical vessels entering from the pia mater are much less numerous, and the capillary network is far less complex in the region of the second layer than in the deeper layers (*vide* Obersteiner[1]); secondly, I venture to state that the large size of the nucleus, in comparison with the total magnitude of the cell in the second layer, is of greater importance in this connection than is generally imagined.

Yet another point which supports the toxæmic theory which is here advanced is, that vacuolation is obviously a fatty change; it is also in all probability an acute change, for I have seen it in cases of toxic diseases which have proved fatal after some few weeks or even days; and in these cases, in the absence of any other known cause, must be the vacuolation attributed to that toxic infection. I venture to regard the change as one analogous to, and possibly coincident with, the cloudy swelling and subsequent fatty degeneration of cells of other organs, such as the liver and kidneys, which occur in the toxic diseases to which I have referred. The swelling of the nucleus, and the alteration in the normal susceptibility to dyes, and such like initial changes, seem to correspond to the cloudy swelling stage of cells of other organs. I have observed such alterations in the cortical cells in cases of septicæmia, and in these cases I am inclined to think that the attack has been so virulent and rapidly fatal that vacuolation has not had time to occur.

There remains to be added but one remark bearing upon the question under consideration—it refers to the occurrence of *phthisis pulmonalis* in the epileptic subject. It is well known that in epileptics under asylum treatment these two affections are particularly commonly associated, and my investigations have led me to believe that much of the vacuolation seen in the brains of epileptics suffering from phthisis must be due to that phthisis. I have seen an extreme degree of vacuolation in the cells of the second layer in young individuals, who have suffered from epilepsy with frequently recurring convulsions, and who have died of acute phthisis; while, on the other hand, those subjects of epilepsy, whose attacks have been infrequent, who have been free from tubercular taint, and in whom one has reason to suppose there has been less virus circulating in the system, have exhibited a less degree, in some cases almost no vacuolation, and the change has been evenly scattered in the various cell layers.

[1] "Ueber den Bau der nervosen Centralorgane," 2nd edition.

Concluding Summary.

The following is the conclusion to which I have been led in the study of this change:—That vacuolation of the nerve cell of the cerebral cortex is probably in all cases dependent upon a toxic poison of some nature circulating in the blood.

The probabilities in favour of this conclusion are so cogent as almost to amount to demonstration, and the following are the steps which I have taken to prove my view:—

1. I have shown that in all the conditions in which vacuolation has hitherto been described as occurring, there is such a poison at the root of the disease. Epilepsy (idiopathic) cannot be excluded from this class.

2. I have demonstrated the existence of vacuolation in *phthisis pulmonalis* and acute lobar pneumonia, and in cases of certain acute infective fevers, these being all instances of toxæmic diseases.

3. I have proved that vacuolation of the cortical cell is almost invariably associated with acute vascular degeneration.

4. I have pointed out that vacuolation of the nerve cell is probably an acute fatty change, analogous to that occurring in the cells of other organs, in the case of individuals dying of toxæmic diseases.

Note.—Though all the subjects investigated, with the exception of one case, that of a man who succumbed to typhoid fever, have been patients suffering from some form of insanity, it is obvious that I do not hold that vacuolation does not occur in the brains of individuals who are not afflicted mentally. On the contrary, I feel convinced that if the brains of perfectly sane individuals, who have succumbed to such toxæmic affections as have been mentioned, were examined after the method indicated such alterations would be demonstrable.

Hereto is appended a synopsis of the microscopical examination, etc., of the cases of phthisis, pneumonia, and infective conditions, upon which these observations are based.

[Table.

CASES OF PHTHISIS PULMONALIS.

No.	Sex.	Age.	Mental Condition.	Autopsy Notes.	Microscopical Examination of Cortex Cerebri.
1	M.		Chronic mania	Scattered miliary tubercle	Some vacuolated cells in layer 2 only.
2	F.		Do.	Early phthisis	A few vacuolated cells in layer 2; more numerous in deeper layers.
3	M.	33	Mania	Tubercular peritonitis, some small vomicæ at apices	All layers equally but not extensively vacuolated.
4	F.	41	Do.	Acute tubercular infiltration; no vomicæ	Distinct vacuolation of cells of layer 2.
5	F.	40	Melancholia	Advanced phthisis	Very few superficial cells changed; cells in deeper layers occasionally vacuolated.
6	F.	12	Microcephalic idiot	Extensive phthisis	Vacuolation in all layers and marked fatty degeneration of vessel walls.
7	F.	32	Mania	Pulmonary phthisis and tubercular enteritis	Some cells in layers 1 and 2 vacuolated; also fatty degeneration of vessels.
8	F.	39	Do.	Extensive phthisis	Only slight vacuolation.
9	F.	40	Dementia	Moderate phthisis	No vacuolation.
10	F.		Chronic mania	Extreme phthisis	Vacuolation in all layers, and fatty degeneration of vessels.
11	M.	48	General paralysis	Chronic phthisis and heart disease	Some vacuolation of nuclei of cells of *stratum cellularum pyramidalium of cornu ammonis.*
12	F.	52	Melancholia	Tubercular peritonitis; little pulmonary phthisis	Slight vacuolation; marked fatty degeneration of vessels.
13	M.	45	General paralysis	Acute phthisis	Marked vacuolation in the superficial layers, but little in deeper ones.
14	M.	40	Do.	Early phthisis	Distinct vacuolation in superficial cells and a little fatty degeneration of vessels.
15	M.	31	Do.	Extensive phthisis	Much degeneration and vacuolation of nerve cells throughout and vessels fatty.
16	M.	45	Dementia, sec. to mania	Extreme phthisis	Many cells of layer 2 have vacuolated nuclei; a considerable number of cells of deeper layers in a similar condition; vessels fatty and some nuclei of neuroglia also seem vacuolated.
17	M.	35	Chronic melancholia	Extreme phthisis	Sections from ascending frontal and ascending parietal regions only examined; no vacuolation discovered.
18	M.	51	Melancholia	Apical phthisis	Fatty vessels, but no vacuolated cells.
19	F.	31	Chronic melancholia	Extensive phthisis	A few second-layer cells vacuolated; more large pyramidal and other cells; slight fatty degeneration of the vessels.
20	M.	26	Melancholia	Extensive phthisis; tubercular ulcers in intestines; empyema	A few instances of vacuolated second-layer cells in different parts of the brain.
21	M.	33	Chronic mania	Advanced phthisis	A few instances of vacuolated cells in occipital region.
22	F.	28	Confusional mania	Moderately advanced *tuberculosis pulmonum*	Cells of all layers vacuolated.

CASES OF PHTHISIS PULMONALIS—*continued.*

No.	Sex	Age.	Mental Condition.	Autopsy Notes.	Microscopical Examination of Cortex Cerebri.
23	M.	36	Dementia, sec. to mania	Miliary tubercle; little cavernisation	Almost no vacuolation.
24	F.	29	Acute mania	Phthisis not advanced in lungs; ulcers in intestines; slight goître	Vacuolation of layer 2 and of motor cells in ascending parietal region; fatty degeneration of vessels throughout; pyramidal cells of cornu ammonis also vacuolated.
25	M.	27	Melancholia	Advanced phthisis	Instances of vacuolation rare, but many pyramidal cells are swollen and show altered staining of nucleus and protoplasm.
26	M.	16	Imbecility	Advanced phthisis and ulcers in intestine	Cells vacuolated in all layers.
27	M.	35	General paralysis	Very little phthisis; tubercular peritonitis	Little vacuolation; scarcely a cell in layer 2 altered.
28	M.	38	Chronic mania	Extreme phthisis; waxy liver and intestines	Fairly numerous vacuolated cells in layer 2 and in neuroglia; fatty vessels.
29	M.	30	Melancholia	Advanced phthisis	Some second-layer cells and a few small pyramidal cells vacuolated; more pronounced in some regions of brain than in others.
30	F.	60	Melancholia	Advanced phthisis and ulcers in intestine	Unmistakable vacuolation of a good many cells of layer 2.
31	F.	36	Chronic mania	Advanced phthisis (hæmorrhagic spleen)	A few vacuolated cells in all layers; a number of pyramidal cells atrophied and bereft of nuclei and processes.
32	M.	43	Do.	Advanced phthisis	Many pyramidal cells vacuolated; vessels fatty.
33	M.	66	Adolescent general paralysis	Advanced phthisis	Very slight but still undeniable vacuolation in layer 2; the cells are obscured by collections of small round cells.
34	M.	46	Chronic melancholia	A few small cavities at apex; ulcers in intestine; acute pericarditis	Only slight fatty degeneration of vessels and few vacuolated cells.
35	F.	35	Melancholia	Apices riddled with cavities	Extensive vacuolation of small and large pyramidal cells; varying in different parts of the brain.
36	M.	38	Chronic Melancholia	Phthisis not advanced; cerebral thrombosis	Marked fatty degeneration of vessels, and vacuolation of nuclei and protoplasm of pyramidal cells.
37	M.	24	Do.	Acute phthisis; endocarditis	Vacuolation of protoplasm or nucleus in cells of all layers; also fatty vessels.
38	M.	42	Delusional insanity	Chronic phthisis; tubercular pleurisy	A few cells of layer 2 and some small pyramidal cells vacuolated.
39	M.	40	Chronic mania	Chronic phthisis; pneumothorax	Extensive vacuolation especially marked in sections from second frontal and ascending parietal regions; vessels fatty.
40	M.	35	Dementia	Extreme pulmonary tubercle	Vacuolation of nucleus or protoplasm in all layers.
41	F.	48	General paralysis	Scattered miliary tubercle	Many cells of all layers vacuolated.

CASES OF PHTHISIS PULMONALIS—*continued.*

No.	Sex.	Age.	Mental Condition.	Autopsy Notes.	Microscopical Examination of Cortex Cerebri.
42	M.	41	Melancholia	Acute phthisis	A few cells in layer 2 vacuolated; more in deeper layers.
43	M.	27	Acute mania	Tubercular peritonitis	Many cells of deeper layers vacuolated.
44	F.	57	Chronic melancholia	Fibroid phthisis at left apex and scattered tubercle	Much vacuolation in all layers.
45	M.	38	Melancholia	Advanced phthisis	Vacuolation in all layers.
46	F.	67	Acute melancholia	Advanced phthisis	Vacuolation in all layers.
47	F.	21	Acute melancholia	Extreme phthisis	Extensive vacuolation in all layers; hardly a cell in layer 2 untouched.
			CASES OF ACUTE LOBAR PNEUMONIA.		
1	F.	36	Acute melancholia	Left-sided pneumonia, upper and lower lobes; grey hepatisation	Most extensive vacuolation in all layers and fatty degeneration of vessel walls.
2	M.	41	Acute mania	Left basal pneumonia; grey hepatisation	Marked fatty degeneration of vessel walls.
3	M.	39	Do.	Double basal pneumonia; red hepatisation	Some vacuolation in layer 2, and in large pyramidal cells.
4	M.	77	Senile melancholia	Right basal pneumonia; myocarditis	Vacuolated cells not very numerous, most are found in layer 2; fatty vessels.
5	F.	65	Organic dementia	Pneumonia, right; gangrene; cerebral thrombosis	Distinct vacuolation.
6	F.	61	Delusional insanity	Right lobar pneumonia; red hepatisation	A good many cells seen with swollen nuclei, but there is practically no vacuolation.
7	F.	45	Chronic mania	Right basal pneumonia (double); grey hepatisation	Most extensive vacuolation, involving all layers of cells, and spread all over the brain; very marked fatty degeneration of vessels.
8	F.	60	Do.	Apical (right) pneumonia	Unmistakable vacuolation, most marked in layer 2; fatty vessels.
9	F.	44	Do.	Right side, both lobes; grey hepatisation	Numerous in cells from angular region.
10	F.	61	Chronic melancholia	Right apical pneumonia; red hepatisation	Some vacuolation, but not much; fairly numerous instances of swelling of nucleus and body of cell, particularly in layer 2; early condition of fatty vessels.
11	F.	32	Melancholia	Right basal	Early vacuolation changes.
12	F.	19	Imbecility	Right apical	Well-marked vacuolation in all sections and in all layers; marked fatty degeneration in vessels.
13	F.	42	Melancholia	Right side, both lobes; grey hepatisation	Not much vacuolation.

CASES OF TYPHOID FEVER.

No.	Sex.	Age.	Mental Condition.	Autopsy Notes.	Microscopical Examination of Cortex Cerebri.
1	M.	(?)	Not insane	Perforation	Marked vascular degeneration and vacuolation in cells of all layers.
2	M.	63	Melancholia	Early typhoid	Slight vacuolation in layer 2 and initial changes.

CASES OF DYSENTERIC DIARRHŒA AND ENTERITIS.

1	M.	36	Imbecility, hydrocephalus	Ulcers throughout large intestine	Considerable nuclear vacuolation in all layers.
2	M.	51	Melancholia	Long - standing dysentery	Cells show every degree of vacuolation and subsequent shrinkage.
3	M.	53	Chronic mania	Croupous enteritis	Vacuolation of cells in all layers and fatty disease of vessels.

CASES OF ERYSIPELAS.

1	M.	64	General paralysis	Erysipelas affecting face and scalp	Cells of layers 1 and 2 and nuclei of small pyramidal cells in many cases vacuolated; vascular degeneration.
2	M.	41	Do.	Do.	Slight vacuolation of nuclei of cells and cell bodies; slight fatty degeneration of vessels.
3	F.	39	Mania	Erysipelas affecting arm	Early vacuolation changes and slight fatty degeneration of vessels.
4	M.	39	Chronic mania	...	Isolated vacuolated cells here and there.

CASES OF PYÆMIA.

1	M.	48	Chronic mania	Inflamed hæmorrhoids; septic infarcts in kidney	Early vacuolation changes noticeable in all layers, and granular degeneration; vessels markedly fatty.
2	F.	26	Puerperal mania	Septic uterus	Early changes in second layer cells; some cells in deeper layers vacuolated.

CASE OF SEPTIC ENDOCARDITIS.

1	F.	19	Acute mania	Acute parotitis; vegetations on mitral and aortic valves	Numerous cells in layers 2 and 3 have vacuolated nuclei, others have swollen and intensely-stained nuclei; deeper layers also involved.

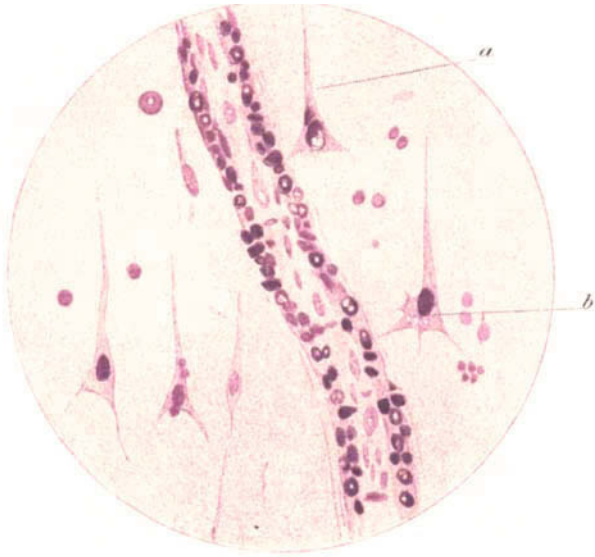

Fig. 1.

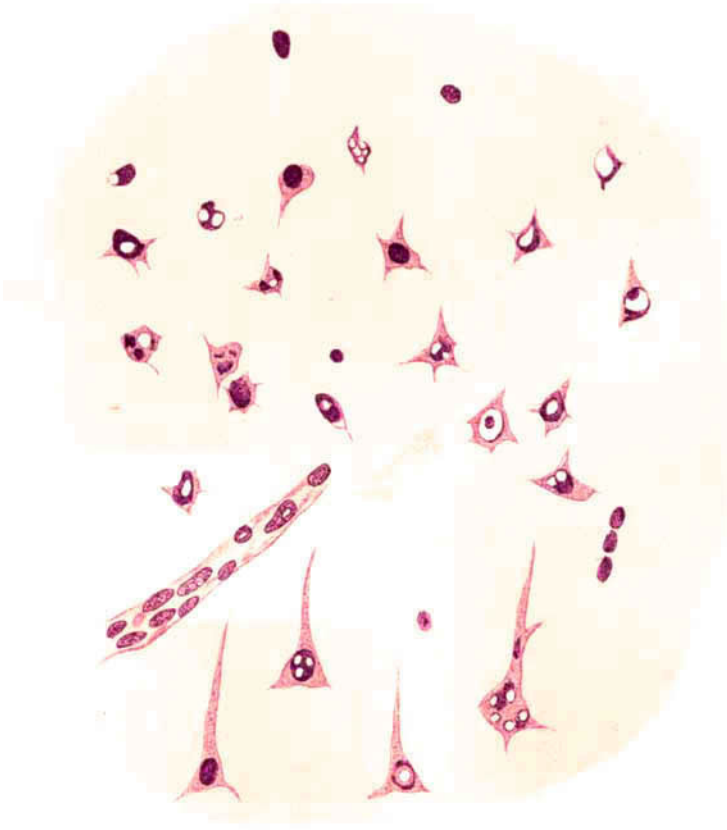

Fig. 2

DESCRIPTION OF PLATE XXIV.

FIG. 1.—Cortical artery showing the fatty changes referred to in the text. From the brain of a man æt. 39, who died in the *status epilepticus*. Occipital region; fresh cut section; stained with aniline blue black. Reichert oil immersion. Obj. $\frac{1}{12}$. × 750.

a. Small pyramidal cell with vacuolated nucleus.

b. Small pyramidal cells showing three vacuoles in cell body.

FIG. 2.—Showing various vacuolation changes in the second and third layers, from a case of acute phthisis.

Section from paracentral convolution. Fresh cut section; stained with aniline blue black. Reichert oil immersion. Obj. $\frac{1}{12}$. × 750.

The outlines of the cells and vacuoles were secured with the Zeiss camera lucida.