

ON HUNTINGTON'S CHOREA.

BY J. MICHELL CLARKE, M.A., M.D., F.R.C.P.

*Physician to the General Hospital, and Professor of Pathology, Univ. Coll.,
Bristol.*

THIS form of Chorea, characterised by its appearing first in adult or late adult life, its tendency to affect several members of a family, to be inherited, and to end in insanity, is now well-known, but cases are rarely met with in ordinary practice, and there have been few opportunities for *post-mortem* investigation of the morbid changes.

James T., a painter, aged 54, was admitted into the Bristol General Hospital for chorea and weakness, in September, 1895. The family history is given in the accompanying scheme. We could get no further back than the patient's grandfather, and no very definite account of him. The disease, however, appears to have come into the family through him, and not through either of his wives. On the male side there is also a history of rheumatism running through the family, and in both males and females a tendency to premature senility as shown by early grey-ness of the hair, and loss of the teeth is noticeable. Both the patients seen had the arcus senilis and well-marked degeneration of the arteries.

The patient was, like his brother, a small, thin man, looking older than his years, with marked arcus senilis and thickened, tortuous arteries. He had always worked hard, lived a regular and temperate life, had had no venereal disease, nor any bad illness. There was no history of any fright or great mental emotion, nor of any kind of fit or apoplectiform attack. There was no evidence of any past or present lead-poisoning. According to his wife the first symptom noticed was involuntarily stamping of the right foot five years previously; two or three months later, twitchings came on in the right and then in the left arm; soon all four limbs were affected. The patient himself said that he first noticed the twitchings on waking up one morning five years previously, and that they had persisted ever since,

GRANDFATHER OF PATIENT, JAMES T.
By second wife.

By first wife.

Female, single. Not known if affected with chorea. Died insane in an asylum at age 60.

Female, died, aged 60. Always nervous, but died sane. Lost her teeth and became grey haired very early.
Three children all healthy.

MALE, DIED, AGED 54. Chorea came on before insanity. Became grey and lost his teeth early. Died in Fishponds Asylum; notes say "mental disorder—mania. Duration of disease, 2½ years; first attack; was incoherent, violent, had aspect of chorea disease, his arms and legs constantly jerking." Wife healthy.

MALE, LIVING, over 80 years of age. Chorea came on at 50, and he had lost his teeth and had white hair then. Has been in and out of asylum several times, but is sane in intervals. Farmer; unmarried.

Male, died, aged 56. Tailor; married. No choreic symptoms. Died insane in an asylum. Had eleven or twelve children, of which history of two only could be obtained

Elderest son died, aged 23, in an asylum.

SON, AGED 32. Chorea came on about two years ago. Is now in Bath Asylum. Married, and has two or three children, who are healthy.

JAMES,* AGED 54, the patient.

Female, aged 29. Married, healthy

Son, aged 27. Healthy.

Daughter, aged 25. Healthy.

George, aged 50. Died in Fishponds Asylum, 1895. Chorea and insane (the second patient).

Two sons and one daughter, all quite healthy.

Sister, aged 42. Has lost all but one or two teeth, and is growing grey. Is very nervous and excitable, but shows no distinct signs of chorea.

Three sons and two daughters, all healthy.

* A twin brother died when two days old.

gradually growing worse. During the last six months he had been less intelligent, his memory had been failing, and his manner was changed. For two nights before he was admitted his wife had to sit up all night with him, as he was in a very excited state, looking wild, and talking constantly and incoherently. After admission he was quite quiet.

State on Admission.—Abdominal and thoracic viscera normal. No cardiac murmurs; heart sounds being normal. Urine normal. Constant choreic movements affect all the muscles of the trunk and limbs; walking is difficult on account of them, but though the knees are often suddenly flexed, the spasms are not strong enough to throw him down. The facial muscles are affected, the patient making grimaces from time to time; the tongue can be protruded, but is jerked backwards and forwards. The ocular muscles are unaffected. During voluntary movement the chorea becomes worse, and the hands and arms especially are agitated by spasmodic jerking movements when he tries to do anything with them. He can, however, feed himself if his food is cut up for him. Though voluntary actions are thus interfered with they are not distinctly ataxic. Muscular power rather weak; dynamometer, 22 kilos., both for right and left hands. The muscles are small but show no wasting. Electrical reactions normal. The choreiform movements are constant during the waking hours, but cease entirely when he is asleep.

Eyes.—Pupils equal, of normal size, react well to light and accommodation. There was marked error of refraction; on ophthalmoscopic examination the right optic disc was pale, with mottling of choroid on nasal side (Guttate choroiditis). Left optic disc not so pale, choroidal changes were the same as in the right eye.

Superficial reflexes active, a well-marked "goose-skin reflex" is obtained over the skin of the chest and abdomen. Knee-jerks normal; no ankle clonus; front tap contraction present; no muscular rigidity. Sensation to touch and pain normal, and power of localising sensations fairly good, but very slightly deficient over the hands. No affection of smell, taste or hearing. The functions of micturition and defæcation are natural. His face is somewhat expressionless, and he does not succeed in frowning or expressing surprise. He answers simple questions well, but if they are at all complicated he answers irrationally. He often repeats his statements. He has no delusions or hallucinations. His memory is defective and inaccurate. He sleeps

well and has a good appetite. When in bed he can move his feet and legs well, and to any desired position, and there is no loss of the sense of position. The muscular sense appeared to be quite normal. He improved in nutrition during his stay in the hospital, but otherwise his condition was unchanged. He was given liq. arsenicalis in gradually increasing doses.

The younger brother of the above patient, George T., was in the Bristol Lunatic Asylum at the same time. I am greatly indebted to Dr. J. V. Blachford, Assistant Medical Officer to the Asylum, for notes of the case and of the *post-mortem* examination, and for the opportunity of seeing the patient and making the microscopical examination of the central nervous system. He was a small, thin, grey-haired man, who had for several years suffered from choreic movements affecting the limbs and trunk. He had never had syphilis. The diaphragm was unaffected, and he had no difficulty in swallowing. For three months previous to admission into the Asylum on July 1, 1893, he was irritable and dangerous, and for twelve months his memory had been failing. He was demented, and had the delusion that the attendants were keeping back money that had been sent to him, but apart from this delusion he was quiet, and showed some amount of intelligence and power of memory. He answered questions as to his past life readily and correctly. The thoracic and abdominal viscera were normal; the heart being unaffected. The skin showed a condition of mild ichthyosis, best marked over the abdomen and thighs. The muscles though small showed no decided wasting. The knee-jerks were somewhat exaggerated, but there was no ankle-clonus nor muscular rigidity. The pupils were equal and reacted well, the ocular movements were unaffected by spasm. He protruded his tongue spasmodically, and after much effort, and he walked with some difficulty on account of the muscular spasm. It is unnecessary to describe the choreiform movements, which were constant, and affected the muscles of the face, trunk and limbs, as they were precisely similar to those above described in the elder brother's case. They ceased entirely during sleep. In both cases the spasmodic movements were exactly like those of ordinary chorea. This patient died in the Asylum, after a few days' illness, of pneumonia, in November, 1895. The *post-mortem examination* was made twenty-seven hours after death by Dr. J. V. Blachford. There was lordosis of the lumbar spine. The *skull cap* showed a slight degree of transparency all over with some thinning at bregma. Pacchionian depressions well-marked. Diploë dense and scanty.

Measurements :

Average thickness	45 cm.
Diameters (Internal)	{	Antero-posterior	...	17 cm.
		Transverse	...	13 cm.
Circumferences	{	Antero-posterior	...	31.2 cm.
		Transverse	...	31.2 cm.
Horizontal	52 cm.

Except for some injection of the pia-arachnoid the membranes were normal, and the pia-arachnoid stripped easily, and was not adherent to the cortex. The gyri appeared normal. The grey matter over the motor area was well differentiated into a light intermediate band between two darker bands. The ventricles contained some excess of cerebro-spinal fluid. No abnormal changes were visible to the naked eye in the basal ganglia, pons, medulla, cerebellum, or spinal cord.

The whole brain weighed 44 oz., the pons, medulla and cerebellum, 6 oz. The xiphoid cartilage of the sternum was bifid. The *right lung* weighed 44½ oz.; the lower lobe was in a state of red hepatization, portions sinking in water, the rest of the lung was intensely congested and œdematous. The *left lung* presented some fibrous contractions at the apex; there was some general congestion and œdema. The pleural cavities were obliterated by general adhesions. The other thoracic and abdominal viscera presented no morbid changes. The brain and spinal cord were hardened in Müller's fluid.

The following table gives the average of numerous measurements of the grey matter taken from the convexity of the convolutions in the several lobes of both cerebral hemispheres, after hardening about three months in Müller's fluid, together with those of a case reported by Dr. Charles L. Dana, and of the normal grey matter as given by him in his paper.¹

The measurements are in millimetres.

	This case		Dana's case	Normal
Frontal lobe ...	2.50		2.85	3.1
Motor convolutions ...	2.56	Superior central ...	2.2	2.75
		Parietal lobule ...	2.2	
		Third central ...	1.9	
		Lower central ...	2.2	3.0
Temporal lobe ...	2.75		3.2 and 3.1	3.1
Occipital lobe ...	2.58		2.1	2.6 to 2.5

¹ *Journal of Nervous and Mental Disease*, vol. xx., p. 577.

Sections of the fresh cerebral cortex were cut and stained by Bevan Lewis's method ; and of the hardened brain from all parts of the cerebral cortex and from the cerebellum, after embedding in celloidin, were stained in hæmatoxylin and eosin, methylene blue, aniline blue-black, hæmatoxylin and picro-fuchsin (Van Giesen), and by Weigert's method.

Pia-mater.—Vessels full, especially over the frontal and motor convolutions, their walls were, as a rule, normal, but, in a few instances, slightly thickened.

Convolutions of frontal lobe ; vessels prominent, their walls healthy, and the perivascular spaces distended ; in superficial layers of the cortex there were a few microscopic hæmorrhagic extravasations. The layer of small granule cells was narrow and stained badly. The small pyramidal cells showed morbid changes, many of them appearing shrunken, others deeply pigmented, their nuclei obscure and processes stunted. The large pyramidal cells and branched spindle or multipolar cells of the fifth layer appeared healthy.

In the motor convolutions the vessel-walls were healthy, but here and there a few red blood cells had escaped from the vessels. In a very few places the perivascular sheaths contained numerous leucocytes, which were passing into surrounding tissues. The small pyramidal cells showed the same changes as in the frontal region ; a few of the large pyramidal cells contained much pigment obscuring the nucleus, but they were mostly normal. Cells of fifth layer normal. In both frontal and motor regions the number of small branched glia or interstitial cells seemed to be excessive.

In the occipital and temporo-sphenoidal lobes similar microscopic changes, but in less degree, were observed ; in the former the glia cells were especially conspicuous, and in a few places wandering cells were present in the pericellular spaces around the nerve cells. Sections of the cerebellum, prepared by the above methods, showed injection of the small vessels of the cerebellar cortex, but otherwise presented no abnormal changes. The fibres in the white core of the convolutions, the cells of Purkinje and of the granule layer, appeared healthy. Unfortunately the nitrate of silver process was for some reason, a failure in the cerebellum.

Sections were also prepared according to Dr. Berkeley's modification of Golgi's nitrate of silver method (BRAIN, vol. xviii., p. 473). This gave good results, with the drawback that in some cases in cutting the sections the cell processes became broken across by the microtome knife, and also, like all the nitrate

of silver processes, the staining is very capricious, only a proportion of the cells being stained; larger or smaller, as the case may be. Further, we do not know whether normal or abnormal cells best take the stain; so that so far as proportion of normal to abnormal cells is concerned, no conclusions can be drawn from the sections, but it was quite evident that there were a large number of morbid cells, and this stain also brought out the fact, observed in sections stained by the other methods, that the change is a partial one, healthy cells lying side by side with diseased ones. The most superficial layer of the cortex was healthy, the second layer stained very badly in all sections, and appeared narrow; those cells that were stained mostly appeared normal. The small pyramidal cells, as in the other sections, showed the most marked changes, many being shrunken, irregular in shape, their processes stunted with small nodose swellings upon them, and disappearance of the little "gemmulæ" in the affected processes. No such swellings were seen, however, upon the axis cylinder processes, when these were visible. The large pyramidal cells, and the cells of the fifth layer, showed much less marked changes, being, where stained, with some few exceptions, healthy. The nerve fibres of the white and grey matter and collaterals stained well and appeared healthy, both by the nitrate of silver and by Weigert's method. The glia cells were conspicuous in all parts of the cortex, especially in the frontal and motor regions, from their great number and large size, and appeared in many instances to be attached to pyramidal nerve cells, lying in immediate proximity to them. The occipital cortex was also rich in large, fine and richly-branched glia cells in its deep layer and subjacent stratum of white matter. In the parts of the cortex most affected by the morbid changes, the processes of the glia cells showed little nodose enlargements upon them, which I have not before observed. The pons and medulla appeared to be healthy. Spinal cord: grey matter in all parts normal; nerve cells in all parts healthy. The pia matter was thickened, and there was a slight increase of the processes running into the cord from it, and of the neuroglia throughout the cord. No system-degenerations were present, the white matter being otherwise healthy.

It should have been mentioned above that the fibres in the white centre of the cerebral convolutions appeared healthy, the vessels in parts, but not universally, much injected. The glia cells were conspicuous and abundant throughout all sections. No further changes were noted in the white matter.

To sum up, the morbid change consisted in a widespread but partial degeneration of the cells of the cerebral cortex, especially the cells of the second and third layer, most marked in the frontal and motor convolutions, together with an increased amount of interstitial tissue and number of neuroglia cells.

In this family males have been chiefly affected. It will be noticed that the first patient showed evidence of mental affection; and that in the case of the sons of the patient's youngest uncle, both insanity and chorea have come on at an earlier age than in the others. According to Diller and Suckling, the disease comes at an earlier age in each generation, but this is by no means always the case. Wharton Sinkler (*Journal of Nervous and Mental Disease*, 1889) states that the disease may skip a generation.

Another case of this disease was under my care in the Bristol Hospital in 1893. In this patient, a compositor, 46 years of age, the family history could not be fully obtained, but so far as could be ascertained, the tendency to insanity was less marked. His father was affected with choreiform movements, which came on two or three years before his death at 42 years of age; he was a temperate man, and was killed by falling from the roof of a house; the spasmodic affection of the muscles was said to have been the cause of the fall. The patient had two brothers and two sisters alive and well; two other sisters are affected with choreiform movements, one of the latter is in the workhouse, and is said to be crazy: her children are mentally defective, the Board-school teachers finding it impossible to teach them. There is no other case of insanity in the family. The patient himself used to drink at one time, but had been a teetotaler for twelve years. The illness began with loss of power in the legs, then the twitchings came on, and soon extended to all parts of the body. He also suffered from dyspepsia, and occasionally from attacks of frequent micturition. He was grey, poorly nourished, and looked ten years older than his age. The thoracic and abdominal organs were healthy. Heart of normal size, and the sounds normal. His face was rather expressionless; he spoke slowly and indistinctly, with a

somewhat slurred utterance. Intelligence defective; memory very bad, and inaccurate; he showed a marked want of power of sustained attention, and answered questions badly, wandering off to other subjects.

The muscular system generally was only moderately well developed; there was no wasting, the muscles being well nourished, but flabby and weak. No rigidity, nor excessive muscular irritability to percussion. The dynamometer gave 21 kilos. right, and the same left hand. No fibrillary tremor. No paralysis. The muscles of head, neck, arms, and legs, and to less extent those of trunk, were agitated by constant spasms, in their general characters exactly resembling those of ordinary chorea, but rather more sudden and shock-like. These choreiform movements ceased during sleep, were aggravated by movement, or by talking; when lying down his head was occasionally suddenly raised up from the pillow. The movements interfere with walking, and have caused him to fall down. The facial muscles are affected, and those of the eyelids, but not of the eyeball. He protrudes the tongue well, and has no difficulty in swallowing. The respiratory movements were occasionally noted to be a little irregular. There is no in-coordination of movement.

The special senses were unaffected; sensation of all forms was normal, except that there was some loss of the temperature sense over the feet. Knee-jerks normal. Superficial reflexes; cremasteric and right abdominal not obtained, others present, plantar exaggerated. Pupils normal, equal in size, react well to light and accommodation. The temperature was constantly sub-normal, 97° to 97.5° . The bowels acted regularly.

This patient's daughter, aged 14, was said by him to be suffering from the same disease; but I saw her, and found that she was affected with diplegia and athetosis, most marked on the right side of the body, and the result of injury to the brain during birth. This bears out an observation in the *Lancet* (December 21, 1895), "that this is almost invariably the actual condition in cases of so-called congenital chorea, so that the term is probably a misnomer, and the movements would be more correctly described as those of athetosis."

In a paper by Dr. E. S. Reynolds (*Med. Chron.*, vol. xvi., p. 21) will be found an excellent account of several cases, with references to the history and literature of the subject.

Important contributions to the study of the pathological anatomy of the disease have been made recently. Menzies (*Jour. Mental Science*, October, 1892, and January, 1893) describes two families: in the first, 25 persons out of 100 traced were affected, the average age of onset was 27·6 years, and of death 43·7 years. In the second family: 13 persons out of 74 suffered, the average age of onset being 37·2 years, and of death 54 years. He concludes that the disease may descend from either parent to either sex, but that males are more commonly affected.

The *post-mortem* changes in the brain were slight coarseness of neuroglia, thickening of vessels, cell-degeneration, and, in hardened specimens, a few spider cells; in the cord, a diminution in the cells of Clarke's column, slight sclerosis of the ascending antero-lateral tract in all parts, and sclerosis of the posterior columns in the cervical region.

Oppenheim (*Centralb. f. innere Medicin*, 1894, p. 918) reports two cases: (1) a man who died of apoplexy, aged 75, in whom the disease had lasted sixteen years; and (2) a woman, who died of influenza, aged 56, in whom the duration was five years. There was a history of heredity, but I find no mention of insanity. *Post-mortem*, the heart was healthy in each case. In the brain the gyri were narrowed, and the sulci broadened in the motor, parietal and occipital regions; in these regions there were foci of hæmorrhagic infiltration in recent, fibrillar in later, stages in the sub-cortical layer. In the cortex, the small round cells next below the uppermost layer were deficient in number. The pyramidal (? large) cells were normal. The basal ganglia were normal. In the cord there was increase in the neuroglia cells and fibres, chiefly in the lateral columns; these changes he does not regard as secondary to the cerebral lesions, as they are not systematic, and further, affect only the neuroglia and vessels. The peripheral nerves examined were found degenerated; and this he attributes in the first case to old age, in the second to influenza. He thinks the essential morbid con-

dition to be a miliary disseminated encephalitis, cortical and sub-cortical, followed by atrophy of the cortex.

Dr. Charles L. Dana's (*Jour. of Nervous and Mental Disease*, vol. xx., p. 565) patient was a man in whom symptoms first appeared at the age of 33, and who died of typhoid fever at 37. The case constituted a transmission through females to the fifth generation. The convolutions of the brain showed anomalies in an interruption of the fissure of Rolando, and absence of the superior "*pli de passage*." There was a general thinning of the grey matter, most marked over the central convolutions; areas of cell-degeneration, the angular and small pyramidal layers being most affected, the cell-defect being primary, the vascular changes secondary. He considers the disease belongs to teratology, being an innate defect in cell structure.

Kronthal and Kalischer (*Virchow's Archiv.*, Bd., cxxxix., Abs. in *Neurol. Centralb.*, May 15, 1895), on the basis of the examination of three cases of chronic hereditary progressive chorea, conclude that the morbid process in Huntington's chorea consists in diffuse, rarely circumscribed, changes in the cortex of the brain; these are essentially disease of the vessel walls, increase of nuclei, cell accumulations, small hæmorrhages, and increase of the interstitial framework; whilst the nervous elements are only slightly affected.

There seems then to be no doubt that the cerebral cortex, especially of the motor convolutions, is the seat of disease; the chief difference of opinion being as to whether the primary change is in the nerve cells themselves or in the supporting tissue. So far as my own sections go they point to a degeneration of the nerve cells, with a concomitant increase of the neuroglia.

Changes of a similar nature to those above described, but less marked, have been observed in cases of severe chorea of the ordinary type. Severe cases of ordinary chorea occasionally end in mania. In a girl, who suffered from an acute attack of extremely severe chorea, which became complicated with acute mania, and who died from exhaustion, I found, *post-mortem*, intense congestion of the small arteries and capillaries of the cerebral cortex. The bright injection

of the vessels was obvious to the naked eye, and, under the microscope, sections of the cortex showed injected capillaries in extraordinary abundance, with some minute hæmorrhagic extravasations and cell-exudation, most marked over the motor area. The vessels of the basal ganglia and pons were also injected, but in much less degree.

The identical character of the spasms in cases of Huntington's chorea, and of ordinary chorea, points to affection of the same part or parts of the central nervous system in both cases. The severity, long duration and intractability of the symptoms in the former should render the recognition of the underlying lesion more easy, because the morbid changes would naturally be more extensive. The *post-mortem* changes above described indicate the cerebral cortex, especially of the motor convolutions, as the seat of the morbid change. The conclusion seems to be that all forms of chorea are due to disturbance in this region of the brain, although in each form the exciting cause of this disturbance is probably of a different nature, and the precise nature of the resulting alterations and capability of recovery vary accordingly.

In conclusion, I must express my best thanks to Mr. James Taylor for his kindness in making many excellent photographs of my sections, and to my clinical clerk, Mr. C. P. Mackie, for taking much trouble in investigating the history of the family above recorded.

EXPLANATION OF PHOTOGRAPHS.

FIG. 1.—Frontal cortex, low-power magnification; shows nearly whole thickness.

Degenerated and healthy cells in second and third layers; there are several degenerated cells to the left of the figure. Glia cells.

FIG. 2.—Motor cortex, low power. The surface of cortex lies to the left and above.

In the pyramidal cells of the second and third layers, some are healthy, others swollen, rounded, and irregular in outline. In uppermost part of figure is seen a glia cell attached to degenerating small pyramidal cell (a); above this, again, is a healthy pyramidal cell.

(In some cases the main process of the cell is artificially separated with a sharp fracture by the microtome knife.)

- FIG. 3.—Motor cortex, high power. Degenerating pyramidal cells; the one (a) on the left hand shows swellings on main processes, and absence of "gemmulæ," and the cell body is deformed. (The process itself shows fractures caused by the knife.)
- FIG. 4.—Motor cortex, high power. One or two healthy and other degenerate pyramidal cells. (Processes of some cells have again been broken in cutting.) (a) Healthy cell with neuron.
- FIG. 5.—Motor cortex, high power. Glia cells, with small nodosities on their branches.
- FIG. 6.—Occipital cortex, high power. Group of large, richly-branched glia cells in subcortical layer.

NOTE.—*The first two photographs should be viewed with a hand-lens.*

FIG. 2.

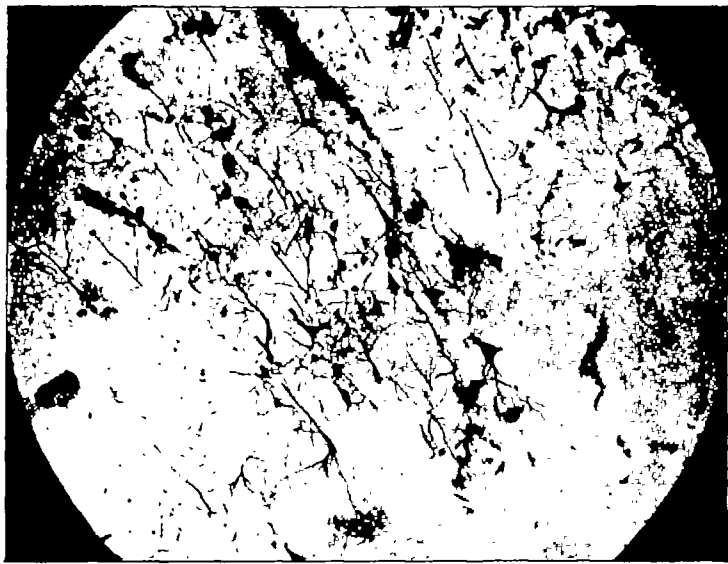


FIG. 1.



FIG. 4.

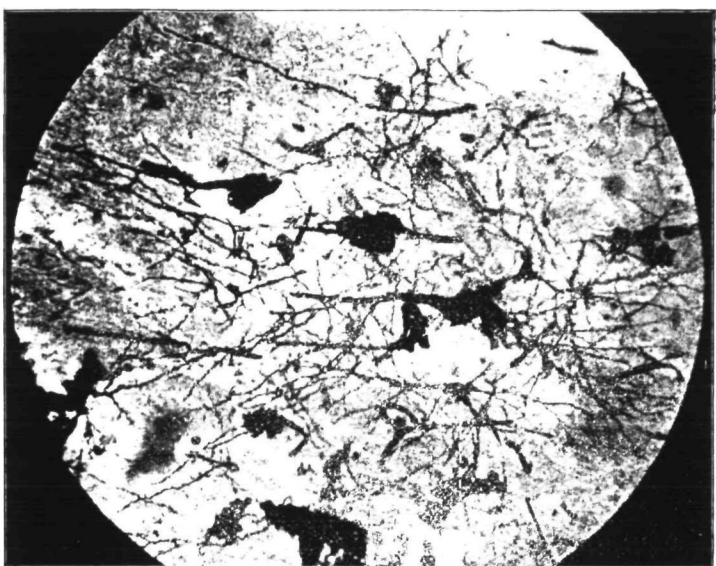


FIG. 3.

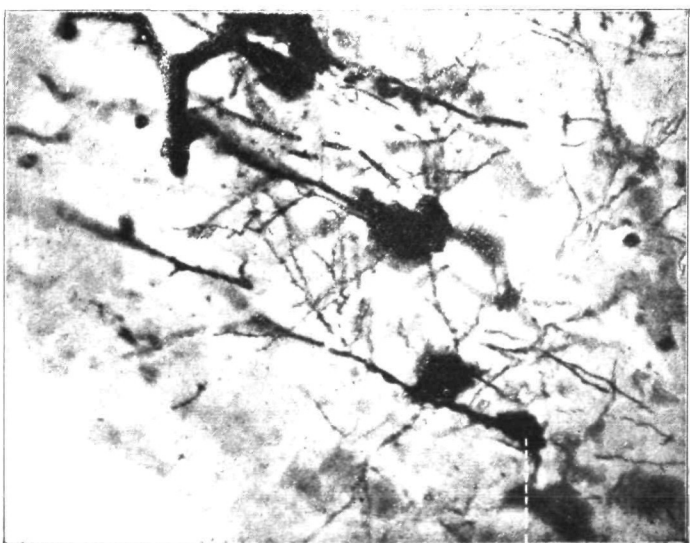


FIG. 6.

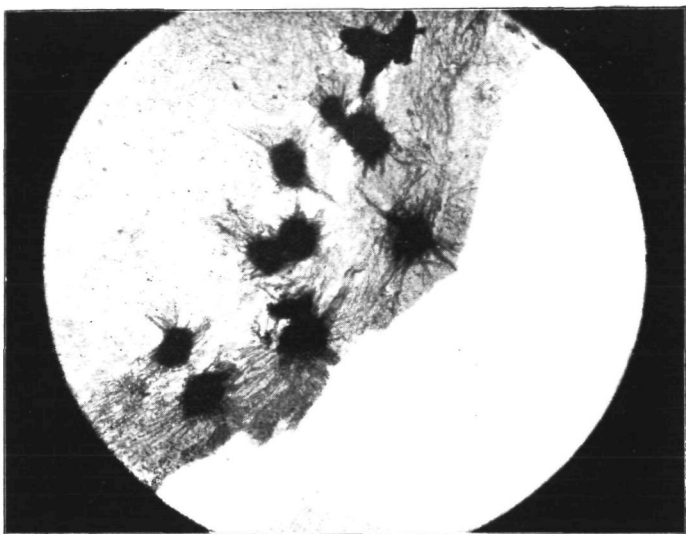


FIG. 5.

