THE JOURNAL OF NEUROLOGY AND PSYCHOPATHOLOGY.

Vol. V. NOVEMBER, 1924. No. 19.

Original Papers.

ON THE OCCURRENCE OF ABNORMAL DEPOSITS OF IRON IN THE BRAIN IN PARKINSONISM WITH SPECIAL REFERENCE TO ITS LOCALISATION.*

By JEAN LHERMITTE, Paris, WALTER M. KRAUS, New York, and DOUGLAS McALPINE, London.

HISTORICAL REVIEW.

The literature dealing with the occurrence of iron in the brain is now extensive, considerable attention having been given to this subject during the last few years. Some investigators have concentrated on the question of intracellular iron, others on the presence of iron in the walls of vessels and in the form of globules, and others on the presence of 'masked' iron as revealed by staining the brain macroscopically.

It appears to us that the literature dealing with this subject will be made clearer to the reader if a somewhat arbitrary classification be made on the lines indicated above :—

1. Intracellular iron occurring normally.
2. 'Masked' or 'functional' iron.
3. Abnormal deposits of iron in the vessel walls and in the form of globules.

1. *Intracellular Iron.*—Marinesco and Draganesco [34] have in a recent article reviewed the literature dealing with this part of the subject.

Mackenzie,[4] in 1897, in a report on the microchemistry of nerve cells to the British Association at Toronto, was the first to prove the

* From the Laboratory of Neuropathology, University of Paris.

normal presence of iron in certain cells of the central nervous system. This observation was confirmed by Scott [6] in 1899.

Marinesco [8] in 1909, in a further study of the subject, again insisted on the normal presence of iron in nerve cells. He demonstrated the existence of iron granules in the nucleus and protoplasm of certain nerve cells and found that the granules occurred almost exclusively in the chromophilic network. He further stated that, in many cells, the pictures obtained by the method of Perls (specific iron reaction) and the method of Nissl were superimposable. These observations have been confirmed in the main by Spatz,[27] Müller,[29] Lubarsch,[11] and others, who have shown that intracellular iron occurs particularly in certain regions, viz., the globus pallidus, substantia nigra, red nucleus, and dentate nucleus of the cerebellum. As regards the substantia nigra, iron is chiefly found in the cells of the zona reticulata and in other non-pigmented cells scattered throughout the region. The pigmented cells themselves do not contain iron. Iron has also been found by several observers in the cells of the caudate nucleus and putamen, and even in the cervical sympathetic ganglia (Marinesco and Draganesco [34]). In pseudobulbar palsy (two cases), epidemic encephalitis, congenital myxœdema, senility and general paralysis of the insane, these authors have found an increase in the iron contents of the cells in the regions which normally contain iron.

2. '*Masked*' *or* '*Functional*' *Iron.*—Guizzeti,[10] in 1915, described the normal presence of iron in the brain in certain regions by means of a macroscopic test with potassium ferrocyanide and hydrochloric acid. This test is easily performed as follows: the fresh brain, sectioned in such a way as to expose the basal ganglia, mid-brain, etc., is placed in a solution of ferrocyanide of potassium, and allowed to remain there for about thirty minutes. A two per cent. solution of hydrochloric acid is then poured on to the specimen, after which it will be seen that certain areas show a characteristic blue staining (Prussian blue reaction). Guizzeti pointed out that the areas which showed this iron reaction were (*a*) globus pallidus, (*b*) substantia nigra, (*c*) red nucleus, (*d*) dentate nucleus. He was able to verify these findings in animals. He further noted that the reaction was negative in the fœtus and the new-born, and became positive in the first few months of extrauterine life, occurring initially in the globus pallidus and later in the red nucleus, dentate nucleus and substantia nigra. The observations of Guizzeti were later confirmed by Lubarsch,[11] Müller,[29] Spatz,[27] and Gans.[33] The reaction appears first of all and with greatest intensity in the globus pallidus and locus niger. Later a less intense reaction is seen in the putamen, dentate nucleus and red nucleus. After a much longer interval, a very feeble staining can be detected in the thalamus and cortex of the cerebellum. Spatz [27] divides the iron which normally occurs in the brain into two

groups: (*a*) 'functional' or, better, 'masked' iron, revealed macroscopically by the application to the fresh brain of a method such as has been described, and (*b*) 'iron of disintegration,' which is seen microscopically in nerve and neuroglial cells and in the walls of vessels in the same areas as have been mentioned. Spatz has found iron only in the regions which constitute the centres of the extrapyramidal pathways, and he suggests that those areas which show an intense iron reaction play an important part in the regulation of muscle tonus.

3. *Abnormal Deposits of Iron in Vessel Walls and in the Form of Globules.*—Aschoff,[7] in 1902, first drew attention to the occurrence of calcium and iron deposits in vessel walls in the brain. Perusini,[9] in 1912, in a case of idiocy, made an exhaustive chemical study of certain globules which he found in the brain of his patient. Ellischer [1] described these globules as 'chorea bodies' (Körperchen), as he found them in a case of chorea gravidarum. This name is most misleading, since these globules occur in many conditions other than chorea, as was shown by Jakowenko [2] and Wollenberg.[3] Nevertheless, it is still retained in the German literature on the subject.

Within the last ten years the occurrence of these globules along with iron or so-called calcium deposits in the vessel walls, particularly in the globus pallidus, has been noted in various conditions by a number of workers, e.g., by Pierre Marie, Trétiakoff and Stumpfer,[15] and more recently Marinesco [35] in cases of congenital myxœdema; Perusini [9] and Weimann,[24] in cases of idiocy; Herzog,[17] in fatal monoxide poisoning; Buzzard and Greenfield,[12] Dürck [20] and McAlpine,[31] in cases of epidemic encephalitis; Dürck [19] and Weingarten,[18] in fatal malaria; Lewy,[32] in paralysis agitans, and various authors in cases of senility. The reader is referred to the works of Dürck,[20] Spatz [27] and Lewy [32] for further references to this subject.

Chemistry of Globules and Deposits in Vessel Walls.

Perusini,[9] in 1912, made a detailed chemical examination of these globules and of the deposit in the vessel walls in his case of idiocy. Little, if anything, has been added to our knowledge of the chemical constitution of these deposits since his work. He came to the conclusion that they were formed for the most part by iron. He was unable to prove the presence of calcium salts, as the specific tests for these were negative.

Lewy [32] in his recent book agrees with the findings of Perusini and states that calcium salts are rarely secondarily deposited. Lewy further alludes to the work of several observers who have regarded the deposits as being composed of calcium, basing their deduction on the characteristic staining reaction with hæmatoxylin.

In the majority of such papers, no mention is made of the use of a

specific iron reaction, such as that of Perls, the presence of calcium being based simply on the characteristic reaction with hæmatoxylin. Dürck,[20] however, states that he examined the globules, which he found in epidemic encephalitis, for iron and was unable to detect its presence. This is the only reference we have been able to find in which iron was absent from these globules when looked for, and we cannot but think that some error in technique or too prolonged formalinisation must be held responsible for the negative iron findings in Dürck's cases.

Lewy uses the adjective 'siderophilic' in discussing the chemical properties exhibited by these deposits. This term appears to us to be a good one, in that these deposits contain in addition a substance other than iron (*vide infra*). Spatz considers that besides a constant iron content, these deposits may sometimes contain calcium, but more usually the second element present does not give the specific calcium reactions. He applies the term 'pseudo-calcium' to the material composing these globules, a term which seems poor to us, since, on close analysis, it describes iron and a substance which is not calcium, and whose character and composition we do not know.

Perusini in his case of idiocy failed to find any evidence of a pre-calcification stage in the vessel walls. Alzheimer,[5] Schroeder [23] and Lewy have confirmed this observation in that they were unable to find any evidence of a degenerative process as a forerunner of the deposit.

Areas affected by Abnormal Deposits of Iron.

Both Guizzeti and Spatz have pointed out that the affected sites are those which *normally* contain iron. Most writers on the subject have noted the deposits in the walls of the vessels of the globus pallidus. Spatz further observed that the oral half of the globus pallidus was particularly the seat of these deposits, and this observation has been confirmed by one of us in an article already referred to. In addition to the globus pallidus, the putamen, dentate nucleus, cornu ammonis, and rarely the cortex of the cerebellum and cerebrum may show these deposits. Weimann [28] recently described, in a case of dementia, particularly widespread changes of this kind, affecting even the pons.

It is well recognized that iron may be found in parts of the brain other than those normally containing iron, i.e., in the neighbourhood of certain tumours and in the cortex in cases of general paralysis of the insane. Marinesco and Draganesco [34] have recently noted iron in the region of a softening in the occipital pole. In such cases the iron is not in the form of globules or in masses in the vessel walls, such as have been described above, but occurs as granules in nerve cells or as discrete deposits around the vessels. This iron is hæmatogenous in origin, and, as Spatz has pointed out, must be differentiated from the iron in the globus pallidus.

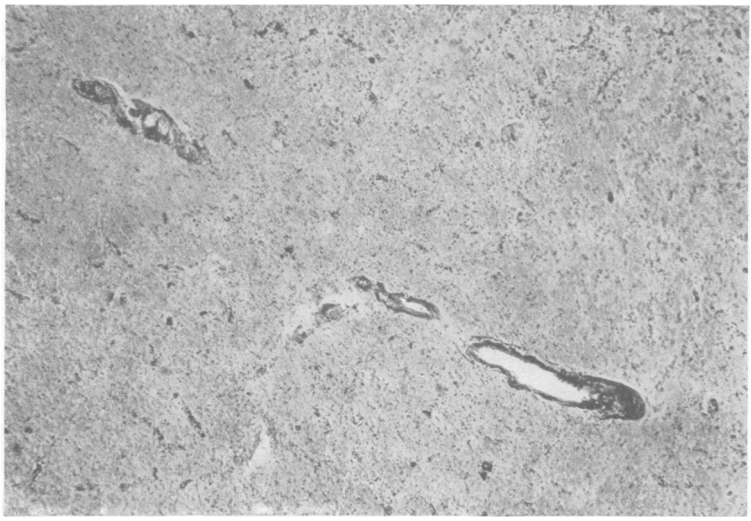

FIG. 3.—Globus pallidus. × 60. Deposit in vessel walls. Hæmatoxylin and Van Gieson.

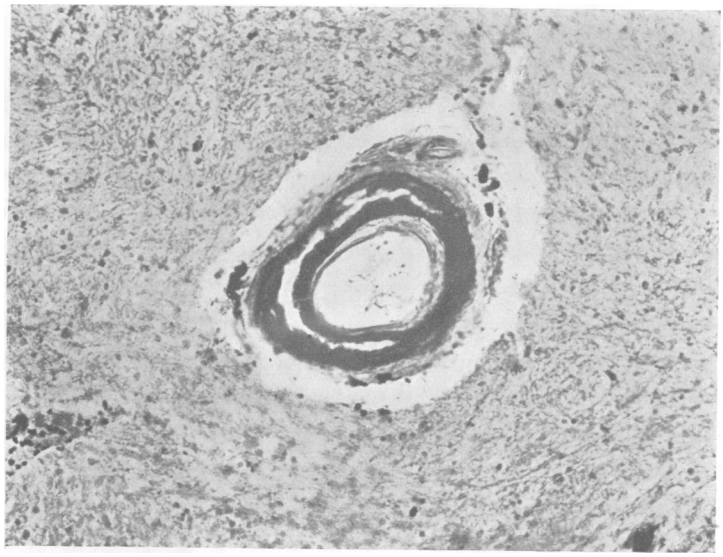

FIG. 4.—*Idem*. × 180. Magenta-verte lumière.

IRON DEPOSITS IN A CASE OF PARKINSONISM.

This paper is based on the pathological findings observed by us in a case of paralysis agitans in a male who was aged fifty-three at the time of his death in 1923. The disease first showed itself in 1919. Clinically his affection was notable for the complete absence of tremor. The following is a description of the siderophilic deposits which were abundantly present in the globus pallidus.

1. Normal Iron.

(*a*) *Intracellular.*—This was diminished in amount in the cells of the globus pallidus. On the other hand, the unpigmented cells of the substantia nigra showed a normal amount.

(*b*) '*Masked*' *Iron.*—This was not tested for.

2. Abnormal Iron.

This was present in large amounts in the form of globules in each globus pallidus, and in the form of deposits, but to a less extent, in the walls of its vessels.

(*a*) *Globules.*—The most striking feature of these was their number, which was greatly in excess of that previously observed by one of us (Lhermitte [30]) in a large number of observations dealing with this region. They corresponded in form to the description of these bodies as given by previous writers on this subject. They were distributed in relation to the capillaries. The larger forms, however, seemed to have little, if any, vascular relationship, although we cannot be certain of this, as successive serial sections were not made. In some places the capillaries showed numerous small globules ranged along their walls, while in the smaller arteries they were actually in the wall of the vessel. Their size varied considerably from the minute paravascular rounded form to large mulberry masses, lying apparently free in the parenchyma.

(*b*) *Vessels.*—The abnormal deposits of iron were seen in arteries, veins and about capillaries in the globus pallidus, though occurring most constantly in the arteries. In the latter the media was chiefly affected; in a few the internal limiting membrane stained more deeply than the remainder of the vessel wall. In one or two vessels this structure alone seemed to be involved.

3. Chemical Characteristics of Abnormal Iron Deposits.

In addition to staining deeply with hæmatoxylin, these deposits gave a positive Perls or Prussian blue reaction, thus showing the presence

of iron. In this reaction ferrous salts of iron are tested for, while, in the Turnbull blue reaction, ferric salts react.

The chemical formulæ are as follows :—

$$3K_4Fe(CN)_6 + 4FeCl_3 = Fe_3Fe_4((CN)_6)_3 + 12\ KCl$$
$$= \text{Prussian Blue.}$$
$$2K_3Fe(CN)_6 + 3FeCl_2 = Fe_3Fe_2((CN)_6)_2 + 6KCl$$
$$= \text{Turnbull Blue.}$$

Our results were all positive with the first reaction and negative with the second, thus indicating the presence of ferric salts. Further, by the employment of a saturated solution of ammonium sulphide, as a preliminary step, ferric salts were reduced to ferrous, and the same result was obtained.

The iron was present in the form of an organic compound, as none of the globules stained with ferrocyanide of potassium alone, but only appeared after the addition of hydrochloric acid.

In speaking of organic iron compounds, Lee [25] writes : " These will not give the iron reaction unless the complex iron compound has been broken up, that is, the iron ' unmasked ' by some reagent, i.e., acid alcohol."

That iron alone did not constitute the whole of the material in the deposit was further proved by the fact that, after sections were left in a concentrated solution of oxalic acid for twenty-four hours, the globules, although no longer giving the reaction for iron (this substance having been dissolved out by the action of the oxalic acid), still stained with hæmatoxylin, though less intensely than before oxalization.

In sections stained by hæmatoxylin or by the method of Perls the globules of medium or large size showed a more intensely staining centre. In sections stained by Perls' method, and counterstained either with hæmatoxylin or neutral red, the centre of some globules showed a characteristic blue colour (iron) while the peripheral zone took on the counterstain. In oxalated sections, stained by the method of Perls, and using the same counterstains, the centre no longer gave the reaction for iron and, indeed, scarcely stained at all with the counterstain, while the peripheral zone stained well with these.

These findings would seem to show that the centre of the globules was mainly composed of iron salts, while the periphery was composed of some other substance.

4. The Presence of Fat in the Globus Pallidus.

In frozen sections of the basal ganglia many fat globules were observed in the globus pallidus, but in no other situation. They were distributed throughout all segments of the globus pallidus, but their

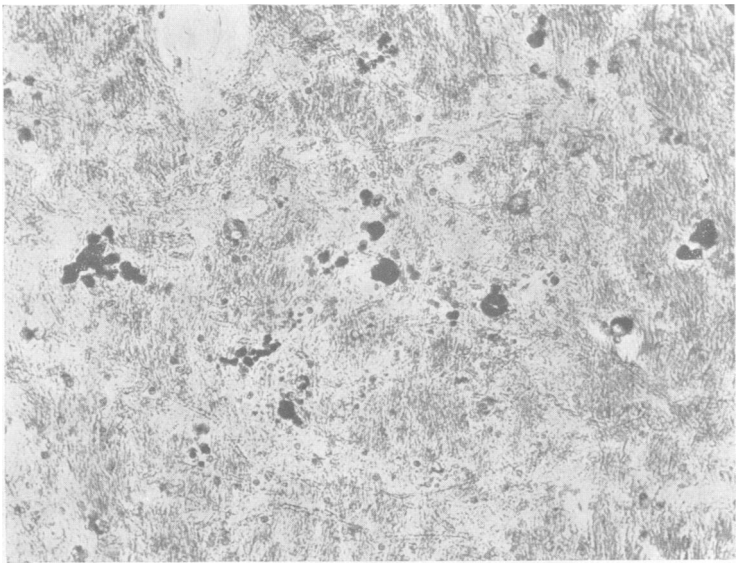

FIG. 5.—Globus pallidus. × 200. Frozen section showing siderophilic deposits and fat globules. Scharlach R and hæmatoxylin.

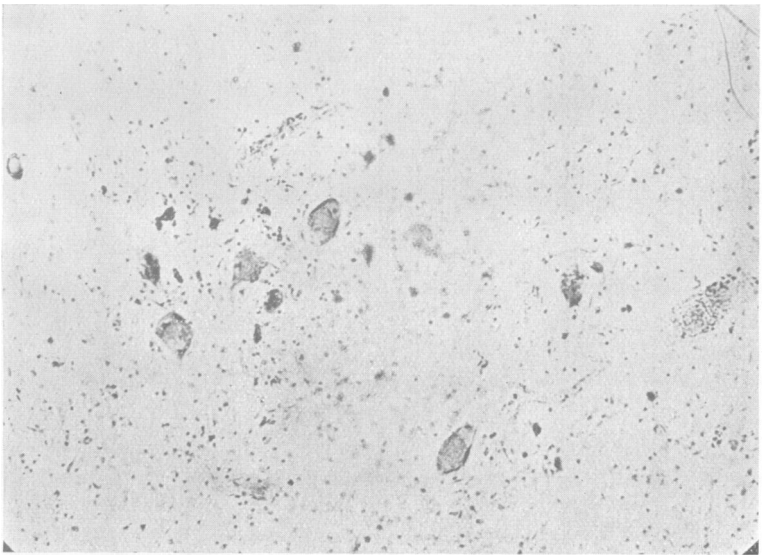

FIG. 6.—Substantia nigra. × 140. Note diminution in cells, chromatolytic changes, and deposition of pigment in the connective tissue meshes. Nissl's method.

number was fewer in the area which showed the siderophilic deposits, i.e., the oral half of the globus pallidus.

Little attention has been paid by the majority of observers to the occurrence of fat in this region. Spielmeyer [26] states that fat occurs normally in the brain and that its appearance must not be regarded as indicating pathological degeneration of the nervous tissues. He states that it is increased in amount as age advances. It occurs in nerve cells and in vessels which otherwise show no evidence of degenerative changes. He has observed fat in the cortex, particularly in the molecular layer, and also in the globus pallidus, in which region it occurs in the form of droplets free in the parenchyma.

We have examined frozen sections from the basal ganglia from three other cases of paralysis agitans and from one case of hemiplegia. In all of these we have found globules of fat, localized to the globus pallidus. No normal controls have been examined.

From the findings of Spielmeyer we may conclude that the presence of fat in the globus pallidus is not an abnormal finding. The question arises whether there is any relation between these fat globules and the siderophilic globules which are found in this region. McAlpine [31] has demonstrated the presence of a substance in the interior of these fatty globules which stained with hæmatoxylin, and has suggested that these indicate an intermediate stage between the fatty globules and the 'calcified globules.' (Iron was not tested for.)

In the present case, in sections stained with Scharlach R and counterstained with hæmatoxylin, some globules, irregular in outline, were observed, which stained a pale olive green. Under higher magnification, it was seen that these contained broken-down fat globules, while, in addition, darker staining areas (hæmatoxylin) were observed. More rarely a rounded globule was seen possessing a central area which stained blue black with a peripheral zone of pale olive green. In frozen sections, stained by the method of Perls and counterstained by Scharlach R, this darker staining substance in the centre was coloured blue, indicating the presence of iron.

These findings would seem to point to the possibility of the conversion of a fat globule into a siderophilic globule by precipitation within it of iron.

5. Calcium.

We were unable to prove the presence of this substance in the siderophilic globules.

Sections were treated by solvents of calcium salts, such as 2 per cent. solutions of hydrochloric acid and of sulphuric acid, for seventy-two hours. At the end of this time the globules and deposits in the vessels still stained with hæmatoxylin, though not quite so intensely as

before this treatment. This is some proof of the absence of calcium. When a 2 per cent. solution of hydrochloric acid was allowed to run under the coverslip on to an unstained section, no bubbles were observed. Further, no crystals of calcium oxalate were seen after sections had been treated by oxalic acid.

As to the chemical composition of the substance which still stained with hæmatoxylin after treatment with oxalic acid, we have been unable to come to a definite conclusion. It would seem that it is of complex chemical composition, and possibly formed of a combination of molecules of fatty substances, calcium, and iron.

6. Localization of the Deposit.

The fact that these deposits within the globus pallidus may be limited to but a part of it has been recognized. Spatz has commented on the greater amount of iron normally present in the more oral parts. McAlpine has observed that the oral portion alone is affected in some cases of chronic epidemic encephalitis. Our findings were as follows: the deposits of siderophilic globules were limited to the medial portion of the globus pallidus in its superior and oral parts. The distribution in the oral direction, however, was not found up to the tip; a definite zone was quite free from these globules. The external segment showed deposits for only a short distance below the plane shown in *Fig. 7*. Below, the deposits were limited to the internal segment (NLI). How far above the plane shown the deposits occurred we do not know. As far as we could determine the deposits began about one-twelfth of the distance (i.e., 1–2 mm.) from the base of the globus pallidus.

This limitation was not observed in regard to deposits in vessel walls. Vessels outside of the area described as containing globules were seen to have deposits, although no such affection of the vessels in the caudal half of the globus pallidus was observed. This we believe may be due to the carrying of deposits along the vessel walls.

7. Significance of the Abnormal Iron Deposits.

It seems to us of importance that the amount of these deposits, rather than their occurrence, should be taken into account in considering their significance. In Lhermitte's experience, these deposits occur rarely in paralysis agitans and other diseases involving this region. The deposit, when it does occur, is chiefly in and about the vessel walls, and the number of globules is small. Lewy,[32] in fifty-three cases of idiopathic paralysis agitans, found siderophilic deposits in the globus pallidus in only eight cases (14 per cent.).

We have already referred to the finding of these deposits in the

globus pallidus in a number of conditions by various observers. Some of these conditions were toxic or infective in origin, namely, epidemic encephalitis, malaria, carbon monoxide poisoning, while others had no such origin, i.e., congenital myxœdema, idiocy, Huntington's chorea, etc. We consider that the presence of siderophilic deposits in large quantities, especially when it occurs in globules, points to the presence of some toxic or infective process.

The present case was that of a middle-aged man, who showed a

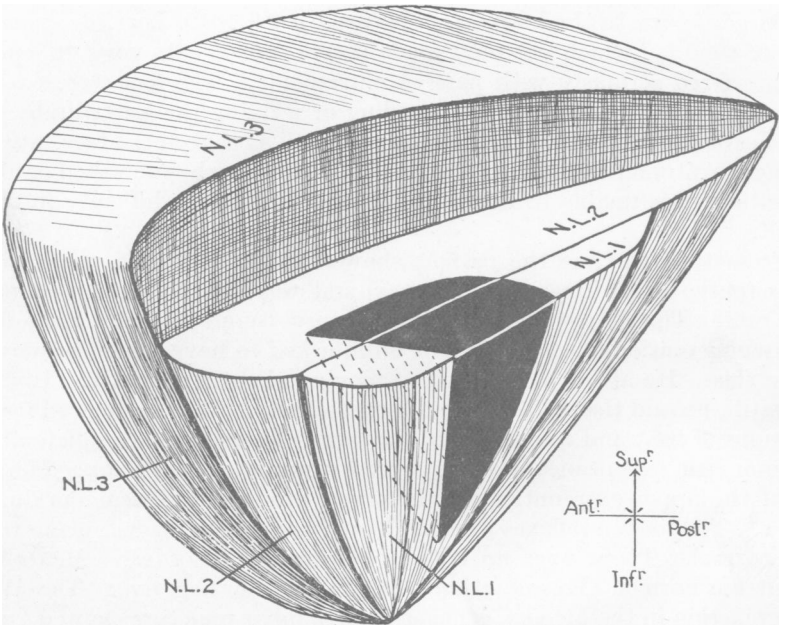

FIG. 7.—Diagram of right lenticular nucleus seen from the mesial aspect. The top of the globus pallidus has been removed, since this portion was not sectioned in series. Our observations were limited to the parts shown. N.L.1 = inner segment of globus pallidus. N.L.2 = outer segment of globus pallidus. N.L.3 = putamen. Area with cross hatching indicates the vertically cut surface, the cut corresponding to external medullary lamina. Area in black = iron deposits.

typical picture of paralysis agitans sine tremore. As Lhermitte and Cornil [21, 22] have pointed out, cases of senile or presenile Parkinson's disease show evidence of more general involvement of the brain, while cases due to the lacunar state, syphilis or epidemic encephalitis are more predominantly rigid with little or no tremor. We think that by virtue of the large amount of siderophilic deposit in the globus pallidus, the age of the patient and the complete absence of tremor, his condition originated in an encephalitic process. The lack of history of this infection cannot be regarded as satisfactory negative evidence in view of the clinico-pathological findings.

CLINICAL CASE REPORT.

Lor . . . . Age forty-nine. Admitted in 1919 to the Paul Brousse Hospital, Paris, for Parkinson's disease, with marked rigidity, which prevented all work.

P.H.—Beyond a severe injury to the leg occurring in 1900 causing a fracture of the left tibia, the past history was unimportant. No evidence of epidemic encephalitis could be obtained.

The illness began in 1919 with difficulty in using the left leg which had been injured. The rigidity then attacked the left arm and subsequently the right arm and leg.

On admission to the hospital on November 24, 1919, Lor . . . presented a severe rigidity, which not only made active movements very difficult but also interfered seriously with passive movements. The feet were extended and could not be flexed, and on standing or walking the lower limbs rested upon the balls of the feet. This rigidity, as well as that of the face, was most striking. Automatic movements were either very much diminished or absent. The patient was unable to dress himself and had much difficulty in feeding himself.

From time to time the patient showed the metadromic progression of Tilney (paradoxical kinesia of Souques) and was able to cross a room at a rapid rate. The hypertonia was accompanied by an uncomfortable feeling of muscular tension, and the patient often asked to have his limbs moved to relieve this. He also felt the need of moving about frequently. Unable to stand still, he said that he had to walk continually. He experienced frequent sensations of heat and congestion in the face. There was a complete absence of tremor either spontaneous or provoked by movement. Prolonged faradization of the upper extremities did, however, produce a typical Parkinsonian tremor. The tendon reflexes were moderately active. The cutaneous reflexes were normal. There were no tropic or sphincter disorders. Mentally the patient was normal. Examination of the viscera was negative. The Wassermann reaction in the blood was negative. Lumbar puncture showed a normal cerebrospinal fluid, in which the Wassermann test was also negative.

During his long stay in hospital the patient's condition progressed very slowly. During the final months the hypertonia and akinesia were at their maximum. The patient, confined to bed, was unable to perform any movement. He had to be fed ; occasionally there was incontinence. At this time it was noted that irritation of the sole of the foot evoked extension of the great toes, and an attack of rhythmic tremor, Parkinsonian in character, of that leg.

Symptoms of progressive cachexia and mental feebleness appeared and the patient died on January 12, 1923, after an attack of bronchopneumonia associated with mental confusion.

Remarks on the Clinical History.

The chief points of interest were (1) the comparative youth of the patient ; (2) the marked rigidity and absence of tremor. In this respect

the case recalls the variety of Parkinsonism following epidemic encephalitis. Although no history of this disease was forthcoming, it is not uncommon to see such cases in young persons, in whom no history of this disease can be obtained, but in whom it is certain that a ' fruste ' attack has occurred at an earlier date.

FURTHER PATHOLOGICAL FINDINGS.

Cortex.—No alteration in cell structure was noted, nor was there any increase in the neuroglial element. The vessels showed a definite ' *état criblé* ' and ' *précriblé.*'

Basal Ganglia.—There was no appreciable diminution in the number of cells in the caudate nucleus or putamen. In the globus pallidus, on the other hand, the motor cells were reduced to approximately half their normal number. This estimation was arrived at by counting the number of cells in six different fields (low power), the same being done in a section from a normal control of about the same age, cut at the same level.

Many of the remaining cells showed varying degrees of neuronophagia. These changes were general throughout the globus pallidus, and were no more marked in the region showing siderophilic deposits than elsewhere.

Throughout the basal ganglia there was some increase in the number of neuroglial cells, but this was most marked in the globus pallidus. The cells were for the most part of the small, neuroglial type.

Vessels.—As in the cortex and elsewhere, an ' *état criblé* ' and ' *précriblé* ' was moderately well developed.

Thalamus.—Appeared normal.

Fibre Tracts.—There was no evidence of any appreciable degeneration of striopetal or striofugal fibres of the globus pallidus.

Internal Capsule.—Normal.

Cerebellum.—Normal.

Midbrain.—The vessels in this region showed no perivascular lymphocytosis or other changes, except that in some there existed an ' *état précriblé.*'

The substantia nigra on both sides showed definite changes. The cells were considerably reduced in number. This appearance was not confined to any one part of the substantia nigra but was generalized. The majority of the remaining cells showed degenerative changes in varying degrees. There was much free pigment in the parenchyma. Neuroglial cell overgrowth, strictly limited to the substantia nigra, was observed. There was no accompanying neuroglial fibre overgrowth (method of Lhermitte).

There seemed to be a slight reduction in the number of nerve fibres in the substantia nigra. The cells of the locus cœruleus showed similar though less marked changes.

The remaining cell structures in the midbrain appeared normal.

Pons.—Apart from the locus cœruleus, no abnormal findings were noted.

Medulla and Spinal Cord.—Normal. Sections stained by the method of Loyez showed no tract degeneration.

The Significance of the Pathological Changes in the Substantia Nigra.

The reduction in the number of motor cells in the globus pallidus and the accompanying neuroglial cell overgrowth are in accordance with the previous findings of the Vogts,[16] Lhermitte and others, in cases of idiopathic paralysis agitans.

The changes in the substantia nigra were definite, consisting, as we have said, in a reduction in the number of cells and an accompanying sclerosis. It is not uncommon to find changes in the substantia nigra in cases of idiopathic paralysis agitans, where at the same time a definite lesion can be demonstrated in the globus pallidus. These changes usually consist of a reduction of the number of cells, although this is not uniform, and a group of apparently normal cells may be seen; in addition, in the area in which the cells have disappeared there is considerable neuroglial cell overgrowth.

Lewy in a series of fifty cases of idiopathic paralysis agitans, all of which showed a lesion in the globus pallidus, found alterations in the substantia nigra in eleven cases (22 per cent.). He states that these changes are never so marked as in the Parkinsonian syndrome following epidemic encephalitis.

Trétiakoff[14] considers that a lesion of the substantia nigra is responsible for paralysis agitans, basing his views on the examination of nine cases, in all of which he found alterations in the substantia nigra. We feel that very little importance can be attached to the findings of Trétiakoff, as in none of his cases does he make any reference to an examination of the globus pallidus.

We consider that the changes found in the substantia nigra in some cases of idiopathic paralysis agitans are secondary to the diminution of and alteration in the cells of the globus pallidus. It is also possible that a toxic or infectious process may affect simultaneously both structures.

This remark particularly applies to the postencephalitic form of Parkinsonism, in which both these structures may be affected. Almost invariably, however, the changes in the substantia nigra are much more marked than those in the globus pallidus, the cells of which may show no reduction in their numbers.

It may be a matter of considerable difficulty, in a case which has shown the clinical syndrome of Parkinsonism, to decide whether the changes in the substantia nigra, viz., a paucity of cells and sclerosis, are due to a primary lesion in that region, as in the postencephalitic form, or to the secondary results of a primary affection of the globus pallidus.

CONCLUSIONS.

1. Intracellular iron normally present in the globus pallidus was diminished in amount. In the substantia nigra, it was present in normal amounts.

2. Abnormal deposits of a siderophilic substance were found in each globus pallidus, in the form of globules; this substance was also found in vessel walls. The deposit was mainly in the form of globules, while the vessels were much less affected. This distribution is unusual and differs from that found occasionally in paralysis agitans and other conditions, in which the deposit is for the most part in the vessel walls. The present findings more closely resembled in this respect the deposits present in some cases of epidemic encephalitis.

3. The chief chemical component of these deposits has been shown to be ferric salts. Fat has been found which, when uncombined with iron, cannot be considered abnormal. We have been unable to prove the presence of calcium to our satisfaction. After removal of the iron component with oxalic acid, a substance which is insoluble in sulphuric and hydrochloric acids, which stains with hæmatoxylin, but which does not give the characteristic reactions for calcium, is left. We have been unable to determine the chemical composition of this substance.

4. We have shown that the siderophilic deposit was only found in the oral half of the globus pallidus in its medial and more superior parts. The tip of the oral part was not involved. Also, in this connection, it must not be forgotten that according to Spatz it is the oral half of the globus pallidus which *normally* contains most iron.

5. We have no proof that these deposits play any part in the symptomatology of the disease. It must be remembered that similar deposits have been reported in a variety of conditions, which as far as we know are unrelated to a disturbance of function of the globus pallidus.

6. Cellular changes were present in a typical form in the globus pallidus, the cells being reduced to half of their normal number. This finding is in accordance with Lhermitte's previous experience in the pathology of paralysis agitans.

7. A definite lesion was also present bilaterally in the substantia nigra.

REFERENCES.

[1] ELLISCHER, J., "Über die Veränderungen im Gehirne bei Chorea minor," *Virch. Arch.*, 1875, lxiii, 104. (32.)

[2] JAKOWENKO, "Zur Frage über die Lokalization der Chorea," *Neur. Centralb.*, 1889, viii. (32.)

WOLLENBERG, "Zur pathologischen Anatomie der Chorea minor," *Arch. f. Psych.*, 1892, xxiii, 167. (32.)

[4] MACKENZIE, J. J., "Microchemistry of Nerve Cells," *Rep. Brit. Assoc. Toronto*, 1897. (34.)

[5] ALZHEIMER, A., "Die Kolloidentartung des Gehirns," *Arch. f. Psych.*, 1898, xxx, 18. (32.)
[6] SCOTT, F. H., "Structure, microchemistry and development of nerve cells," *Trans. of Canad. Instit.*, 1899, vi. (34.)
[7] ASCHOFF, "Verkalkung," *Ergebn. d. allg. Path. u. path. Anat.*, 1902, viii. (32.)
[8] MARINESCO, G., *La cellule nerveuse*, Paris, 1909. (34.)
[9] PERUSINI, G., "Über einige eisengierige nichtkalkhaltige Inkrustierungen in Zentralnervensystem," *Folia Neurobiol.*, 1912, vi, 465.
[10] GUIZZETI, P., "Principali resultati dell' applicazione grossolona a fresco delle reazioni istochimiche, del ferro sul sistema nervoso centrale del l'uomo a di alcuni mammimiferi domestici," *Riv. d. patol. nerv. e. ment.*, 1915, xx.
[11] LUBARSCH, O., "Zur Kenntniss der im Gehirnanhang vorkommenden Farbstoffablagerungen," *Berl. klin. Woch.*, 1917, liv, 65. (32.)
[12] BUZZARD, E. F. and GREENFIELD, J. G., "Lethargic encephalitis: its sequelæ and morbid anatomy," *Brain*, 1919, xlii, 305.
[13] MARINESCO, G., "Études histologiques sur les oxydases et les paroxydases," *Soc. de Biol.*, 1919. (34.)
[14] TRÉTIAKOFF, C., "Contribution à l'étude de l'anatomie pathologique du locus niger," *Thèse de Paris*, 1919.
[15] PIERRE MARIE, TRÉTIAKOFF, and STUMPFER, "Étude anatomo-pathologique des centres nerveux dans un cas de myxœdeme congenital avec crétinisme," *L'Encéphale*, 1920, xv, 601.
[16] VOGT, C. and O., "Zur Lehre der Erkrankungen des striären Systems," *Journ. f. Psych. u. Neur.*, 1920, xxv. 131.
[17] HERZOG, H., "Zur Pathologie der Heuchtgasvergiftung," *Münch. med. Woch.*, 1920, lxvii, 558. (20.)
[18] WEINGARTEN, *Arch. f. Schiffs. u. Tropenhygiene*, 1920, xxiv. (20.)
[19] DÜRCK, H., "Die pathologische Anatomie der Malaria," *Münch. med. Woch.*, 1921, lxviii, 33.
[20] DÜRCK, H., "Über die Verkalkung von Hirngefässen bei die akuten Encephalitis lethargica," *Zeit. f. d. g. Neur. u. Psych.*, 1921, lxxii.
[21] LHERMITTE, J., and CORNIL, "Récherches anatomiques sur la maladie de Parkinson," *Rev. neurol.*, 1921, xxviii, 587.
[22] LHERMITTE, J., and CORNIL, "Étude clinique de la maladie de Parkinson et les syndromes parkinsoniens du veillard," *Rev. neurol.*, 1921, xxviii, 625.
[23] SCHROEDER, P., "Über Kolloidentarterung im Gehirn," *Zeit. f. d. g. Neur. u. Psych.*, 1921, lxiii. (32.)
[24] WEIMANN, W., "Über einen eigenartigen Verkalkungsprözes des Gehirns," *Monat. f. Psych. u. Neur.*, 1921, l, 202. (32.)
[25] LEE, A. B., *The Microtomist's Vade Mecum*, 1921.
[26] SPIELMEYER, W., *Histopathologie des Nervensystems*, Berlin, 1922.
[27] SPATZ, H., "Über den Eisennachweis im Gehirn besonders in Zentren des extrapyramidalmotorischen Systems," *Zeit. f. d. g. Neur. u. Psych.*, 1922, lxxvii, 261.
[28] WEIMANN, W., "Zur Kenntniss der Verkalkung intracerebrale Gefässe," *Zeit. f. d. g. Neur. u. Psych.*, 1922, lxxvi, 533. (20.)
[29] MÜLLER, M., "Über physiologiches Vorkommen von Eisen in Zentralnervensystem," *Zeit. f. d. g. Neur. u. Psych.*, 1922, lxxvii, 519. (34.)
[30] LHERMITTE, J., "Les syndromes anatomo-cliniques du corps strié chez le veillard," *Rev. neurol.*, 1922, xxix, 406.
[31] MCALPINE, D., "The pathology of the Parkinsonian syndrome following encephalitis lethargica, with a note on the occurrence of calcification in this disease," *Brain*, 1923, xlvi, 255.
[32] LEWY, F. H., *Die Lehre vom Tonus und der Bewegung*, Berlin, 1923.
[33] GANS, A., "Iron in the brain," *Brain*, 1923, xlvi, 128.
[34] MARINESCO, G., and DRAGANESCO, ST., "Récherches sur le metabolisme du fer dans les centres nerveux," *Rev. neurol.*, 1923, xxx, 385.
[35] MARINESCO, G., "Contribution à l'étude des lesions du myxœdeme congénital," *L'Encéphale*, 1924, xix, 265.

References without numbers in brackets have been read in the original. The numbers in brackets indicate the source of references referred to by others and not read in the original by us.