STUDIES ON LESIONS OF THE BASAL GANGLIA IN DEFECTIVES:

(1) A CASE OF *ÉTAT DYSMYÉLINISÉ* (HALLERVORDEN-SPATZ DISEASE).

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IN the following paper a case of *état dysmyélinisé* of the globus pallidus, or as it is often synonymously called, "Hallervorden-Spatz disease", will be presented. Records of thoroughly studied cases of this condition are still rather scanty and there is much need for a systematic extension of experience, the more so since, as Helfand (16, 17) has recently pointed out, progress in the elucidation of the condition has not always been enhanced by generalizations from findings based on too small a case-material. We are happy in having at our disposal the vast resources of the London County Mental Hospitals. It is hoped to follow up this paper by publishing further cases of a rather different nature, though with some characteristics in common with the case described here.

As a side-issue to the investigation there arises also the problem of selective vulnerability of the globus pallidus and other centres, which, in its broader aspects, has been dealt with by one of us recently (A. Meyer (19)).

CLINICAL HISTORY.

R. C—, a male idiot æt. 18 years and 3 months, was admitted to Caterham Mental Hospital on July 1, 1931. The following history was obtained:

Family history.—Patient is the sixth of seven children, the seventh being his step-sister. The father was aged 37 and the mother 40 years at the time of his birth. The grandparents were dead, and no details beyond the fact that they were stated to have been "normal" were available. The father is stated to squint and to "walk badly". The family are of superior artisan class. Of the siblings, the eldest, a woman of 30, is said to be "backward", but is self-supporting. The second, a boy, was accidentally killed when aged 16 years; the third and fourth died when aged 3 years and 2½ years respectively—cause of death not known. The fifth child, a girl of 22, is normal, as is the step-sister. The mother died of post-partum hæmorrhage at the patient's birth.

Personal history.—Stated to have been normal at birth. No record of jaundice, or of signs suggesting birth injury. The whole account of the neonatal and early infantile history is very scanty.

The patient was first admitted to an institution when aged 4. He was then unable to stand or walk, to speak, or to understand speech. He was wet and dirty in habits. He grimaced continually, and was at times noisy, but there is no

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note of choreo-athetosis. The knee-jerks were not obtainable, nor were the abdominal reflexes.

During the next three years there was some physical improvement, though he had occasional major epileptiform attacks.

The first definite record of choreo-athetosis was made in 1931, though it had evidently been present for some time. The plantar reflexes were then stated to be extensor, and the abdominals present. Definite mental improvement had taken place. His habits were clean, and he could feed himself with a spoon, and could " propel himself about the floor after a fashion of his own ". He was stated to be happy and cheerful.

He was admitted to Caterham Mental Hospital in the same year, as stated above.

He then showed paralysis with rigidity in all four limbs. Some voluntary movement remained, but he was unable to walk or stand. All the tendon reflexes were increased, the plantars were extensor, and the abdominals absent. Choreo-athetosis was very severe, the motor overflow involving the entire musculature The cerebro-spinal fluid showed an increase of protein but no other abnormality. The Wassermann reaction was negative in both the blood and cerebro-spinal fluid.

Mentally he appeared to be an idiot, but gave the impression that but for his severe physical handicap he might have been of somewhat higher grade. There was much facile giggling, and he was unable to speak at all. The speech disability was thought to be due to the nervous lesion affecting the musculature. of the speech organs, since he understood speech and could make peculiar noises· He was friendly and appreciated attention, and took an interest in events in his ward. His power of locomotion was remarkable in view of his disability: he could get about the ward floor, compensating in a remarkable manner for his choreo-athetosis and his rigidity, and taking immense pains in the process.

During the following year his toilet habits were at times faulty, and he had one major epileptic fit. There was no other change. He died on February 27, 1934, of Ludwig's angina. During his last illness he had several attacks of generalized clonic movements.

Pathological Findings.

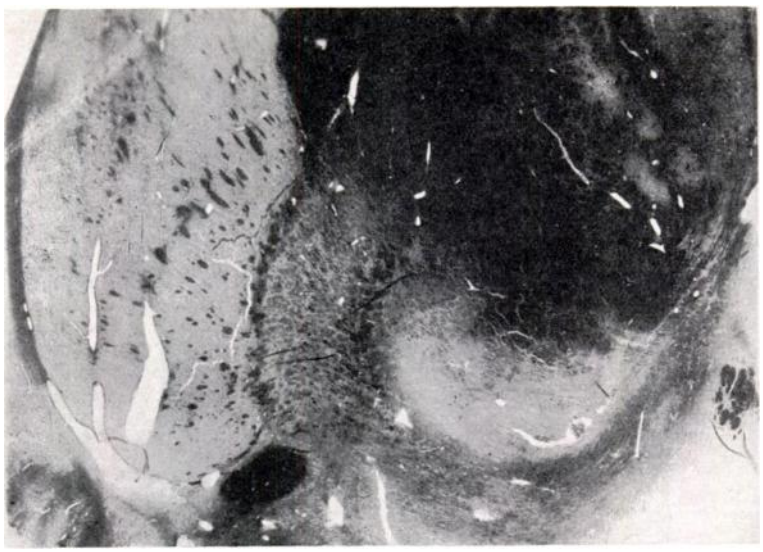
Macroscopic Inspection of the Brain.

The brain has been hardened in 10% formalin. Convolutional pattern and size about normal. Pia mater not thickened. Arteries of base normal. In coronal sections, cortex throughout of normal appearance. The white matter in general is of a slightly greyish colour, more so in the posterior than in the frontal areas, whereas the arcuate fibres have preserved their normal appearance. The difference in colour is so slight that it is not noticeable unless particular attention is paid to it. The same condition, although less marked, can be seen within the cerebellar white matter.

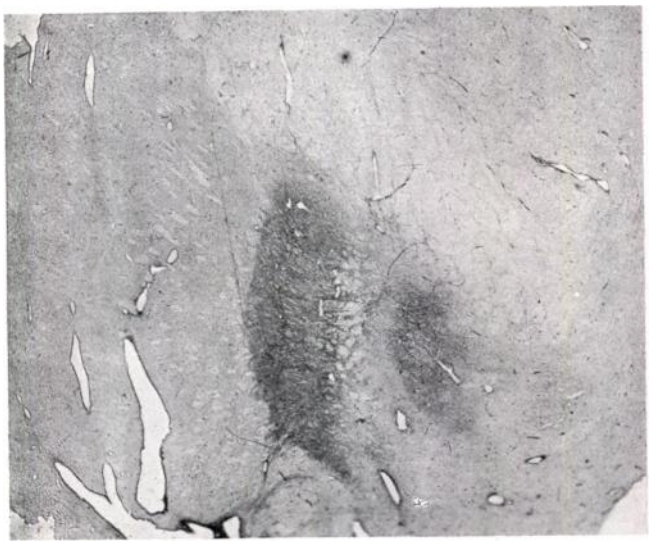
The basal ganglia are not diminished in size. The structure of the globus pallidus on both sides is not as distinct as in the normal, and is of a slightly yellowish-brown colour. The same is seen in the zona rubra. The zona compacta of the substantia nigra contains a considerable amount of melanin pigment, which is also seen, with the naked eye, within the locus cœruleus.

Histological Examination.

The most striking feature was the symmetrical and selective lesion within the globus pallidus and the zona rubra. Figs. 1*a* and *b* show demyelinization and glial sclerosis within the globus pallidus. It is easily recognized that the glial proliferation is more marked than the demyelinization, which is nowhere complete save in the medial limb of this nucleus. The fine network of fibres and the big transverse bundles have suffered equally. The lamellæ and the ansa lenticularis



(*a*)



(*b*)

FIG. 1.—*Globus pallidus*, showing demyelinization and glial sclerosis. (*a*) Spielmeyer's stain ; (*b*) Holzer's stain.

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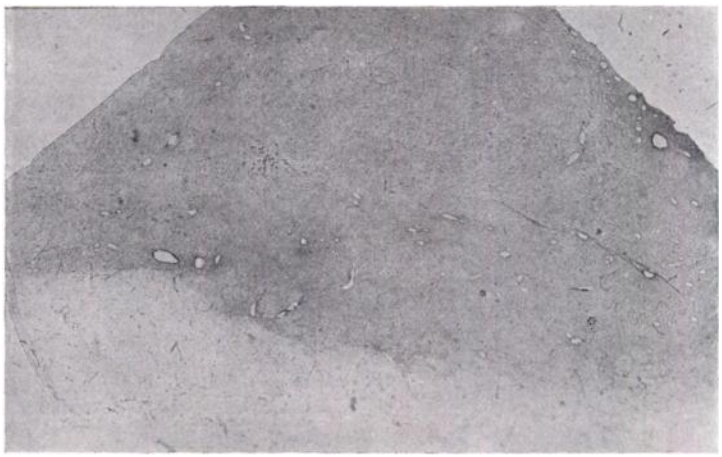
are better preserved, as seen in both the myelin and the glia picture. There is a corresponding degree of loss of axis cylinders, the remains of which are seen to be swollen and to show other signs of damage.

(*a*)



(*b*)

FIG. 2.—*Substantia nigra.* (*a*) Spielmeyer's stain ; (*b*) Holzer's stain.

A similar gliosis plus demyelination is noticed within the zona rubra (Fig. 2*a* and *b*) and, again symmetrically, within the corpus Luysii (Fig. 3*a* and *b*). In this nucleus the lateral areas are more affected than the medial, although the latter are not free from changes. Marked dropping out of ganglion cells was noticed only in the lateral areas.

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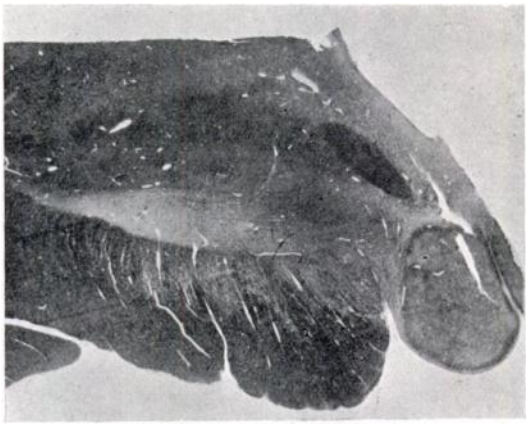
With Nissl's stain both the globus pallidus and the zona rubra exhibited a marked increase of dark green or yellowish-brown pigment in glial cells, adventitial cells and granular compound cells. The so-called pigment-globules were also found, particularly in the neighbourhood of vessels. It is not necessary to give a detailed



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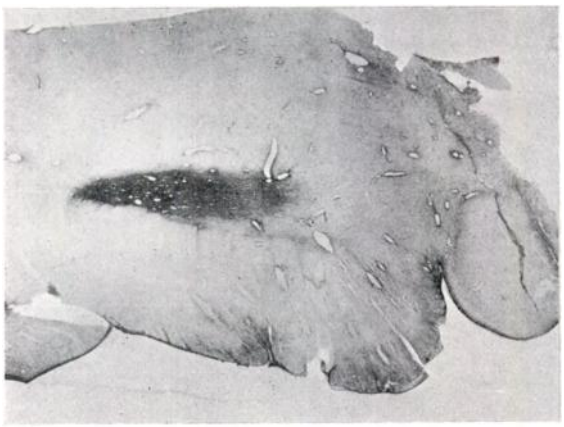

(*b*)

FIG. 3.—*Corpus Luysii*, showing gliosis and demyelinization, most marked in lateral areas. (*a*) Spielmeyer's stain; (*b*) Holzer's stain.

account of the variety of pigment, since in all essential properties it does not differ from previous descriptions. It must, however, be stated that it is not comparable in degree with other cases, e.g., the original case of Hallervorden and Spatz, preparations of which were available for comparison through the kindness of the late Prof. Spielmeyer. The pigment gave also (after prolonged treatment in formalin) only a feeble iron reaction. The amount of pseudo-calcium was negligible. It was

only slightly stainable with Scharlach R, whereas in the globus pallidus the free lipoid globules were found somewhat more frequently than normally. Many ganglion cells of the globus pallidus as well as the zona rubra had disappeared. Those remaining showed marked changes, particularly swelling of the cell-bodies and processes. Some of the cells had a balloon-like shape, due to swelling, but this was an infrequent finding. The nuclei of the ganglion cells were usually swollen and pale. Neither pink inclusions with the Nissl stain nor argentophile inclusions were found. There was a marked proliferation of the glia, particularly the macroglia. The size and appearance of Alzheimer cells was generally not attained, although in some places there was a striking similarity. The glia fibres formed a dense, often anisomorphic network.

The striate system was free from changes of note, except for perivascular gliosis, which was fairly often found and corresponded in the myelin picture to

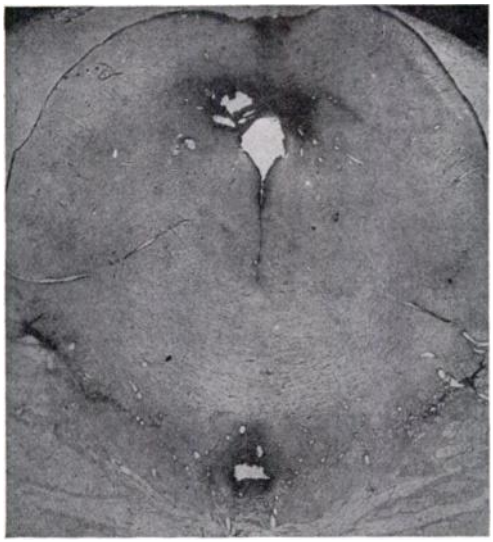

FIG. 4.—Pons. Holzer's stain. See description on this page.

the *état criblé*. This was also a frequent finding in other centres of the brain-stem, e.g., the thalamus, etc. No *état marbré* was present in the striate body. It is, however, worth recording that in the lamellæ of the globus pallidus, particularly that bordering on the putamen, network-like glial scars were encountered, brought about by the big bundles being spared (Fig. 1*b*). There was some gliosis in Forel's field and the capsule of the red nucleus, the latter being otherwise intact. The thalamus showed a marked subependymal gliosis, which was also found round the third ventricle and below the floor of the fourth ventricle (Fig. 6). The gliosis round the aqueduct (Fig. 4) was particularly heavy, containing cyst-like cavities, differing from those in syringomyelia by the absence of mesenchymal tissue. Between the pes and tectum of the pons a wing-like gliosis stretched to both sides (Fig. 4). Melanin in the zona compacta, locus cœruleus and ala cinerea was entirely normal. Where the nuclei of the cranial nerves were included in the gliosis, as, for instance, below the aqueduct and the floor of the fourth ventricle, their ganglion cells and nerve-fibres were left intact, as far as could be made out.

The dentate nucleus on both sides was heavily affected (Fig. 5*a* and *b*). In

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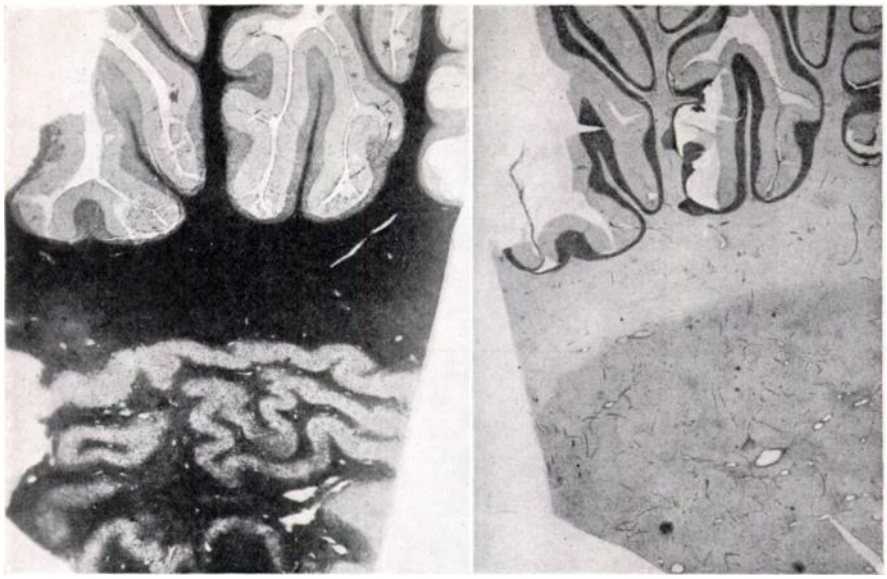

(*a*) (*b*)

FIG. 5.—Cerebellum and dentate nucleus, showing patchy loss of myelin with gliosis, with preservation of ganglion-cells. (*a*) Spielmeyer's stain; (*b*) Holzer's stain.

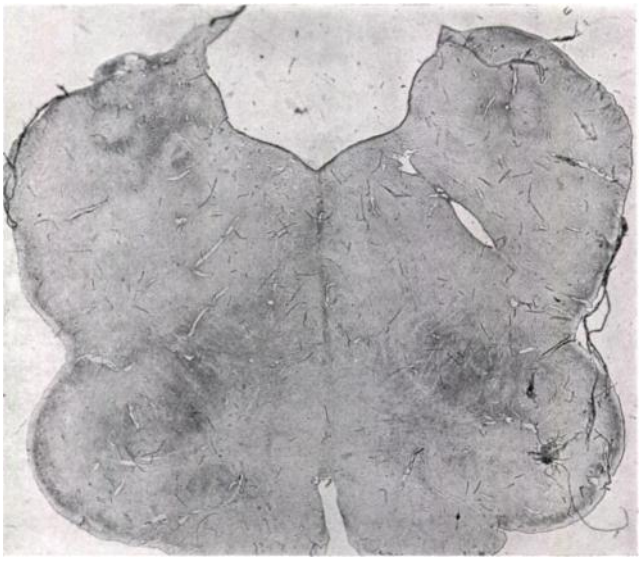

FIG. 6.—Medulla, showing sclerosis of olivary bodies and subependymal gliosis of floor of fourth ventricle. Holzer's stain.

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the myelin picture there was a patchy loss of myelin within the hilum, often perivascular as in *état criblé* with corresponding patchy and perivascular gliosis. Within the strands of ganglion-cells there was also a considerable glial proliferation. The ganglion cells themselves had, however, resisted destruction to a remarkable degree. The rest of the white matter of the cerebellum was not free from changes, although the myelin stain did not indicate them distinctly. There was a patchy glial fibrous proliferation, particularly heavy at the branching off of the small lobuli, like those described by Scherer and Maas (28) in a different cerebellar condition. Cerebellar cortex (Purkinjë cells, baskets and granular layer) was intact throughout. This discrepancy between the lesion of the dentate nucleus and the rest of the cerebellum seems to point, in spite of the criterion of Scherer (27), to a primary lesion of the hilum of the dentate nucleus, which is also indicated by the pronounced focal and often perivascular character of the process.

Both the olivary bodies showed sclerosis (Fig. 6), with only slight demyelinization

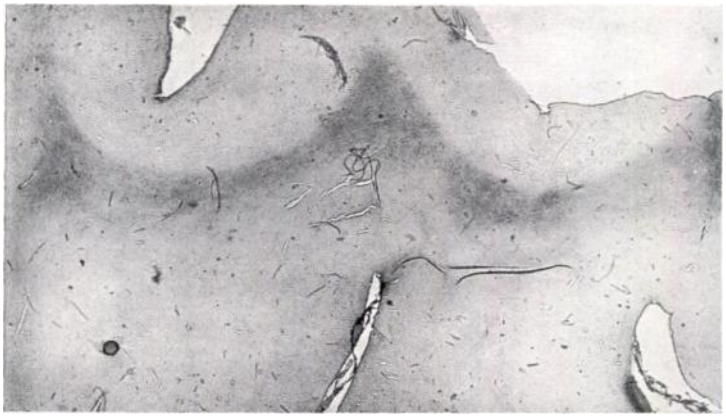

FIG. 7.—Occipital lobe, showing gliosis, with comparatively slight demyelinization. Holzer's stain.

in the hilum. Here the appearance of the lesions pointed to the secondary nature of the change. The ganglion-cells, not decreased in number, showed marked pigment degeneration without any noticeable local predilection. The pyramidal tracts and the rubro-olivary tracts were preserved.

The cerebral cortex showed a diffuse subpial glial proliferation. Otherwise there were only minor changes. Neither swelling of the ganglion cells nor argentophile enclosures was found.

In all the parts of the white matter which showed by naked-eye inspection a slightly greyish discolorization, histological examination reveals a definite gliosis (Fig. 7). It is not accompanied by any considerable degree of demyelinization. It is only on close inspection that the myelin picture shows some slight degree of rarefication. In none of the numerous blocks examined was there any trace of fresh breakdown of the myelin or any other sign of a recent process. The network of glial fibres was in parts very dense and poor in glial cells, partly consisted of numerous astrocytes with intertwining processes. The macroglial proliferation could be seen also in the Nissl picture, although this did not nearly convey a true impression of the severity of the process.

The spinal cord was not available for examination. As to the bodily organs, there was marked congestion in both liver and spleen with deposits of hæmosiderin in the liver-cells. No other changes worth recording were noticed.

DISCUSSION.

The significant feature of the case described is that there is a highly selective symmetrical and complete lesion of the globus pallidus and the zona rubra and, on the other hand, a wide spread of additional changes in various regions, among which the corpus Luysii, dentate nucleus and olivary bodies, the subependymal regions and the white matter of the cerebrum and the cerebellum are the most important. The lesion of the globus pallidus and the zona rubra is characterized by glial proliferation, demyelinization, and by a marked but by no means abundant increase of the Hallervorden-Spatz pigment.

The combination of additional lesions, although very unusual as an entity, is, on closer analysis, not as unfamiliar in this group as it appears to be at first glance. An affection of the Luys body, although more or less summarily described, has been seen in the original cases of C. and O. Vogt (31), Bielschowsky (2), Urechia and Mihalescu (29), and to a very slight degree in Hallervorden and Spatz's case (14). We have already drawn attention to the histological appearance, which might point to the degeneration being in our case secondary to the lesion of the globus pallidus. The case of Bouché and van Bogaert (6) is better omitted because connection with this group seems doubtful. Casper (8) reported affection of the dentate nucleus and subependymal regions. A participation of the dentate nucleus was also seen by Ammosow (1), and it reached impressive significance in the case of *état dysmyélinisé* published by Bostroem and Spatz (5).

It is therefore only the diffuse affection of the cerebral and (less diffuse) of the cerebellar white matter that adds a new variation to the histological picture of the condition in question. Lesions of the white matter with a practically complete preservation of the cortex have, as far as we are aware, not yet been reported. They suggest the findings seen in diffuse sclerosis. The condition is, however, to be separated from the type of diffuse sclerosis, described by Schilder, because of the almost entire lack of demyelinization and of the characteristic lipoidal breakdown products. It actually represents a type of diffuse gliosis, sparing the arcuate fibres, and thus comes near to the first type of diffuse sclerosis, described by Bodechtel and Guttmann (3, 4).

There is no doubt about the nosological position of our case, if one accepts the identification of *état dysmyélinisé* and Hallervorden-Spatz disease by Hallervorden (13). The selectivity of the lesions in the globus pallidus and zona rubra, together with the pigment increase and the clinical data, would sufficiently warrant the inclusion of the case in this wider group. It would be a non-familial (as far as the rather scanty family history permits one to state) example of this condition, with rather unusual additional features. Difficulties, however, arise if a closer grouping of the case is attempted. Efforts in this direction have been repeatedly made, the most recent ones being those

of Winkelman (32), Helfand (16, 17), and Vincent and van Bogaert (30). Winkelman described a familial case in which the lesions were limited to the " pallidal " system, including globus pallidus and zona rubra, and he suggested that such pure cases should be regarded as a system disease *sui generis*, called by him progressive pallidal degeneration. In a somewhat similar manner Vincent and van Bogaert, giving a complete review of the cases on record, want to separate under the term of " Hallervorden-Spatz disease " those cases in which there is a more or less systematized degeneration with pigment increase of the globus pallidus and the zona rubra. This group, comprising the cases of Hallervorden-Spatz, Kalinowsky (18), Casper (8), Winkelman (32) and their own, is regarded by these authors as a heredo-degenerative disease, in contrast to the rest of the cases, in which the lesion is of a more diffuse character. For the latter group the term *état dysmyélinisé* is reserved, although it no longer describes the main stigma of the group, demyelinization of the globus pallidus being often also a sign of the heredo-degenerative group. As long as subdivisions of the type attempted by Winkelman and Vincent and van Bogaert serve merely descriptive purposes, no objection need be raised. They are even very valuable in that they bring some order into the variety of lesions. Great care must, however, be exercised as to the nosological interpretation of such classifications. After all, there is in the heredo-degenerative group outlined by Vincent and van Bogaert considerable gradation with regard to the " purity " of the condition, as is admitted by the authors themselves. Where does our case find its place? It is certainly one of the most " impure " of cases, yet with regard to the selectivity, completeness and symmetry of the lesions within the globus pallidus and zona rubra, it fulfils most of the conditions required by Vincent and van Bogaert. In dealing with a condition in which nosological classification is attempted without the slightest knowledge of the ætiology, it is useful to compare with similar processes, the ætiology of which we happen to know. We refer to the selective lesions of the globus pallidus and the zona rubra occurring after poisoning with carbon monoxide, ether or cyanide of potassium, which have been particularly studied by one of us (A. Meyer (20–23)). Especially relevant were the results of an experiment with cyanide of potassium, in a dog, the histological examination of which revealed nothing but a selective and symmetrical lesion of the zona rubra. Nobody would regard this as a system disease which can be separated from other cases, in which the lesion of the globus pallidus and the zona rubra is incomplete or even entirely lacking, or accompanied by most pronounced lesions in other varying parts of the brain. Such experiences make us chary of ascribing too much significance to differences in the " purity " of the lesions; nosological classifications based upon this point might yet prove to be of an artificial nature, obscuring the issue rather than being helpful.

It might be said that our case lacks the abundance of the pigment increase

which is so predominant a feature in most of the cases of the "heredo-degenerative" group. There is, however, no unanimity as yet about the dominating significance of this symptom. It might well be that it is only one feature of the process, and that it depends upon circumstances not yet known and individually varying; in some cases, like that of Helfand, the pigment increase is almost the only finding; in other cases it may be accompanied or even surpassed by neuronal degeneration and gliosis. It is premature to regard it as limited to the familial group, since it has been described by Helfand and Vincent and van Bogaert in sporadic cases. The case-material available for consideration is far too small and, particularly in the earlier cases, too unevenly investigated to permit as yet of a definitive opinion. Hallervorden's (13), Gamper's (12) and Helfand's (17) experiences point to a more general occurrence of what Helfand called the "status pigmentosus". On the other hand, we hesitate very much to follow the suggestion of Helfand, who considers the pigment increase to be an indication, independent of other lesions, of a primary disorder of a pigment metabolism. His proof, based on a simultaneous deficiency in lipoids, melanin and iron in his case, is somewhat slender, and certainly not supported by other cases. One is reminded *mutatis mutandis* of similar and often unsurmountable difficulties of decision in other spheres, e.g., whether an inflammation is primary or secondary, or whether a malformation indicates a primary tendency to mal-development or only an arrest of development due to a histopathological process. It is hard to believe that a metabolic disturbance in melanin formation should be limited to a few centres only, and not manifest itself in other signs of albinism.

It is strange to find how little discussion of the pathogenesis of the condition has been stimulated by the fact that the centres prevailingly affected are the very ones particularly susceptible to the effects of anoxæmia, whether produced by poisoning with CO, ether, KCN or morphine or occurring in conditions of anæmia, methæmoglobinæmia or respiratory failure. A survey on these effects of anoxæmia has been given recently by A. Meyer (19). Osman and Schükrü alone (26), in considering the CO effect upon the globus pallidus, have called attention to a possible toxic damage occurring in *état dysmyélinisé*, without defining this more closely. This reluctance to bring the lesions of *état dysmyélinisé* into comparison with the effect of the poisons mentioned is in some part caused by histopathological differences. In fact, in all the findings in cases of poisoning we are dealing with lesions of a vascular or ischæmic character, whereas in Hallervorden-Spatz disease we are facing a "degenerative" process with a most peculiar pigment increase. On the other hand, many of the traditional characteristics of histological pictures have lost much of their specific value, since it has become clear that considerable histological differences are often due to tempo, intensity, or the age of onset rather than to any fundamental difference in the nature of the nocuous agent. Thus the

question at least is justified whether there is any concrete suggestion that *état dysmyélinisé* might be the consequence of interference with the supply or the utilization of oxygen.

The original cases of C. and O. Vogt (31) had a distinct relation to birth trauma, and so it was with one of Onari's (25) and Fünfgeld's (11) cases. In our case nothing is known of a birth trauma except for the mother's fatal hæmorrhage after the birth of the patient. It must be borne in mind, however, that the early history of the case is rather poor. Birth trauma would indeed supply ample opportunity for the production of ischæmic changes in the brain. Birth trauma plays an important role in *état marbré*, and it is known that *état marbré* may occur together with *état dysmyélinisé* (Onari, A. Meyer and L. C. Cook (24)). Yet, as a whole, birth trauma is recorded much less frequently in the condition dealt with here; in addition there is much greater incidence of familial occurrence. In familial cases particularly the onset of the disease appears to occur at about the end of the first decade or even later, after an obviously normal development. The fact, however, that birth trauma seems to play a role in a small group of cases might be indicative of the pathogenic mechanism in the other cases.

A very interesting sidelight is thrown upon the condition by the recent findings in *Kernicterus*. This is the term applied to the phenomenon of bile-staining in the brain, particularly in the lenticular nucleus, corpus Luysii, thalamus, mammillary body, subependymal regions, cornu ammonis, dentate nucleus, cranial nerve nuclei, olives, etc. It accompanies icterus gravis neonatorum. The question whether this condition is connected with birth trauma or not will not be discussed here. It is interesting to note that degeneration of the corpus Luysii following *Kernicterus* has been described by several authors (A. Eckstein (10), Hawksley and Lightwood (15)). Quite recently Brouwer (7) demonstrated a selective lesion of the globus pallidus and the corpus Luysii. This is the more noteworthy as quite similar clinical sequelæ (progressive rigidity with or without choreo-athetosis and mental defect) have been reported in *Kernicterus* (Zimmerman and Yannet (33)). It is noted that *Kernicterus* can occur in a familial form.

Icterus gravis neonatorum is, according to recent research, not of hepatic but of hæmolytic origin and often associated with severe anæmia. Thus, again, we find anæmia at the root of a condition which may be associated with selective lesions of the globus pallidus.

At present our knowledge about the lesions in *Kernicterus* is far too superficial to enable us to assess the degree of histopathological similarity to the group of *état dysmyélinisé*. In our own case the agreement is rather striking, if one takes into consideration the lesions of the corpus Luysii, dentate nucleus, olivary body and of the subependymal regions, which also are, as already pointed out, not entirely foreign to other cases. It can therefore be hoped that systematic histological studies of brains showing *Kernicterus* may be of

considerable value to the pathogenic elucidation of the condition dealt with in this paper.

The clinical aspect of the case needs only a few remarks, since the clinical symptomatology does not differ greatly from that presented in previous publications. Owing to the widespread nature of the lesions, the case cannot be utilized as a contribution to the problem of the localization of choreo-athetosis. On the psychological side, the resemblance to the clinical psychological picture described by Doll, Phelps and Melcher (9) is striking, though our patient was studied before their monograph was published, and was, moreover, too severely affected for mental measurement by any known technique. In personality he showed the same persistence of effort, so exceptional among defectives, that these workers reported, and that we have since observed in many cases. For such a boy to acquire the power of locomotion, for example, requires a tremendous degree of persistence. In his mental development, too, there is a marked similarity to their cases. From the records before admission, scanty as they are, it is obvious that the patient developed mentally after the age of sixteen years, whereas in the vast majority of defectives of his mental level such development has ceased by the twelfth year. We are faced here with the problem of deciding to what extent the clinical picture is due to a true lack of potential intelligence, and to what extent to the rigid limitations of experience and expression imposed by the severe neurological lesion present.

Summary.

The case here described of *état dysmyélinisé* (Hallervorden-Spatz disease) is noteworthy for the widespread nature of additional lesions within the cerebral and cerebellar white matter, corpus Luysii, dentate nucleus, olivary body and subependymal regions.

The current views on the classification of the condition are discussed.

With regard to the pathogenesis, the vulnerability of the globus pallidus to anoxæmia is stressed. The recent observations on *Kernicterus* may also provide a clue to the pathogenesis of the condition. Further research in this direction is advocated.

The case shows a psychological picture strikingly similar to that described in cases of choreo-athetosis due to birth injury.

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