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EDITORIAL

THE BASAL GANGLIA

The great basal ganglia, the caudate nucleus, the thalamus, the globus pallidus and the putamen, are as a rule, not very familiar objects in a medical man's daily talk and thought. Once he recalls that the thalamus has something to do with rage and pain, that the caudate nucleus and the globus pallidus are together known as the corpora striata, and that somewhere nearby lies the putamen—strange name—the limits of his knowledge are in clear sight.

But recently the metabolism and intracerebral connections of the basal ganglia have begun to attract attention. In 1912 Kinnier Wilson[3] had already described the hepatolenticular degeneration which has gone by his name, and had suggested that an unknown poison was the cause of the liver damage as well as the damage to the globus pallidus. Quite recently, copper has been found to be this poison, and after a series of reports in which deposits of copper in unusually large concentrations were found in the globus pallidus in this disease, treatment with substances such as BAL, which mobilizes the heavy metals and permits them to be leached out of the circulation through the kidneys, has brought new hope and a certain amount of relief to sufferers in the early stages of this rare hereditary disease.

Naturally, the earlier the patients come up for treatment, the more benefit can they expect to derive from this new therapy, and it has now become of practical importance to recognize cases of Kinnier Wilson's disease early, so that treatment can be started as a matter of urgency.

The difficulties in making an early diagnosis lay in the fact that the nature of normal copper metabolism was not well understood, as copper is harmful in certain combinations only. Until more was known about the exact derangement of the copper metabolism, no advance could be made. However, the theory has been propounded that in Kinnier Wilson's disease, an increased absorption of copper from the alimentary tract takes place, and that there is a decrease in the synthesis of caerulo-plasmin, which is the copper-alpha 2-globulin form in which 95% of the copper is transported in the serum. Coincidentally, there appears to be an associated failure of renal tubular function which is reflected in a fall in the blood-uric acid, this low blood-uric acid, combined with liver-biopsy subjected to Uzman's[4] new analysis may help in arriving at a diagnosis.

VAN DIE REDAKSIE

DIE GANGLIA BASALE

Die groot ganglia basale, die nucleus caudatus, die talamus, die globus pallidus en die putamen is nie in die reël onderwerpe waarmee die dokter in sy daaglikse denke te kampe het nie. Wanneer hy daaraan dink dat die talamus iets te doen het met woede en pyn, dat die nucleus caudatus en die globus pallidus saam bekend staan as die corpora striata, en dat die putamen—vreemde naam—daar naby geleë is, besef hy dat hy met dié feite feitlik die perke van sy kennis bereik het.

Maar onlangs het die belangstelling in die metabolisme en die intraserebrale aansluitings van die ganglia basale al meer die aandag geboei. Reeds in 1912 het Kinnier Wilson[3] die voortskrydende ontaarding van die nucleus lenticularis (met lewersirrose en bilirubinurie) wat na hom vernoem is, beskrywe, en hy het voorgestel dat 'n onbekende gifstof die beskadiging van die lewer en ook van die globus pallidus kan veroorsaak. Dit is kort gelede bevind dat koper hierdie gifstof is. Na 'n reeks verslae, waar koperneerslae in besonder sterk konsentrasie in die globus pallidus by hierdie siekte gevind is, het behandeling met stowwe soos BAL nuwe hoop op herstel en 'n sekere mate van verligting aan pasiënte op 'n vroeë stadium van hierdie seldsame oorerflike siekte gebring. BAL is tewens 'n stof wat die swaar metale mobiliseer sodat hulle deur die niere uitgeskei kan word.

Hoe eerder die pasiënte met die behandeling begin, hoe meer kans het hulle natuurlik om baat te vind by hierdie nuwe behandeling, en dit is dus nou van groot praktiese belang om gevalle van die Kinnier Wilson-sindroom vroeg te diagnoseer, sodat die nodige behandeling dringend ingestel kan word.

'n Vroeë diagnose was moeilik omdat die aard van normale kopermetabolisme nog nie goed verstaan was nie, aangesien koper slegs in sekere verbindings skadelik is. Biopsie van die ganglia basale word beskou as onprakties en lewer nie goeie resultate nie, en dikwels was die diagnose aansienlik vertraag (weens hierdie struikelblokke).

Voordat die presiese aard van afwykende kopermetabolisme nie goed verstaan was nie, kon geen vordering gemaak word nie. Dit is egter teoreties voorgestel dat daar by die Kinnier Wilson-sindroom 'n verhoogde absorpsie van koper uit die spysverteringskanaal is, en 'n vermindering in die sintese van caerulo-plasmien—die koper-alfa 2-globulien vorm waarin 95 persent van die koper in die serum vervoer word. Dit blyk ook dat daar 'n gelyktydige en verwante versaking is ten opsigte van die werking van die nierbuisies wat geopenbaar word as 'n daling in die bloeduriensuur. Hierdie daling, tesame met die lewerbiopsie

Of the many unhappy features of congenital cerebral palsy, perhaps none is so distressing to the onlooker as athetosis. In these tragic cases, involuntary writhing movements often persist during all the hours of waking for the patient's natural life. The degree and intensity of the athetoid movements varies from individual to individual, and they may be so violent that they interfere with feeding and the patient may require to be strapped to a chair or to his bed to prevent the violence of his own movements from inflicting further injuries on himself.

Not all cases of athetosis are due to congenital conditions, many are caused by injuries to the intracerebral pathways connected with the basal ganglia. The pathological processes and changes underlying the affliction were obscure and little known, and the whole nature of involuntary movement was not clearly understood. In 1912 Horsley,[2] the pioneer English neuro-surgeon, attempted to relieve the condition by ablating portions of the cerebral cortex. The effects were unsatisfactory; any benefits which accrued being due solely to the weakening of the movements concerned. Until recently, the whole question of extrapyramidal involuntary hyperkinesis was considered rather mysterious. In recent articles Cooper[1] who has been interested in applying surgery to cases of Parkinson's disease, considered the matter, and after analyzing the effects of injections and operations on the globus pallidus in 400 cases of this condition, concluded that 'these hyperkinetic manifestations, namely tremor and rigidity, can be completely alleviated by operations on the globus pallidus without sacrifice of either motor or sensory function of the involved limbs'. He applied some of the lessons he had learnt from operating on these cases of Parkinson's disease to certain cases of athetosis in younger people. Using a method of guided needles introduced through trephine holes, he has devised a means of injecting small quantities of absolute alcohol or of a plastic substance dissolved in absolute alcohol to destroy the posterior and medial portion of the globus pallidus. This operation he calls 'chemopallidectomy'. He reports 30 such cases and describes 4 in detail. The illustrations of Case 3 could not unfairly be considered as perhaps the most dramatic pictures in medical illustration that have been seen in the last few years. A completely helpless, writhing child with no prospect of a future and apparently no hope of normal existence is converted within a few days into a normal looking, easily standing individual, completely relaxed.

Naturally not every case of cerebral palsy is suitable for 'chemopallidectomy', but a ray of hope is beginning to shine on a particularly dark corner of medicine.

1. Cooper, I. S. (1957): J. Amer. Med. Assoc., **164,** 1297.
2. Horsley, V. (1909): Brit. Med. J., **2,** 25.
3. Wilson, S. A. K. (1912): Brain, **34,** 295.
4. Uzman, L. L. (1956): Lab. Invest., **5,** 299.

volgens Uzman[4] se nuwe ontleding, sal die dokter moontlik help om sy diagnose te maak.

Atetose is vir die bystaander seker die droewigste van al die tragiese aspekte van aangebore serebrale verlamming. By hierdie treurige gevalle hou die onwillekeurige krullende bewegings aan gedurende al die ure wat die slagoffer wakker is—solank hy lewe. Die graad en heftigheid van die atetotiese bewegings wissel van pasiënt tot pasiënt, en hulle kan só heftig wees dat die voeding bemoeilik word. Die pasiënt moet soms vasgegespe word aan sy stoel of bed om te verhoed dat hy hom deur sy eie bewegings verder beseer.

Nie alle gevalle van atetose spruit uit aangebore kondisies nie; dikwels word dit veroorsaak deur beserings aan die intraserebrale gange van die ganglia basale. Die grondige patologiese proses en veranderings by hierdie siekte was duister en onbekend, en die aard van onwillekeurige bewegings was iets wat dokters nie heeltemal verstaan het nie. In 1912 het Horsley,[2] die Engelse pionier in die neurochirurgie, probeer om hierdie kondisie te verbeter deur sekere dele van die harsingskors te verwyder. Die resultate was onbevredigend; die bate wat wel daarby gevind was, was slegs te danke aan die versagting van die rukkende bewegings. Tot onlangs is die hele vraagstuk van buitepiramidale hiperkinese as taamlik geheimsinnig beskou. Cooper,[1] wat belang stel in snykundige ingreep by gevalle van Parkinson se siekte, het in onlangse artikels ook hierdie saak bespreek, en nadat hy die uitwerking van inspuitings en operasies aan die globus pallidus by 400 gevalle van hierdie kondisie ontleed het, het hy tot die slotsom gekom dat hierdie hiperkinetiese manifestasies, naamlik trilling en styfheid, heeltemal verlig kan word deur operasies aan die globus pallidus sonder om die motoriese en sensoriese funksie van die betrokke ledemate enigsins te belemmer. Hy het die ondervinding wat hy opgedoen het met sy operasies aan sy gevalle van Parkinson se siekte toegepas op sekere jong atetotiese pasiënte. Sy metode is om deur middel van gerigte naalde deur die trepaangaatjies klein hoeveelhede watervrye alkohol of 'n plastiese stof opgelos in absolute alkohol in te spuit om die agterste en binneste gedeelte van die globus pallidus te vernietig. Hy noem hierdie operasie ‚chemopallidektomie'. Cooper rapporteer 30 sulke gevalle en beskrywe 4 van hulle in besonder. Die illustrasies by geval 3 kan met reg beskou word as die mees dramatiese mediese foto's wat oor die laaste paar jaar gesien is. Die totaal hulpelose, verwringe kind, met geen hoop op 'n toekoms en klaarblyklik geen hoop op 'n normale lewe nie, is binne 'n paar dae verander in 'n normale persoon wat maklik kan staan en heeltemal ontspanne is.

Nutuurlik is nie alle gevalle van serebrale verlamming geskik vir ‚chemopallidektomie' nie, maar vandag word hierdie besonder donker hoekie van die medisyne darem met hoop bestraal.

1. Cooper, I. S. (1957): J. Amer. Med. Assoc., **164,** 1297.
2. Horsley, V. (1909): Brit. Med. J., **2,** 25.
3. Wilson, S. A. K. (1912): Brain, **34,** 295.
4. Uzman, L. L. (1956): Lab. Invest., **5,** 299.

ALKALINE PHOSPHATASE DEFICIENCY

In 1948 Rathbun,[1] in Canada, described the case of a male infant who died at the age of 9 weeks and in whom there were metaphyseal changes resembling severe rickets. There was a mild hypercalcaemia, and the alkaline-phosphatase activity was found to be extremely low in serum, bone, kidney and intestines. Rathbun invented the term 'hypo-

phosphatasia' to describe this condition. In 1953, Sobel *et al*[2] described a similar case. A 19-month-old girl showed severe rachitic changes and premature loss of deciduous teeth. There was no evidence of renal disease. The serum calcium was normal and the alkaline-phosphatase activity very low. In the same communication preliminary data from 5 additional cases were given, all having radiographic signs of severe rickets and low serum-alkaline-phosphatase activity. In 1954, Neuhauser and Currarino[3] presented 4 other cases. In them, the diet and vitamin intake were normal. The skeletal disorder was characterized by defective bone formation in some or all areas of endochondral or membranous bone development, while non-osseus growth processes continue. There is reduced rebuilding of bone and deficient mineralization of newly formed organic matrix. Growth of extremities is retarded, the diaphyses are small in diameter and there are wide gaps between bones of the limbs and of the calvarium.

Several more cases have been described, and it has become apparent that renal disease may also be present, even (as in a case of Engfeldt and Zetterström[4]) to the extent of nephrocalcinosis. This kidney affection is not, however, the primary lesion, but is a secondary manifestation, probably caused by the hypercalcaemia. These two strange concomitants, hypercalcaemia and renal damage, are found only in some of the cases. The cause of the hypercalcaemia is presumably an absorption of calcium from the bowel which is greater than the abnormally low requirements of the hypophosphatasic child. Whether or not these children are also abnormally sensitive to vitamin D remains to be investigated. It is an interesting fact that vitamin-D intoxication also produces a raised serum calcium and a reduced serum alkaline phosphatase[5], and this biochemical combination is also seen in idiopathic hypercalcaemia of children[6], who are believed to be over-sensitive to the action of vitamin D.

An entirely different facet of this disorder has been reported by Dent[7] who, with Casworth, subjected the urines of 6 typical cases to chromatographic analysis. All these showed the same abnormality, namely a greatly increased output of phospho-ethanolamine. The identification of this substance from every case so far investigated appears to be beyond doubt, although a pure sample has not yet been isolated and analyzed. However, the paper chromatographic analysis shows identity with synthetic material, as also does the paper-electrophoretic separation technique, and the behaviour on ion exchange resins is exactly that of pure phospho-ethanolamine.

The connection between phospho-ethanolamine excretion and the bone disease is yet obscure. There is no doubt, however, that this phosphatic substance is a substrate readily hydrolysed by alkaline phosphatase, and the exciting possibility therefore arises that phospho-ethanolamine is indeed the true natural substrate for bone alkaline phosphatase, and that it appears in the urine because there is insufficient enzyme to metabolize it. This would fit nicely with the idea that a metabolic block is present, an inborn error of metabolism. The disorder would then be comparable to alkaptonuria, in which homogentisic acid accumulates because of lack of its specific enzyme; or to female pseudohemaphroditism, in which androgens accumulate because of lack of the enzyme next concerned in the pathway of adrenal synthesis of hydrocortisone.

There is evidence of the hereditary nature of hypophosphatasia in that parents and other close relatives of affected children, while themselves normal, have been found to have low serum-alkaline-phosphatase activities. This may indicate the possession of a single recessive gene for hypophosphatasia, the affected (homozygous) children having a double dose. It seems that we may consider the disorder as an inherited one, of foetal origin, and in this way comparable to other osseous dystrophies such as osteopetrosis and osteogenesis imperfecta. We have learnt, perhaps, more of the underlying abnormalities of hypophosphatasia in a few years than of the other osseous developmental disorders in decades or centuries.

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