CHOREOATHETOSIS AND INFRACORTICAL NERVOUS MECHANISMS.

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(Received May 4, 1939.)

DURING the last twenty-five years it has come to be recognized that a fairly large amount of mental deficiency appears to coincide with or result from faulty intracranial myelination. In some such children little or no post-natal development occurs, in others recession is already occurring at birth; a few remain fairly normal for some years. Spastic contractures, especially of the legs, grow progressively worse, epilepsy may appear, the child goes steadily downhill and early death is the usual termination. In some cases choreoathetosis is present, and this may either, if the patient lives long enough, disappear spontaneously, or, more usually, become impossible when the spastic contractures have immobilized the extremities. Post-mortem one finds one of two conditions—demyelination of the brain (the *status dysmyelinatus* of Hallervorden-Spatz) or hypermyelination (the *status marmoratus* of the Vogts). In both forms there is much hypergliosis, evidently secondary to some irritating but slow myelin poison which finally produces anoxia. Clinically during life both varieties appear much the same, and that is all that is known about its nature at present. Cases were recorded by the Vogts in 1920, Hallervorden and Spatz in 1922, Kalinowski in 1927, Helfand in 1931, Spatz and Peters in 1938; in this country by Meyer and Cook in 1936, Meyer and Earl in 1936. By these authors the views of others are summarized—Bielschowski, Loewenberg and Malamud, Urechia and Michalescu, Bouché and Van Bogaert, Casper, Ammosow, Bostroem, Bodechtel and Guttmann. If epilepsy has been present, it generally disappears after some years. By no means all cases end up as helpless idiots; some learn to attend to their own wants, but few ever walk freely.

This article has nothing to do with the pathology of this class of mental deficiency, but only with the syndrome called "choreoathetosis" (paramyoclonus multiplex); for it was a reasonable assumption that if a patient was fairly sensible and could respond to questioning, however imperfectly, the uncontrollable spasms and wild jactitations might possibly throw some light upon the mechanism of normal co-ordination between the intention of a muscular act and its resultant performance—in other words, might give a hint as to the position and nature of the process which normally co-ordinates voluntary and

automatic movement. From this standpoint other necessary restrictions on the choice of choreoathetotic cases were freedom from epilepsy and from spastic contracture. Patients who fulfil all these conditions must necessarily be few and far between. A rather severe handicap to full recording of mental defectives whose condition alters as they grow older is that it is hardly ever possible for the same medical officer to follow a case for more than twenty years, and the older histories are mostly fragmentary. So it must happen that many choreoathetotics who grow spastic in adult life and lose the irregular spasms pass unrecognized, while the rapidly regressing case often dies about puberty and drops out of notice. Where the spasticity is not too severe, choreoathetotics share many physical signs with other imbeciles and idiots, especially general muscular hypotonia, increased knee-jerks, often a positive Babinski, occasionally ankle clonus, commonly sexual retardation. It is not alleged that choreoathetosis occurs *only* in dysmyelinate cases, whether of hyper- or demyelination; in fact, the frequency with which one or other of these conditions is limited to the basal ganglia or even to lower brain levels, where various alternate pathways exist, renders such an assumption improbable. All one can say is that post-mortem records appear, as far as reading and experience go, invariably to show faulty myelination, generally with more or less hypergliosis, where the quite specific syndrome called choreoathetosis has been present during life.

My interest in the condition was first aroused when two children who were admitted about eleven years ago to the Infants' Block at Cheddleton turned out, as time passed, very different from the average choreoathetotic. The medical officers often discussed these two cases, and when one died late in 1935, Dr. G. M. Griffiths, who was for several years at Cheddleton with them, kindly undertook to report upon the brain. The two patients, a boy and a girl, were unusual in that (1) they were of moderately high mental grade and did not deteriorate as they grew up; (2) the irregular and uncontrolled jerks and spasms were, as far as such could be analysed, largely representative of ordinary normal subcortical patterns; (3) they had at first no spasticity, and even after ten years, only slight stiffness of ankles and toes, with foot-drop; (4) epilepsy was absent; (5) there was no evidence that sensation was involved. As both had received orthopædic treatment from an early age, it was hoped that in the course of time they would learn to walk and talk, and gain more or less muscular control. This expectation proved too sanguine; all we could do was to train them in self-control, to be clean in habits, and to feed themselves with solids, to enjoy concerts and cinema shows, and by encouragement and explanation keep the involuntary jerkings at a minimum. They never learned to balance or walk. In assessing the mental condition of such children one has to consider that their only experience of life has been from a hospital bed; inability to control the speech muscles or to write sadly limits thought expression, and rules out most intelligence tests. On the other hand they showed

considerable power of learning the meaning of what they saw or heard, and they understood conventional signs for making known organic needs. They could read the clock and pick out numbers and letters on blocks, but as a rule nurses are too busy to spend much time in encouraging such patients in the practice of asking for things by name ; it is so much easier to accept a nod or head-shake for " yes " or " no ".

When I left Cheddleton late in 1936 the opportunity arose of examining other choreoathetotics in colonies near London. The several medical superintendents received my request for permission to visit with the greatest kindness ; their assistant medical officers were unsparing in their efforts to collect the records and demonstrate cases. The various theories of causation with the treatment and prognosis were fully discussed. To the following medical superintendents, together with their professional and lay staffs, I must return my grateful thanks for all they did to help: Dr. T. Lindsay, of Caterham ; Dr. R. M. Stewart, of Leavesden ; Dr. J. E. S. Lloyd, of the Fountain ; Dr. N. H. M. Burke, of Cell Barnes ; and Dr. H. E. Beasley, of the Middlesex Colony. We went through 45 cases, to which I added 5 at Cheddleton. Most of these were either of low grade or severely spastic, or both. In a good many the choreoathetosis had ceased, and these were often fairly sensible and had learned to do simple work in the ward. Histories of epilepsy earlier in life were common among the adults. The medical officers regretted the poor records in many who had grown up at home or in workhouses belonging to various authorities before London and the surrounding counties had organized colonies and clinics. This will not occur in future, for the children will receive orthopædic and psychological treatment from infancy. Several medical officers emphasized the diligence and perseverance shown by improving cases, far greater than by the ordinary school child. They would practise muscle control all day. Most were too old to show mere retardation of sex characters, but a few had a history of such defects. A girl of 19 had menstruated only once, 1½ years ago. Pubic and axillary hair was present, but no breast enlargement. A youth of 27 exhibited the close connection between irregular movements and emotion. The former were slight and confined to the hands ; earlier in life the legs, too, had been involved, although now spastic. But whenever attention was drawn to his case, as when the nurse began to undress him for examination, sweat broke out all over. It ran in streams down face and chest, so that his garments were soaked ; his mental grade was medium imbecility. Another, a girl of 19, was free from spasms until she heard her bath-water running, or even a door slam. The contortions then became violent. On the whole it appeared that none of the cases I saw were sufficiently " pure " cases of choreoathetosis to be of much use in throwing light on the nature of the inco-ordination, so I decided to describe only my two originals, at the same time making some remarks on the anatomy and physiology of the central nervous system, as shown by these two, which did not seem to be stressed in published works. Some of these may

sound somewhat fanciful, but it will help our knowledge of central nerve mechanisms if they stimulate discussion.

CASE 1.—W. C—, male, aged 7, admitted to Cheddleton January 16, 1925. A well-developed child of healthy appearance. Facial bones large; maxillæ and mandible stand well out; was almost prognathous. Teeth large and well formed. The contortions were severe and frequent, no doubt made worse by the excitement of coming to strange surroundings. They occurred when anyone approached his bed or looked at him, or asked him a question, and when he attempted to perform any voluntary act. They began suddenly, involving all the voluntary musculature. They ended after about 5 to 10 seconds, leaving severe oxygen debt. He sweated copiously, but appeared to suffer no pain; consciousness was not clouded. Forced respiration followed without a pause, and a very important point was prominent, viz. the neck, shoulder, arm and trunk muscles of forced respiration, which the second before had helped to hurl the arms about and twist shoulders and head, immediately resumed their normal respiratory functions in perfect co-ordination with the intercostals, diaphragm and abdominal walls, apparently without loss of energy. The rest of the body and limb musculature became hypotonic, as in so many mental defectives, accounting for the increased knee-jerks. Further physical state: Abdominals present; plantars gave flexor response. Palate broad and flat; testicles in scrotum. Pupils 6 mm., normal to light. Eyeballs partake in the incoordinate spasms, moving consensually up or down or to either side; no residual nystagmus. Tongue can be held out only for a second or two, the effort bringing on a spasm. It is never bitten, and all jaw and throat movements involved in swallowing are normal. As far as could be ascertained sensation was not involved. The contortions distressed him very little; no cyanosis. Asked to point to any spot which the examiner touches, he carefully approaches it with index tentatively pointed, but the whole arm is violently hurled away when he gets near. After about three attempts (with encouragement) he smiles and shakes his head. There is slight beading of ribs; heart and lungs normal, urine normal. Weighing and measuring impossible. Several attempts to examine the discs failed, even at the hands of the visiting ophthalmologist. Wassermann reaction of blood and cerebro-spinal fluid negative. Could not feed himself; habits wet and dirty. He slept well and had no spasms while asleep, or if there was no sound or visible movement near his bed. After a few days he was less nervous, so that a nurse could approach him without disturbance; a few weeks later the medical officer could tickle his ribs and produce only a broad smile. But, to the end of his life, if I asked him to come and have a dance he laughed at the joke as he speculated on the possibility; then I saw his jaws set and fists clench. The next second he was in a convulsion, although by this time these had grown comparatively mild. But I could never decide whether, during the pause, he was weighing up his chances of success, or thought me a fool for suggesting such a thing as dancing.

History (from mother).—Patient is the youngest of five boys, of whom the eldest is in a mental colony; the middle three are normal. Her own and husband's families are free from neurosis. While pregnant with patient she was much worried because her husband had been conscripted quite late in the war. She laid stress upon the early quickening: patient "was much more on the wag than any of the others". The confinement was normal and not prolonged. At four months his head rolled about unduly and he made no effort to sit up; at 5 months "the jerkings began, all over the body, both sides". At 6 months "he started to have fits", and the doctor told her they were epileptic. These continued about fortnightly until he was 5 years old. He has had none since. "When the fits stopped violent outbursts of temper began if he was crossed in any way."

Progress.—Walking exercises were begun at once, a nurse on either side supporting his weight. He could stand by himself as long as he was not asked to balance; he could go through the first (flexor) portion of the step reflex. But as soon as told to put one foot forward (extension), he collapsed into a general convulsion.

Even after months he had made no progress ; he was never able to use the walking chair. But he was taught to be clean, making a noise which the nurse understood when he wanted the urine bottle. Mentally he was sulky and wayward at times, but his parents' description of his temper as " violent " was an exaggeration. About three months after admission he had a severe torsion spasm which threw him out of his cot. He landed on the left shoulder and elbow and sustained a T-fracture into the elbow-joint, with dislocation of head of radius. The orthopædic surgeon found great difficulty in securing union in face of the severe contortions, and in the end he was left with an ankylosed elbow. From time to time efforts were made to recognize automatic postures and reflexes. The rebound phenomenon was common when he tried extra hard to control the jerks. Full double extension of legs occasionally produced extension and pronation of elbow (only the right could be tested). His best voluntary effort was the grasp reflex, as long as he left it " reflex ". But when he tried hard to modify the grip a spasm began, at times with extension and elevation of the opposite shoulder. As time passed the passive head flexion reflex became quite reliable, with flexion at hips and extension at knees, so that the nurse could use it to get him to sit up alone. But if anything disturbed the process (and some slight movement or noise nearly always did within a minute or two), he was thrown back supine in bed. The positive supporting reflex was present in the legs (kneeling position), not in the arms. Testing for the hallux reflex often increased extensor rigidity. In the earlier years torsion spasm was not uncommon. Gave up being wet and dirty after the first year.

By 1930 the violence and frequency of the convulsions had much abated, and he seemed to react to light psychotherapy, viz., gentle and monotonous encouragement to relax and control emotion. For the rest of his life he tried hard to follow instructions. His arms and fingers were more useful ; he liked picture-books, could do simple puzzles, and tried to learn the mouth-organ. But by 1932 spasticity was noticeable in right ankle, and a year later in left ankle. At 15 years no secondary sex characters had appeared, no hair on face, axillæ and pubes, penis and testicles infantile. But during the following year quick growth occurred and by 1935 the delay had been overtaken. In January of that year he had a middle-ear abscess, which left no residual discharge, but in November, 1935, he caught influenza, which was followed by pneumonia, and within a fortnight succumbed to pulmonary abscess. Half an hour after death the cisterna magna was injected with formalin.

Post-mortem report.—For the following summary I am indebted to Dr. J. H. Malloy : Left elbow, bony and fibrous ankylosis. Legs cannot be extended beyond 150° of body line. Measurements : Glabellum to occiput 33 cm., interaural 32 cm., circumference 53 cm. Transverse diameter of skull 14 cm., antero-posterior 18 cm., cephalic index 74. Skull thickness, frontal and occipital, 5 mm., temporal, 4 mm. Large frontal sinuses healthy ; teeth prominent and good ; no M3. Dura, pia arachnoid and subdural space appeared normal ; brain rather small, but well proportioned ; gyri normal in size and pattern (brain preserved unweighed and uncut). Left lung some recent bronchitis. Right chest pleurisy, white hepatization upper lobe ; central abscess with ragged edges, rest of lung congested. Slight congestion both kidneys ; all other organs normal. Pus from lung abscess revealed Friedlander, staphylococci and tetrads ; no spirochætes or fusiforms.

Dr. W. D. Wilkins, present Medical Superintendent of Cheddleton Hospital, kindly sent the brain to London, and Dr. G. M. Griffiths was able to complete the histological examination at the London County Central Laboratory, Maudsley Hospital. I am greatly indebted to her for the following report :

Histological report.—The fixed brain weighed 1050 grm. There was no obvious abnormality on the external aspect ; gyri showed normal development, pattern rather simple, sulci well marked. Horizontal section showed normal grey and white matter, but slight mottling of both putamina, suggesting *status marmoratus*. Otherwise the basal ganglia displayed no abnormalities in pigmentation, and their size and shape were in normal proportion to other parts of the brain. Blocks were cut from both hemispheres ; sections stained by various methods for cell structure,

axis cylinders, myelin, neuroglia, fat, etc., were examined from prefrontal, frontal, precentral, postcentral, parietal, temporal, visuopsychic and visuosensory areas. The cells everywhere, both ganglion and stellate, appeared normal in size, shape, number and distribution; the fibre bundles were normal and devoid of faults in myelination, except the external capsule, where there was slight glial scarring, and in some areas this scarring appeared to run into the putamina, especially in the superior and anterior regions on both sides. Hypermyelinated areas generally coincided with hypergliosis in the putamina, but in the external capsule there was no disturbance of myelination. The putamina showed a fine network of abnormal myelinated fibres in affected areas, the typical appearance of *status marmoratus*, but less marked than in the illustrations of most published cases. There was no apparent outfall of cells in the putamina; they seemed quite healthy, and the Nissl picture showed no pigment increase. The pallidi showed no involvement in the disease process, cells and fibres being quite healthy, although those coming from the putamina seemed to stain somewhat deeply. The giant-cells and ansa lenticularis were perfectly normal. Nothing abnormal was seen in the thalami or corpora Luysii. There was some increase of subependymal glia along the walls of the third and fourth ventricles and aqueduct; this was especially marked in the region of the terminal vein, although nowhere more than moderate. The most striking involvement was in the substantia nigra, on both sides, but to a greater degree on the left. The whole length of the zona compacta disclosed a marked loss of the large ganglion-cells; of those remaining a few contained some melanin, but none, as far as could be judged, a normal amount. Some were mere ghosts, although the outlines of the nucleus, apparently of normal shape and size, remained visible; many others showed swelling or loss of Nissl substance. Melanin pigment could be seen in capillaries and scavenger-cells. There was all through the nigra a dense gliosis, so that it was not easy to be certain about the fibres, but apparently there was a great increase of fine non-myelinated, not all of them being glial. Many were in thick strands, digitating into the crura. It was quite impossible to follow the axons either from the basis pedunculi, or those entering the tegmentum. The pontile region disclosed no abnormality of myelin or glia; there was no observable cell outfall. The cerebellum was practically normal; some fine gliosis was seen in the dentate nucleus and the inferior olives, but scarcely pathological in amount. All the cells and fibres of cerebellar cortex, dentate, globose and emboliform nuclei were normal. Nothing unusual could be found in the red nucleus, corpus Luysii or their connections. In the pineal gland there was a small cyst containing calcareous particles. Especial care was given to the hypothalamus, but none of the nuclei showed any apparent loss of cells; there was no gliosis. Nothing unusual was seen in the inch or so of cord sent with the brain. Reviewing the brain as a whole there was (1) hypermyelination and gliosis of a small portion of both putamina, without cell loss; (2) very serious, probably approaching total, disorganization of substantia nigra, compact zone only, few healthy cells left.

CASE 2.—H. E—, female, aged 8, admitted to Cheddleton April 16, 1926. The child is tall for her age, but thin and sparely built. The inco-ordinate muscular spasms are less severe than in Case 1, but involve all the voluntary muscles. They are moderately slow, large-sized twistings, almost approaching athetosis in type, except that they are apt at times to progress by small, rapid jerks, all in the direction of completing some definite larger, although undesired purpose. This girl is less emotional than the boy, possibly owing to longer hospitalization. But also her disposition is more placid; she always looks cheerful and smiling. She can pronounce a good many words, not completely, but intelligibly; sibilants and dentals beat her. Speech is slow and careful; she knows her age and where she is, says her granny told her. Has no idea of dates; can read the clock. Recognizes nurses and doctors as such; cannot give any connected account of her life. Muscles are small, as well as hypotonic; has no spare fat. Weighing and measuring impossible owing to the spasms. Can hold out her tongue for a second or two; tonsils enucleated. Teeth fair; no third molars, seconds incomplete. Pupils 7 mm.,

reaction normal to light and distance. Abdominal reflexes present; knee-jerks very brisk, no ankle clonus; plantars flexor response; no spasticity of legs, but has the usual toe-drop of hypotonicity. No development of breasts or mons Veneris, no hair on pubes or in axillæ; Wassermann reaction of blood and cerebro-spinal fluid negative, urine normal. Fundi cannot be fixed by ophthalmoscope. Habits clean; can ask for attention; can feed herself with solids.

History (from mother).—Informant's paternal grandfather was in Cheddleton; no other case of mental abnormality known; informant's parents and her original seven sibs are all alive and well. Patient is illegitimate; her father left informant pregnant when he went to the war. When he returned she preferred to marry another man, by whom she has a boy and a girl, both normal and healthy. All three confinements have been easy, normal head presentations. She was 19 when patient was born. From 3 months to 2 years of age the child was constantly ill, first influenza, then measles, then erysipelas. They tried hard to teach her to walk, but she could never stand. When aged 2 she had her tonsils out, which slightly improved her speech, but, informant insists, "brought on the jerks". For the next two years she was an out-patient at the Stoke-on-Trent Orthopædic Centre; was kept in plaster. Informant says that made jerks worse, so that from 4 to 6 she had no treatment. Then was sent to the City P.A. Hospital, where she wore calipers and had walking exercises, but without benefit. Was then sent by the orthopædic surgeon to Cheddleton, where there were classes for younger children. Balance never improved; all they could do was to prevent contractures.

Progress.—By 1928 slight improvement was noticeable. She learned to use a spoon and speech was plainer, but she could not sit up. The spasms became more like athetosis, slow and twisting. She would be set in a deep invalid chair. After a few minutes the legs began to extend by small jerks until she was resting on the shoulders against back of chair, heels on floor. Then she slowly twisted over and lay on her side on the floor, when the legs slowly flexed. During that winter had ultra-violet radiation; tanned well; no muscular change. In 1929 had a two-day attack of Flexner diarrhœa, and in 1930 was pulled down by rather severe influenza. Thereafter lay in the open air or under a vita-glass verandah, naked when possible. Health greatly improved, muscles thickened, a layer of subcutaneous fat formed and she tanned deep brown all over. No sex development occurred until 1935, when she was 17. Breasts swelled slightly, sparse pubic hair appeared; she menstruated two or three times in the year. By the time she was 18 sex development had practically caught up to normal, but as to muscle control, all she could do was to roll along the floor and grasp an object. Simple voluntary acts could be slowly accomplished by hands, but any effort to hurry or to follow complex direction aroused emotion, and a general inco-ordinate spasm resulted. She began to enjoy longer quiet intervals, and sat in her easy chair in a rather cramped, sideways posture, with legs drawn up off the floor. This flexor position of all four limbs seems the normal one for comfort where spasticity is going to develop later. This did not develop as long as exercises were maintained. Hypotonia and foot-drop persisted; no balancing power was gained, nor could she stand alone; a spasm caused immediate collapse unless she was held up. Dr. W. D. Wilkins reports that during the last 2½ years there is little noticeable change. It is very improbable that this girl will ever be able to walk; by the time the irregular muscular movements have disappeared there will be immobilization of the joints, probably in flexion, by spastic contractions.

Discussion.

It is clear that in Case 1 (W. C—) no simple explanation of the inco-ordination of muscular action was disclosed by the post-mortem findings, although the severe lesions of the substantia nigra implicate this structure beyond doubt. But what part was played by the hypermyelination of the external capsule,

and more especially the putamen? And how much gliosis is required to interfere with the transmission of action currents in adjacent nuclei and fibre bundles, in this case the ependyma of the third and fourth ventricles, dentate nucleus and inferior olivary bodies? Is it even possible that in these cases of mental defect there is some chronic circulating toxic agent still active, as there must be in the Parkinsonism of encephalitis lethargica? None of these questions can be definitely answered at present. But there were several life features of the two cases under consideration which suggest a rather fuller explanation of brain action than is generally found in text-books. I shall therefore comment upon certain units.

Cortex.—It may be accepted that both the so-called "voluntary" and the automatic components of muscle movement originate in the same excitable area of the cortex, the precentral (motor, area 4) and the intermediate precentral (premotor, area 6), and that the more specialized movements belong to the premotor, whence some fibres pass directly to the internal capsule; others go through the motor area before reaching the capsule. A moment's reflection makes it clear that it is impossible to keep a movement wholly voluntary; scarcely has it been initiated before extrapyramidal automatic mechanisms step in to complete it, otherwise it would be impossible, for example, to run quickly up or down stairs. As F. M. R. Walshe pointed out a good many years ago, there is no such thing as a completely voluntary or a completely automatic movement; an action can only be more voluntary or less voluntary. Improving choreoathetotics practise slowly and carefully to keep their acts as voluntary as possible, and to keep emotion under control by trying to relax. It is by quiet, monotonous encouragement in this direction that light psychotherapy can be helpful.

It is important to bear in mind that the evolutionary history of the cortex supports the thesis that the supragranular layers are especially devoted to the voluntary aspect of nervous action, whether in the primary or association areas, and that the more complicated the figure pattern of a movement, the more of a voluntary nature does it retain. This view has been held by psychiatrists for many years, yet one still hears doubts cast upon it. Some of the reasons which may be advanced are: (1) The supragranular layers do not differentiate in the lower phylæ, but are specialized more and more as animal intelligence increases, and reach their highest development in man. (2) These layers are the first to fail in the dementia of old age or that following prolonged excitement; the patient then tends to become mild and placid, not bothering to initiate thought or action, little disturbed by emotional discharges. At the same time we must admit that this atrophy may be largely due to the position of the surface layers, exposed to the wash of the cerebro-spinal fluid, which capillarizes in the pia arachnoid network up over the hemispheres from the cisterna magna to the great longitudinal sinus, charged with the toxic products of neuronal dissolution, and which, incidentally, accounts for the

thickened membranes and the growth of the Pacchionian bodies. (3) The shortest association fibres are the inter-radial axons of the supragranular pyramids, which often also send a long apical dendrite up to the surface of the molecular layer. (4) Von Economo (*Cytoarchitectonics of Human Cerebral Cortex*", Oxford University Press, 1929) states that "in general paralysis, senile dementia and chronic alcoholism, the third layer (supragranular pyramids) in the precentral region, next to the frontal, is the first to go; if rigidity is prominent, e.g., in encephalitis lethargica or Huntington's chorea, where the capacity for expression rather than the personality is destroyed, the fifth and sixth layers are attacked." (5) Watson states: "The optic radiations end in a confused and reduplicated line of Gennari, which is formed by the outer of the two inter-radiary plexuses. This line is first definitely reduplicated in the primates." (6) In normal infants at birth, and in some types of idiocy during the whole of life, the supragranular layers are imperfectly developed. To ascertain this is often a very laborious process, involving micrometer measurements of each gyrus at least in three positions—base, half-way up, and summit. It is true that some writers deny that cell-counts of the various layers in congenital cases are reliable, but no one who day by day discussed with the authors the work done at Rainhill under Joseph Wiglesworth by Henry Head (*Brain*, 1905, xxviii, p. 99), J. Shaw Bolton (*Journ. Ment. Sci.*, 1906–7, lii and liii), A. W. Campbell (*Cortical Localization*, Cambridge, 1905), and G. A. Watson (*Arch. Neurol.*, 1906, iii), can doubt the meticulous care which they devoted to their observations.

In asserting that the supragranular layers are primarily concerned with the more voluntary movements I do not for a moment suggest that the various layers can act independently. Of course they cannot, but in thought-out actions there is a tendency towards fewer standardized movements being relegated to subcortical mechanisms. The corticospinal tracts contain many fibres besides the Betz axons, and the Betz cells themselves are much influenced by neurobiotaxis; developmentally they belong to the polymorphic layer; they are situated in the ganglionic layer; functionally they are part and parcel of the pyramidal layer, so that the presence of spasticity following capsular lesions is not a safe guide to the exact origin of the injured fibres, supra- or infragranular, motor or premotor area. Kennard and Fulton (*Brain*, 1933, lvi, p. 213) have done much research on the chimpanzee, and hold that the premotor assists the motor as an integrator of voluntary activity, and governs reflex adjustments, so that only the loss of areas 4 and 6 on both sides is certain to produce final spasticity. But Walshe (*Brain*, 1935, lviii) inclines to the view that the loss of one precentral is sufficient. Choreoathetotics have little spasticity at first, but generally much later on; yet often no sign of the degenerated columns is found post-mortem in the cord. In Case 1 the only lesion upon which suspicion could possibly rest is the hypermyelination and gliosis of the putamina, and after all the contracture of legs was slight.

Corpus striatum.—Meyer and Cook (*Journ. Ment. Sci.*, 1937, lxxxiii, p. 258) record either *état marbré* or *état dysmyelinisé* in most of their microcephalics. The first-named term is evidently meant to imply "hypermyelination", and the second "hypomyelination". The loose French terms need no longer be used in English; the Greek prefix *dys-* implies merely "difficulty" or "error", and "dysmyelination" (not "dysmyelinization") may mean either excess or deficiency of myelin. As far as I have read, the striate body is most commonly involved in dysmyelinate cases, sometimes the dentates and putamen, or putamen and pallidus, sometimes parts of the thalamus also. But in what proportion of these choreoathetosis occurs I doubt if anyone has tried to ascertain. One gains the impression from the few cases reported in England that the whole lenticular system generally suffers, yet in Case 1 the pallidus was healthy. The usual difficulty of allocating the various brain functions to their sites of origin, which confuses us in cases unapproachable by surgery and useless for animal experiments on account of different evolutionary levels, meets us in choreoathetosis. At one time Kinnier Wilson's opinion about the corpus striatum seemed final; now we hear occasionally of derangements in striate motility where there is no spasticity, or where globus pallidus and substantia nigra alone are involved. Perhaps enough importance is not attached to the unknown continuing toxic influence in these chronic affections, of which hepatico-lenticular degeneration, encephalitis lethargica and dysmyelinate mental defect are examples. In view of the position, wide connections and phylogeny of the striate body, it is probably safe to assume that it is the chief centre for the building up of the No. 2 type of reflex movement patterns, such as all the higher vertebrates use (the most recent, No. 1 type, such as produces proficiency in games, and demands long practice, being left to the cortex). No. 3 type, older than that of the basal ganglia, is within the province of the red nucleus; while the spinal group, No. 4 type, oldest of all, includes the vital bulb reflexes upon which life depends. The influence of the cortex over each type lessens as we descend. It is probable that there is serial representation in the caudate, but not in the putamen. Nor is the question of direct cortical connections beyond discussion, but if Kinnier Wilson could not find them, they cannot be numerous. One difficulty in ascribing disorders of movement to the striatum has been that either or both of the principal symptoms have been noted in cases where the lesions have been found elsewhere. These are generally rigidity and rhythmic tremor. But are these two necessarily mutually prohibitive? It is a tribute to the acumen of Hughlings Jackson to recall that many years ago, when little was known of brain topography, he remarked that tremor was rigidity spread thin—a theory which still maintains its foothold. The presumption is that in ordinary neuromuscular activity only a limited number of neurones in any homologous group are employed at once, all depending upon the "field of force" considered necessary by the immediately preceding facilitating group. For a greater effort more neurones are called in;

for a maximum spurt emotional re-enforcement is required. In progressive neuronal dissolution a time comes when the cells in the group susceptible to facilitation are too few to maintain a steady tonus; then tremor appears. When still more neurones fail no current can pass, and either flaccid paralysis or rigidity results, depending upon the potential of the immediately preceding facilitating or inhibiting group on some other pathway. For example, in paralysis agitans stiffness may appear first, then irregular jerkings, lastly rhythmic tremor. Ramsey Hunt (*Amer. Journ. Med. Sci.*, 1921, clxii) divides striatal dissolution into two types: (*a*) paleostriatal, where the large efferent pallidal cells go first, causing loss of automatic associational movement, a paralysing lesion exhibiting rigidity with tremor; (*b*) neostriatal, affecting the ordinary ganglion-cells, a discharging lesion marked by clonic and athetoid movements with rigidity. This may be a convenient classification so long as it is remembered that not all the lenticular nucleus is paleostriatal, nor all the caudate neostriatal.

Substantia nigra.—This was the only part of the brain in Case 1 where there was advanced disorganization, but it is one of the least understood. The tangled mass of both myelinated and unmyelinated fibres is most difficult to trace. It is known that the stout axons from the large, pigmented ganglion-cells send their axons into the tegmentum, where they divide into an ascending and a descending branch.

The strionigral tract of crossed and direct fibres ends in it, and constant collaterals enter from the corticifugal bundles in the basis pedunculi. Connections have been traced from temporo- and frontopontine tracts, from red and subthalamic nuclei, both geniculate bodies and cerebellum, as well as from the rubrolenticular tract, which probably means from all the cranial nuclei through the medial longitudinal fasciculus. Most observers agree that in the advanced Parkinsonian rigidity of encephalitis lethargica severe destruction of substantia nigra cells is found, but generally there are other lesions present as well. Also in some cases the nigral cells have been found healthy and the putamen-pallidal system destroyed. Lucksh and Spatz attribute the rigidity of acute cases to destructive lesions of substantia nigra, but say post-mortem findings do not always accord with clinical signs, so that great loss of cells may be found where there was no rigidity during life. Von Economo states that the substantia nigra probably contains "a shunting station for the arms", and influences "the timing, progression, rhythm and volume of movements, whether originally voluntary or automatic, e.g., mastication and swallowing". He suggests even "mental simulacra" of other mechanisms to be placed here, even hypothalamic, and instances hyperpnœa. Wimmer believes it is part of a rubro-cerebellar-thalamo frontal pathway. A review of the literature of *état marbré* shows that putaminal lesions may accompany nigral. Our case makes it evident that the substantia nigra is an important, although probably not the sole, co-ordinating mechanism between cortical and subcortical

activities whereby automatic (extrapyramidal) movements are correctly timed with the more voluntary (pyramidal). The whole problem teems with apparent contradictions. Why, for example, should widespread loss of ganglion-cells produce severe inco-ordination in choreoathetosis, and extreme rigidity in Parkinsonism? The loss in the former case cannot be total, for if choreoathetotics live long, they lose the irregular movements, although by now the legs are spastic. But I have never seen a case of chronic Parkinsonian encephalitis lethargica which did not end fatally through persistence of the infective organism. Is it possible that in choreoathetosis the unknown systemic toxin which causes dysmyelination persists until it has produced complete flexor fixation of the legs, and incidentally causes the incoordination also? This theory gets over the loss of cells in the substantia nigra by assuming that muscular control is regained in the arms by the constant practice of the patient to develop volitional control over one of the extrapyramidal (cerebello-thalamico-cortical-thalamo-strio-rubral) pathways.

Gliosis.—It is not likely that the slight gliosis at various places had much influence upon the inco-ordination, for there was no abnormality of sensation, the ataxia was not of the cerebellar type, and the only change in the vegetative system was an increased facility in the release of emotion and all it implied. Of course it is possible that the hypermyelination in the putamen might delay the transmission of involuntary action potentials, except that gliosis is present in all dysmyelinate defectives, whereas irregular movements occur only in a small minority. There is also a possibility, although a very remote one, that the gliosis in some efferents from the cerebellar dentate, which, passing by way of the brachium conjunctivum end in the ventral nucleus of thalamus and (or) its arcuate portion, and are relayed to the postcentral and (or) precentral cortex respectively, may influence inco-ordination.

Emotion in choreoathetosis.—In most choreoathetotics who have sufficient intelligence to know what is going on around them an outburst of inco-ordination is accompanied by fairly copious sweating, in some cases excessive. The sequence is not altogether clear, but the more sensible, who have severe spasms, try by every means to avoid attempts at spontaneous movement, knowing what the result will be. Consequently, when they are disturbed by a slight sound or sight, a voice, a footstep, a question, or seeing the nurse approach their bed, one hardly knows whether the emotion starts the outbreak of inco-ordination, or vice versa. My Case 1 never had a severe spasm while asleep, rarely any movement at all; occasionally a slight jerking was reported, no doubt in the dream state. One could see, in his later years, a careful essay in volition, broken by the involuntary spasms after a second or two. The flow of sweat was seen at the same time, nor did it attract attention at any other. It is well recognized that emotion is brought about by a cortical reflex and produced by hypothalamic stimulation. Beattie and Le Gros Clark have done more than any others to clarify our knowledge of hypothalamic function.

The former (*Can. Med. Assoc. Journ.*, 1932, xxvi, p. 400) calls the lateral area the site of the anterior mechanism, and regards it as the parasympathetic centre ; the posterior nucleus he calls the posterior mechanism and regards it as the sympathetic centre. Le Gros Clark (*Journ. Ment. Sci.*, 1936, lxxxii, p. 99) describes the afferent parasympathetic path as from the infundibular portion via the anterior thalamic nucleus, stria terminalis and anterior commissure to the olfactory cortex. The efferent pathway is by the cranial nerves, especially the vagus. The sympathetic path is from the posterior nuclei via the medial thalamic nucleus, to the frontal cortex, the efferent being by the dorsal longitudinal bundle of Schütz right down the brain-stem. The impressions travel by the gangliated cord and paravertebral ganglia along the posterior root-fibres of the cord, with no synapse at the posterior root ganglion.

There is a good deal of confusion over the word "emotion". We have not in English two terms to cover mental agitation, one the slow, comparatively stable state which covers happiness, depression, jealousy, affection, the other the sudden and possibly fleeting condition implied by fright, shock, surprise, anger, rapture. McDougall does nothing to clarify these terms by dividing the general term "emotion" into two groups, instincts and sentiments. Head called the slow process "feeling tone", as does Wohlgemuth (*Pleasure-Unpleasure* [translation], 1933). Pickworth not only distinguishes between the two conditions, but ascribes the more lasting variations to alterations of the blood-supply to the synapses. These variations disclose themselves in the capillary pattern as shown by his staining method. The capillaries may be tenuous, of average thickness or engorged, and upon these changes the supply of oxygen to the cells depends. But he does not explain why all conditions of cortical anæmia or congestion do not cause depression or exaltation, nor why the pattern should so persist through the last illness and process of dying that it appears many hours later on the post-mortem table. It is, of course, the sudden type which we refer to the hypothalamus. It has been stated ("The Hypothalamus", by Clark, Beattie, Riddoch and Dott, Edinburgh, 1939) that excessive emotionalism in pseudo-bulbar palsy and disseminated sclerosis is produced by the hypothalamus being cut off from the control of the cortex. This explanation is not tenable ; such interference should preclude an outburst of emotion, as it does in severe idiocy or dementia or stupor. Emotion in choreoathetosis is caused by excessive hypothalamic activity in which brain cortex, thalamus and an external stimulus (generally of sight or hearing) all share. Most of the physical signs are covered by pituitary-adrenal activity, but not all ; the most common are excessive sweating and increased heart-rate, followed by loss of control over the voluntary musculature. I saw one case, now adult, where in early life fæcal vomiting was present ; now there is only occasional ejection of a meal. My Case 1 was unfortunately never specially examined for blood sugar ; in the usual routine annual test sugar was never found in the urine. He often

flushed with the sweating, but never vomited unless he had been overeating. There was no constipation. As to vagotonic responses such as peptic ulcer or colitis, there was no need to invoke the presence of any doubly acting hormone, such as the hypothetical " sympathin ". We can sum up the present position of choreoathetosis by saying that, in common with some other diseases, such as spasmodic asthma, exophthalmic goitre and dysmenorrhœa, it is " closely associated " with an acute emotional disturbance resulting from excessive adrenal discharge, that it produces loss of association between voluntary and automatic movement, but that it is at present impossible to say whether the excess of adrenaline is causative or resultant, while it is quite certain that some chronic toxic reagent in early life is the *fons et origo* of the mental defect and all its consequences. As to the function of adrenaline in ordinary life, it would appear that an emotional outflow is useful to reinforce maximum muscular effort after all the neurones have been brought into play, and does so by stimulating an increased discharge of acetylcholine at the end-plates of voluntary muscle-fibres—reinforcing, in fact, " the will to do ". To this extent Hunter's theory receives some support. It must also be realized that " the will to do " often implies an intense effort to keep still, muscles braced up to inhibit all movements ; it is impossible to relax during mental concentration.

Direct pyramidal tract.—Earlier in this paper it was mentioned that Case 1, after one of his severe spasms, lay for a time limp and quiet. The voluntary muscles were hypotonic. But there was an exception : the muscles of forcible respiration, which an instant before had been hurling head, arms and legs in every direction, immediately reverted to their normal state of reinforcing respiration, without any resting interval. Many of them have, of course, to reverse origin and insertion. I have not been able to find any concise history of the evolution of the direct pyramidal tract. It is of recent development, appearing later in the higher mammalia than the crossed tract in connection with or in preparation for the assumption of the erect posture. The pyramidal tract is at best not well differentiated, inasmuch as even in man it is constantly receiving and disbursing collaterals all the way down, and is still rather mixed up with other tracts. There are in the anterior horn of the cord three prominent ganglia—anterolateral, posterolateral and median. The first two supply the large voluntary muscles of the upper and lower limbs, as may be assumed by the graded number of the constituent neurones in each. The third supplies the body muscles, principally the intercostals and abdominal wall. This has been established by Bruce, of Edinburgh, in his *Atlas of the Spinal Cord* (Quain's Anatomy). Now, from the lower cervical to the upper lumbar segments there is a fourth group corresponding to the area of origin of the forced respiratory muscles, and making an anteromedian and posteromedian nucleus, the latter gradually fading out below. Clearly they are of use only for the larger muscle masses required for forcible respiration, although Bruce does not assign to them any special functions. There is some, not very conclusive, evidence that

both crossed and direct pyramidal tracts are innervated from both hemispheres, giving a fourfold nerve supply for the bilaterally acting muscle groups, such as the shoulder and upper chest muscles when assisting respiration, when they are to some extent under voluntary control. Do these muscles possess a double supply of ganglion cells and nerve and muscle-fibres? Did the absence of fatigue in Case 1 arise from this, or merely from added emotional stimulus? There is a precedent in the flexor muscle of the crayfish, which has been shown by Harreveld and Wiersma (*Journ. Physiol.*, 1937, lxxxviii, p. 78) to possess different sets of nerve-fibres and motor neurones, the one giving a twitch contracture, the other a slow tonicity. This explanation is improbable, for no mammalian muscle is known to have dual innervation. I never guessed that the effort to maintain the erect posture, together with the extra weight of the heart and solid organs of the abdomen, constituted such a severe handicap to respiratory demands until Prof. Haldane published his gas-chamber experiences, and mentioned that his dog suffered earlier from the lack of oxygen than he did himself, because the dog possessed better pulmonary ventilation.

Summary.

Two cases of choreoathetosis (Case 1, W. C—, and Case 2, H. E—), who had severe spasms and were nearly free from spasticity, as well as being of moderate mental grade, are used as a basis of discussion of the function of various central nervous mechanisms, and the opinion is expressed that the substantia nigra is one of the chief co-ordinating centres between voluntary and automatic muscular action, the spasms being energized by the emotional discharge of adrenaline through hypothalamic sympathetic outflow. A few words are added concerning the evolution of the direct pyramidal tract.

I am most grateful to Prof. F. L. Golla for permission to allow Dr. G. M. Griffiths to use the resources of the L.C.C. Central Laboratory at the Maudsley Hospital for the histological examination of the brain in Case 1, and also to Dr. Griffiths for doing the work.

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