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THE BIOLOGICAL SIGNIFICANCE OF EXTRA- PYRAMIDAL SYNDROMES, APROPOS A CASE OF WILSON'S DISEASE IN THE ADULT:

Second contribution to the biology of extrapyramidal affections.

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'In all the functions of the living organism, without exception, there is an ideal and a material side. By its form the ideal side of function is linked to the unity of the plan of creation or construction of the organism, whereas the material side corresponds by its mechanism to the properties of living matter.'—CLAUDE BERNARD (Discours de réception à l'académie française, 1869).

DURING the last fifteen years the number of studies devoted to extrapyramidal syndromes has been so considerable as to require a large volume for their exposition. Detailed researches, of very unequal value in point of fact, abound: but so far as I know the question of the biological significance of the subject—in the sense, as we shall see, of the totality of phenomena, regarded as most characteristic, embraced under the not very happy term 'extrapyramidal'—has not as yet been approached. In a preceding essay, published some years ago, I showed, apropos a case of torsion spasm, that this class of morbid phenomena, far from being purely and simply synonymous with an affection of the central ganglia, according to the classical doctrine, involved in reality the organism as a whole. It is this aspect which I shall try to render precise from a biological viewpoint, taking as text and example a case of hepatolenticular syndrome or Wilson's disease in the adult which has been followed closely during nearly the whole of its evolution. This latter condition is of capital importance for the biological standpoint, which ascribes prime significance to evolution in time.

CLINICAL OBSERVATION.

1.—M. Ab., shoemaker, age 46. *Family history*: Nothing of importance. *Previous history*: For seven or eight years it had been remarked that at intervals 'his eyes were yellow.' Four days after an emotional experience conjunctival icterus occurred,

The actual affection dates back some two and a half years. The earliest symptoms were pains in the stomach and left hypochondrium, without vomiting or loss of appetite. Thereafter, a continual diurnal cough developed, with pharyngeal irritation. Some paresis of the pharyngeal musculature followed, revealed by inability to spit and trouble in deglutition. Only liquid nourishment has since been taken. During the last two months dysarthria has become pronounced. For two or three months tremors have been in evidence and become worse. They cease in the recumbent position. From the onset, muscular rigidity has been complained of, and been progressive (it appeared as though the arms and the muscles of the neck were being 'pressed in a vice'). His wife noticed reduction of the stiffness during sleep, and greater distinctness of articulation in the mornings. Difficulty in defæcation was remarked.

From a psychical standpoint, his wife affirmed strongly that ever since his marriage (fifteen years previously) she had observed intermittent conjunctival icterus, apart from any clinically recognisable hepatic affection, chiefly with any slight contrariety. Increasing irritability alternated with phases of depression, and unmotivated attacks of spasmodic weeping occurred. Memory and orientation were normal.

On examination: Rigid facies; the head is always held in the same position. Fixed expression, with eyelids seldom lowered. Parkinsonian attitude, but with head and trunk in hyperextension. Considerable dysarthria; speaks as though his mouth were full, according to his own expression. With fingers extended, there is mild tremor of their extremities; no intention-tremor of the classical kind (can drink a glass of water without any shaking), and none when at his occupation. Tremors appear during certain complex actions (dressing, arranging his necktie) belonging to the group of eupraxias. The movement is performed slowly and is decomposed into a number of phases with a slight pause between each. Cutaneous and tendon reflexes normal, except for exaggeration of the knee-jerks without clonus. They cannot be inhibited by 'volition.' Postural segmental reflexes (Westphal-Foix): exaggerated. Oculo-cardiac reflex: 73 before compression, 82 after. Internal and external ocular musculature: normal. Fundi: normal. Wassermann reaction: negative in blood and spinal fluid (Institut Pasteur and Dr. Peyre). Spinal fluid: normal. Urine and blood: see below.

2.—Aug. 14, 1920.—Says he has felt inclined to weep the whole morning, for no reason, explaining that it starts if he contracts the upper facial muscles; 'I wish to control myself, but I can't; it rather annoys me.' Asked whether there is the same sadness as when he experiences a genuine chagrin, his answer is: 'when I weep for a real sorrow, I sob; when I weep as I am now doing, it is not the same thing. I feel the former comes from my heart; but now I am weeping in spite of myself; I feel it comes from the stomach. If I am commiserated with, I am compelled to cry; if I experience enjoyment, I have also the inclination to weep. When I weep, I feel as though I were being gripped (indicating the epigastric region); it is difficult to explain what I actually feel. It seems as if my stomach were shrivelling, and that ends up with pains.' He has often had nightmares (dreams he is fighting, falling, or crying 'thief!').

3. Oct. 3, 1920.—The patient made the following comments spontaneously. 'I have the inclination to cry for no reason, it is because of my great feebleness. When I feel stronger, I am more merry. When I start to walk, sometimes my legs give way under me, but after walking a minute my powers come back. The further I go the greater the tendency to fall forward; formerly it used to be backward. Often enough my head is confused; it seems like a mist, which may last ten minutes. On getting up in the morning, if I do not pay attention I should fall; my balance fails me. Sometimes there is a tendency to go right or left, sometimes forward. My mouth is always full of a thick and sticky saliva. Sometimes there is frequency of desire to micturate without my passing much, in the mornings; sometimes I pass water till it stops; I feel I could pass more but the power fails me.' Sometimes urination is precipitate,

4. Nov. 12, 1920.—During my absence a medical man not acquainted with the nature of the affection administered .15 cgm. neosalvarsan Billon by injection into the gluteal region (Oct. 21). Three days later, cutaneous and conjunctival icterus appeared; from that date, it became intermittent. Further, since the injection tremors have developed; when lying down the patient exhibits marked tremor of the toes, with involuntary twitches in arms and calves. Difficulty in defæcation; intense salivation (like an encephalitic), of parasympathetic type; pollakiuria; dysarthria and dysphagia (swallows even fluids with trouble). Great feeling of fatigue, *even without muscular effort*. Sensation of pressure in muscles of neck. All these symptoms are more pronounced on the left side.

5. Nov. 24, 1920.—Feeling of great coldness especially in the extremities, unrelated to external temperature. Spasmodic weeping more frequent, always accompanied by epigastric pain. Micturition and defæcation always troublesome. For some days has

FIG. 1. Photograph of patient taken several years before apparent commencement of first symptoms.

noticed between eleven o'clock and noon 'stiffening,' more marked on the left side. Salivation unaltered; loss of weight though alimentation is normal.

6. Dec. 27, 1920.—Some fifteen days ago he believed himself cured, for a day or so; assured me that all his symptoms had vanished. Now complains that external cold aggravates his muscular rigidity. Subjectively, the left side is colder than the right. From the point of view of his trade, he cannot smooth off, but can use the hammer well; cuts the leather with the knife without shaking. He declares that rigidity has diminished while trembling has increased during complex actions. Deglutition easier, and dysphonia rather better. No subicteric tinting of the skin. Gross trembling of the tongue; boulimia ('I eat four times a day'). Walking presents distinct difficulty in starting, being shaky to begin with; it then becomes more and more assured. Exhibits antero- and lateropulsion; formerly felt himself 'pushed' backward.

7. Dec. 28, 1920.—Complains bitterly of difficulties in micturating. Passes water twenty times in a few hours. Is not relieved by the act. Sometimes has the desire without

the power. Has insight into his condition in the sense that he fears becoming unable to work at some time. Normal orientation. States that when he is 'weak' vision also becomes 'weak,' meaning thereby having the 'sensation of fatigue,' of pressure in the neck, stomach shrinking, pains like rheumatism over the left shoulder-blade, but also elsewhere, for the pains are not always in the same place. The superficial venous network of arms and legs, especially distally, is very noticeable; the muscles stand out sharply. In the erect position, fibrillary trembling of leg muscles. Shaking of hands during undressing. No defect of sensibility or of segmental attitudes; knee-jerks active, particularly the left; cremasteric, plantar, and achilles reflexes normal. Slight clonus of toes after forced flexion of foot on leg. No myotonic reaction in trapezius with pinching or faradic current.

8. Jan. 26, 1921.—Still complains of desire for micturition without accomplishment except under great difficulty. Similar trouble in regard to defaecation. As before, sleep is interrupted by nightmares (dreams he is 'falling over a precipice, thieves have entered his room, fighting'). In walking, anteropulsion and shaking of the legs. Muscular rigidity 'has now reached my thigh.' Sometimes feels the left side worse. Complains of vision being 'weak.' Speech is more and more defective, salivation more and more intense. Much depressed in view of his consciousness of the serious nature of his malady.

9. March 11, 1921.—Has given up all work at his trade. Walks *en bloc* without using the arms. Extreme slowness of movement. Considerable emaciation. Tremors of finger ends and of tongue accentuated. More frequent spasmodic weeping. Anteropulsion; sudden stiffening of muscles of neck and shoulders when walking. Deglutition and articulation always very defective, as well as defaecation. Feels much better when lying down. Reflex of Léri: absent.

10. March 18, 1921.—When he walks the left arm is held closer to the body than the right. Frequent deep sighing. Hypotonia of calf and arm muscles (where veins no longer in evidence), whereas thigh muscles remain rigid. From time to time, generalised fibrillary twitches confined to the hypotonic muscles. Violent itching at the level of the upper thorax noted for the first time. Brown pigmentation of the abdomen as high as the xyphisternum. Sensation of coldness in the calves. Deglutition more defective than ever.

11. March 25, 1921.—For a month has felt the right side of the body becoming weak. To-day, development of lower facial weakness on the right side, seen by drooping of the labial commissure on that side. Fixed expression, but no involvement of the oculomotor. Great feebleness of the muscles of the legs. The severe feeling of fatigue of which the patient is conscious seems to have coincided with the general diminution of tonus; when the calves were rigid he felt less tired. Shaking of the legs; lateropulsion to the right. Defaecation very difficult, with tenesmus. Normal orientation. Progressive general cachexia. Mimic expression of smiling preserved but dissociated, involving rather the upper part of the face (on the non-paretic side).

12. April 7, 1921.—Recently injections of scopolamine have been tried but abandoned because of their producing a clouded state of consciousness with a general sensation of coldness, especially on the face. During examination of the left plantar reflex, clonus of the contralateral great toe developed, spreading thence to the left. Continued for several seconds, then remained on the right side only. Remarked that these phenomena sometimes develop spontaneously, in 'little attacks.' They reappeared during further examination. When being tested for adiadocokinesia, he said that corresponded to what occurred in his feet, viz. appearance of clonic movements in the toes. On the left, the finger-nose test produced quick movement of the hand to about a few centimetres from the nose, when a sudden twitch followed. Remarks that when in the recumbent position he experiences a sensation of painful pressure in the epigastrium which disappears

whenever he sits up. When he lies down the exaggerated salivation does not occur. Micturition and defæcation as before. Constant diurnal drowsiness; sleeps heavily at night. For several months, hair falling out, though neither from scalp nor moustache.

Reflex of solar plexus (Claude): negative in spite of strong pressure. Oculo-cardiac reflex: 77 before and 73 after ocular compression.

13. April 14, 1921.—Adiadocokinesia persists, but the movement of arrest in the finger-nose test, noted above, is no longer found. Cannot stand on one leg even with eyes open. Knee-jerks: normal on the right, very brisk on left. During testing of plantar reflexes, same phenomenon of crossed toe clonus as before. In the erect position, hypertonus of leg muscles pronounced; in the recumbent position, extreme hypotonus of the same muscles, to such a degree that the fingers can be insinuated on the inner aspect of the tibia, between the posterior surface of the bone and the adjacent muscular masses. Paresis of the lower face as before. When the patient takes to his bed he cannot, with head lowered, support himself on his hand flattened out on the bed, but can do so with fist closed.

14. April 18, 1921.—When standing up to pass water he is obliged to use force; on palpation the muscles of the abdominal wall are strongly contracted. It is as though the vesical sphincter offered great resistance. After the passage of perhaps a cupful of urine, slight trembling of the whole body. After several minutes he is obliged to rise and micturate again, in the same way, to the amount of half a cup.

15. April 19, 1921.—To-day, about half past four, the patient spoke very distinctly without obvious dysarthria. After a series of trials, two hours later his voice became unintelligible. On the legs, where the hairs have fallen out, small black pigmented spots have appeared, like those produced by silver nitrate, as has already been noticed in respect of the abdomen.

16. May 28, 1921.—Pronounced pains, seemingly spontaneous, in both heels, which are not, however, painful on pressure. Says 'when I speak I have the same sensation here (epigastric region) as during the attacks of weeping.' Has two attacks of this in front of me, the first when I ask him how he is, the other when I hand him his photograph. Profuse sweating chiefly on the upper face, especially on the sides of the nose. Abundant perspiration with effort. Saliva thick and in quantity. At certain moments lachrymal secretion without apparent reason. Frequent tenesmus. When at stool he feels 'something which closes up.' Asthenia always extreme; can cut leather, but with great difficulty. Under the influence of emotion (mere entrance of a client into his shop) shaking of the whole body and enormous increase in dysarthria. In finger-nose test, slight arrest before the end of the movement. Cutaneous plantar excitation on the left side produces clonic movement of same and of opposite foot; stronger stimulation causes slight retraction of the opposite foot only. Right knee-jerk, considerable excursion of the leg; left, less, but sudden arrest and more voluminous swelling of quadriceps. When he performs any 'voluntary' act he 'stiffens to the mouth.' When he dresses, intense trembling of the whole body. Moans as he does so. Urination accompanied by very strong abdominal contraction as before.

17. June 17, 1921.—To the great surprise of his wife, dysphagia for solid food has disappeared completely during a fortnight; on the other hand, his speech is understood with difficulty even by her. Profuse sweating over the upper part of the face. Other symptoms unchanged.

18. June 22, 1921.—In the morning, persistent pain in the metatarsophalangeal articulation of the great toe and in the heel. Normal motility of external ocular muscles. Rectal temperature, taken night and morning for eight days, shows no alteration in thermal function.

19. July 7, 1921.—The patient states he feels a coldness in the left knee, less marked in the right. The result of the finger-nose test corresponds to the instinctive state of the

FIG. 2. Photograph of patient taken about three and a half years after apparent commencement of first symptoms.

moment; on the left (where the motor disorders have always been more noticeable), dipping and slight deviation before the nose is reached. Same observation on the right, but less in degree. With encouragement and assurance, the slowness of movement on the left diminishes, and the dip is scarcely noticed; on the right, the movement becomes almost normal and the deviation disappears. When any one enters he cannot reproduce this and says spontaneously that 'everything upsets me.' When in the erect position, on the request to relax completely, it is seen that the left forearm is more flexed on the upper arm and that the fingers are more flexed on the palmar aspect; the attitude recalls that of early hemiplegia (see fig. 2). When the foot is flexed on the leg, the *tibialis anticus* contracts and the posture persists for several minutes in spite of the request to 'let the foot go' (Westphal's paradoxical contraction).

It is impossible to get the patient to breathe quickly, but with slight acceleration there is marked tremor of the toes of the right foot, followed by spontaneous extension and fanning. After twenty minutes a second attempt at rapid respiration was made. A few seconds later, extension of the last four toes on the right, of the great toe on the left, and trembling of the former. The opened mouth has a definite oval shape with disappearance of the right naso-labial fold. Can appreciate correctly differences between weights on right and left; holds a weight of one kilo in the left hand, the arm semiflexed, for 55 seconds without being aware of fatigue, as is practically normal. Pressing the epigastric region causes what he calls 'weak attacks'; he attaches great significance to this part. Complete loss of *libido sexualis* since the commencement of the illness.

20. Aug. 5, 1921.—Sensations of formication and of coldness on the outer side of the left leg; on the outer side of the foot, a feeling of warmth. When he pinches the leg on its outer aspect the sensation of cold becomes one of heat. Says 'when I speak it is always in the stomach I become fatigued.' In order to be understood he has to speak slowly. His wife says he cannot pronounce a long phrase without having to stop. The tiredness felt in the legs varies in degree; it involves upper and lower limbs and spares the trunk. Defaecation, formerly difficult, has become rather easier. Micturition always difficult. Dysphagia continues. Recently, has had trouble in opening the mouth owing to forced contraction of masseters. Intermittent salivary hypersecretion.

21. Aug. 10, 1921.—During the night of Aug. 6, continual cough which ceased suddenly in the morning. Respiratory difficulty without any cause being found by auscultation. Feels better when the head is held forward. Says he would sleep sitting up if he could. Stools are of normal consistence; there is thus no constipation.

22. Aug. 25, 1921.—The more he speaks the greater is the fatigue, localised in the epigastric region. Spontaneous pains much less intense on the right side. Frequent spasmodic weeping with epigastric pain. Brownish pigmentation round the hair follicles in the midline of the abdomen persists. Constant stiffness of the neck. Walks without lifting heels. Conjunctival subicterus. Can no longer wear braces because of their traction on neck muscles. Cannot bear trousers closed over the epigastric region or wear collars at all tight.

23. Sept. 20, 1921.—Is at his worst between eleven o'clock and twelve noon. His wife is impressed with the great variability of his condition; from day to day and even from hour to hour modifications occur in his physiognomy; his neck alters in volume similarly, the same shirt-collar sometimes annoys him, sometimes not (variations in size of thyroid observed). At night, pains in heels and buttocks; last two days, in the left arm. Speech now incomprehensible. Scopolamine and liver extracts are the sole medicaments producing a little satisfaction.

24. Sept. 28, 1921.—When walking, throws the left leg forward more than right and uses the right arm in balancing, not the left, which adopts a hemiplegic position. Considerable dysphagia. Continual trembling of toes; trophic disorder of the left great toe. No definite pyramidal signs. No evidence of catatonia.

25. Nov. 22, 1921.—Paroxysmal pains in the left arm. Vesical and rectal symptoms more pronounced. No appetite; much emaciation. It is remarkable that the dysphagia disappears when his attention is concentrated on the act of swallowing. Increasing muscular asthenia. Gross fibrillary tremors of tongue. Marked intention-tremors. Weeping more frequent; sometimes suffocating attacks. Speech low in tone, but perceptible and normal at the commencement of talking, dysarthria following after a few minutes.

26. April 15, 1922.—Still no pyramidal signs; for efforts of brief duration no loss of muscular force. Dysuria worse than ever; trembling attacks of a generalised kind when trying to micturate at night. Two important points are now in evidence; (1) the erect attitude is no longer one of hyperextension, the head being lowered and the back slightly curved; (2) the right side is as much affected as the left. Cannot dress himself. Disorder of deglutition has disappeared; dysarthria as before, but when insistence is made on the matter he can make his unintelligible speech become quite clear. Desquamation of the whole of the skin except on the face. Generalised tremors with any contrariety. Advanced trembling *en masse* of the tongue. Hands very cold, sometimes violet in colour; respiration shallow, intermittent conjunctival subicterus. Loss of cremasteric reflex. Kohnstamm's phenomenon of catatonus evident in the upper limbs. Extreme fatigability; diminished amplitude of movements; wide movements are accompanied by tremors and moans. Continual salivation. 'Voluntary' opening of mouth limited, but complete on yawning. Cutaneous pigmentation of abdomen reduced.

27. June 16, 1922.—Intermittent swelling of feet and ankles (no albuminuria). Occasional congestion of head (cheeks and ears particularly), which makes his head 'feel bigger.' Brownish pigmentation on buttocks. Desquamation of skin. Deglutition takes place normally.

28. May 27, 1923.—During the last year has been tormented continually by dysuria. Two urologists separately have demonstrated that bladder and prostate are normal.

29. June 27, 1923.—Intense salivation and muscular asthenia; Parkinsonian posture of trunk. Under the influence of powerful emotion (death of a parent) complete urinary and faecal incontinence.

30. Nov. 3, 1923.—His wife writes that 'at present his condition is not too bad; he has an appetite and swallows without trouble, while his articulation is more distinct. I note that when his condition seems better he tends to make bizarre and irrational statements; this is fleeting, and curiously enough, when it is pointed out to him he becomes aware of it and can remember what he has said. Disturbed nights, the patient jumping up in dreams and speaking at the top of his voice; if I answer him, he converses for a moment even though asleep. Difficulty of defaecation—in the case of his bladder, variable.'

31. Nov. 15, 1924.—His wife writes: 'My husband spends his days as if ankylosed, dosing in a chair, his eyes shut; if he walks, his head and chest are carried forward. Trouble at stool severe; urination is never regular. Speech unintelligible, more at one time than another; always salivating; great difficulty in swallowing liquids. Dreams much and talks in his sleep. Has two small sores on his hips which I have managed to dry up with ether.'

32. Sept. 8, 1926.—After progressive cachexia the patient died suddenly on August 20, 1926. In spite of every request the family refused an autopsy. During the last months his condition was as follows: sacral bedsores, asthenia, violent pains in arms, variability of symptoms referable to bladder, rectum, speech. In the case of the last of these, however, spoke to himself, towards the end, with complete unintelligibility. Nail of great toe enormously hypertrophied. Stiffness of neck largely disappeared. Parkinsonian attitude of trunk and head. For some months, no spasmodic weeping; persistent salivation; no particular defect of memory.

The illness extended over eight years; no hereditary factor was found on enquiry among other members of the family. No history of influenza or other febrile attack suggestive of the possibility of epidemic encephalitis was discovered to account for the disease.

Urinary analyses (M. Charles Guillaumin).

1. Dec. 3, 1920.—Lacto-vegetarian dietary.

Amount examined: 950 c.c. Density at 15° C.: 1022.

						Total for 24 hours.	Normal variations.
Total nitrogen (as N)	..	..	..	..	..	7.89	14—16
„ „ (as urea)	..	..	..	..	..	16.95	30—34
Urea	..	..	..	..	..	13.92	24—28
Sal ammoniac (and amino-acids titrable in formol)							
(as NH ₃)	..	..	..	..	..	0.42	0.70—0.90
Creatinin	..	..	..	..	..	1.00	1.30—1.60
NaCl	..	..	..	..	..	13.48	12—15
Urobilin	..	..	..	..	..		traces
Urological percentages:							
Nitrogen of urea	..	..	..	..	..	82.0	82—83
Ammoniacal nitrogen	..	..	..	..	..	4.4	5—5.5
Creatinic nitrogen	..	..	..	..	..	4.7	3.4—3.8
‘Urogenic defect’ (Maillard)	..	..	..	..	..	5.1	6—6.5

2. Dec. 21, 1920.—Lacto-vegetarian dietary.

Amount examined: 2,000 c.c. Density at 15° C.: 1,021.

Total nitrogen (as N)	..	..	..	..	..	12.80	14—16
„ „ (as urea)	..	..	..	..	..	27.40	30—34
Urea	..	..	..	..	..	24.20	24—28
Sal ammoniac, etc. (as NH ₃)	..	..	..	..	..	0.44	0.70—0.90
Uric acid	..	..	..	..	..	0.70	0.60—0.80
Purin bases (as xanthin)	..	..	..	..	..	0.08	0.05—0.12
Creatinin	..	..	..	..	..	1.70	1.30—1.60
Creatin (as creatinin)	..	..	..	..	..	nil	0—10% of the creatinin
Nitrogen (unallotted)	..	..	..	..	..	0.26	0.60—1.10
Total minerals	..	..	..	..	..	40.70	16—22
NaCl	..	..	..	..	..	25.40	12—15
Minerals (achloric)	..	..	..	..	..	15.30	4.75—6.75
Acidity (as P ₂ O ₅)	..	..	..	..	..	0.82	1—1.20
Phosphoric acid (as P ₂ O ₅)	..	..	..	..	..	2.30	2—2.40
Biliary acids	..	..	..	..	..	0	0
Biliary pigments	..	..	..	..	..	0	0
Urobilin	..	..	..	..	..	slight	traces
Urological percentages:							
Nitrogen of urea	..	..	..	..	..	88.3	82—83
Ammoniacal nitrogen	..	..	..	..	..	2.9	5—5.5
Purin nitrogen	..	..	..	..	..	1.8	1.8—1.9
Creatinic nitrogen	..	..	..	..	..	4.9	3.4—3.8
Nitrogen (unallotted)	..	..	..	..	..	2.1	7—8
Urogenic defect (Maillard)	..	..	..	..	..	3.7	6—6.5

Metabolism of nucleins:

Purin bases	..	..	..	..	..	11	7—17
Uric acid	..	..	..	..	..		
Phosphoric acid	..	..	..	..	..	17.8	14—15
Total nitrogen	..	..	..	..	..		

B

Comment of M. Guillaumin: 'In view of the diet I expected to find very different figures. I repeated certain examinations, notably total nitrogen, with the same result. The remarkable lowering of the ammoniac and similarly the increase of the nitrogen percentage may be attributed to the high content of alkaline minerals.'

3. Jan. 28, 1921.—Creatinin (colorimetric method of Jaffé-Folin): 1 gr., 24 per litre.

4. April 12, 1921.—Ditto, 1 gr., 01.

5. May 1, 1921.—Indoxyl (indican)	..	abundant	traces
Scatolic red		abundant	traces
Indol		abundant	traces
6. July 18, 1921.—Urea		18.15 per litre	19—22
Ammoniac		0.82 „ „	0.70—0.85
Total nitrogen		14 „ „	11—12
7. Aug. 12, 1921.—Urea		9.71	19—22
Ammoniac		0.18	0.70—0.85
Total nitrogen		5.60	11—12
8. Sept. 2, 1921.—Urea		10.50 per litre	19—22
Ammoniac		0.34 „ „	0.70—0.85
Total nitrogen		5.35 „ „	11—12
N of urea		4.89 „ „	8.8—10.5
NaCl		10.52 „ „	8—10
Creatinin..		present	
Ureic N to total N		91.4%	84—91%
NaCl to urea		100%	42%
9. Sept. 23, 1921.—Urea		16.50 per litre	19—22
Ammoniac		0.84 „ „	0.70—0.85
Total nitrogen		8.85 „ „	11—12
N of urea		7.68	8.8—10.5
NaCl		13.45 „ „	8—10
Creatinin..		nil	
Ureic N to total N		86.7%	84—91%
NaCl to urea		81.5%	42%
10. Feb. 7, 1921.—Examination of fæces (M. A. Lesure):			
Hydrobilirubin		very small amount	
Hydrobilirubinogen		traces	
Biliverdin		none	
Bilirubin		none	

Conclusion: fæces only contain a quantity below the average of transformed biliary pigments and none of normal pigments.

Cytological examination of the blood.—The following examinations were made in the laboratory of Prof. Sabrazès at Bordeaux.

1. Jan. 7, 1921.—No poikilocytes, basophil granules or polychromatophilia. Most of the globulins have agglutinated. The number of whites does not appear notably augmented, it is certainly not decreased.

Leucocytic formula:

Polynuclear neutrophils		57.1%
Mast-leucocytes		0.4%
Lymphocytes		37.1%
Large mononuclears		3.6%
Large mononuclears (lobed nuclei)		0.4%
Lymphoblasts		0.4%

Nuclear value of 100 polynuclear leucocytes : 341.

Sometimes one up to four minute nuclear fragments are seen in a polynuclear leucocyte. Summary : absence of eosinophilia ; relative lymphocytosis ; nuclear value of polynuclears above average (deviation of nuclear picture to the right).

2. Jan. 19, 1921.—Examination by Prof. Sabrazès himself. No anisocytosis or poikilocytosis. Proportion of granular reds practically normal (not more than 1 or 2 per 1,000). Blood-plates rather above the average.

Leucocytic formula :

Lymphocytes	..	..	..	..	..	..	18%
Monocytes	..	..	..	..	..	..	4%
Monocytes with plurilobar nucleus	..	..	..	..	..	..	1%
Neutrophil polynuclears	..	..	..	..	..	..	76%
Eosinophils	..	..	..	..	..	..	0.6%
Mast-cells	..	..	..	..	..	..	0.6%

Nuclear value of 100 neutrophils : 316 (above normal).

Summary : fairly well marked neutrophil polynucleosis ; reduction of eosinophils. Neutrophilia fits in with sympathicotonus ; in vagotonus there is generally eosinophilia.

3. April 21, 1921.—*Digestive hæmoclasis test.*

Ingestion of 200 gr. of milk fasting, with examination of blood each twenty minutes after.

		Before test.	20 mins. after ingestion.	20 mins. later.
Polynuclear neutrophils		44.2	58.02	68.84
Lymphocytes		38.4	33.7	23.4
Mononuclears		12.6	3.7	4.26
Mononuclears (lobed nucleus)		3	0.96	2.25
Eosinophils		0.9	1.73	1.5

Summary : Before test, marked lymphocytosis and corresponding diminution in percentage of polynuclear neutrophils ; after, increase of latter and diminution of lymphocytes and monocytes.

Pharmacodynamic tests.—*Adrenalin.* Subcutaneous injection of $1\frac{1}{2}$ mgr. adrenalin (Clin) provokes after twenty minutes extremely marked tremors of hands during purposive movements, also of tongue and respiratory muscles (as pneumograms show) ; speech does not undergo any change. After twenty minutes, sudden cessation of tremors ; they then begin again. During the test the patient looks exactly like a true case of paralysis agitans.

Atropin (March 18, 1921).—10.50 a.m. Pulse 80 per min. Subcutaneous injection of 8 mgr. atropin on outer aspect of left forearm.

11.10 a.m. = 68 pulsations. Disappearance of all fibrillary twitches.

11.20 a.m. = 72

11.30 a.m. = 68

11.43 a.m. = 72

11.45 a.m. Development of horizontal nystagmus of fine amplitude.

12 noon = 76. Intermittent nystagmus. Slight mydriasis.

Pilocarpine.—Owing to a tendency to loss of consciousness with sensation of impending death produced by injection of 1/10 mgr., the test could not be carried out properly.

Scopolamine.—4.55 p.m. Pulse 76. Subcutaneous injection of $\frac{1}{4}$ mgr. scopolamine bromhydrate.

5.20 p.m. Intermittent horizontal nystagmus.

5.21 p.m. = 76 pulsations.

5.40 p.m. Persistence of nystagmoid jerking.

5.42 p.m. = 76 pulsations.

5.50 p.m. Persistence of nystagmoid jerking.

If now we attempt to characterise the preceding clinical picture, there will be, we believe, unanimity as regards its belonging to the group of hepatolenticular syndromes; in more precise fashion we shall willingly affirm that it is a case of Wilson's disease in the adult. Without taking part in the scholastic discussions of nosologists, we shall refrain from speaking of pseudosclerosis, in the first place because Westphal himself, in his paper of 1883, said that was not a very happy expression ('nicht sehr glücklich'), and in the second, because all kinds of heterogeneous facts enter not only into his own confused cases, but also into those, even more confused, of Strümpell (1898).

ICTERUS.

It is convenient, at the outset, to draw attention to the following peculiarly interesting feature. Thirteen years before his illness seemingly began the patient exhibited intermittent conjunctival icterus and was subject to emotional icterus. This fact is extremely interesting in view of the discussions still going on relative to the connexion between the hepatic and the striate and other cerebral lesions. It is well known that Wilson has declared for the primary character, in all probability, of the hepatic dysfunction. Yet all researches on the production in the animal of 'experimental Wilson's disease' have hitherto failed. From our standpoint the problem is not properly stated in either case. (1) In experiments no attention is paid to the great difference between the integrative levels of the nervous system in man and the animal respectively. Further, the question of *time* is overlooked; the speed at which certain biological phenomena unroll themselves and that (vastly greater) at which our grosser experimental surgical interventions take place, are utterly different. (2) Though it is customary to oppose to each other the two pathogenic alternatives—hepatic origin or cerebral origin—there is a third alternative which does not appear to have been considered. The presence of habitual emotional icterus leads us to ask whether our case is not one of primary disorder of a functional synergy (as in endocrinopathology) between subcortical organo-vegetative representations and the liver. On the one hand, as a matter of fact, the conditions of biological functioning of the liver depend on the organo-vegetative system; in respect of emotional icterus, it has been practically demonstrated by Eiger to depend on vagal hyperexcitation (vagus being used in its macroscopic anatomical sense). On the other hand it is proved that the normal functioning of the liver is necessary to the functioning of the organo-vegetative system (Danielopulu, 1931). In other words, it would appear that for the physical notion of *unilateral* causality must be substituted the biological idea of *reciprocal* causality. Emotional icterus appears to be the sign of a facilitation of vegetative nervous stimuli in a direction determined towards the liver, and we shall see later that in certain circumstances it is the same for the stomach, also innervated by the vagus. On the other hand, the instance of icterus neonatorum shows that biliary pigments and probably other substances as well can pass the hæmato-encephalic barrier (specially the choroid plexuses)

and reach paraventricular cerebral formations. This, needless to say, is no more than a hypothesis: none the less the notion of a primary affection of organo-vegetative representative centres seems singularly confirmed by the evolution of the syndrome in time. Let us recall its main lines.

VARIABILITY OF SYMPTOMS.

The most characteristic and most general feature is the variability of the symptoms. Whether they consist of muscular rigidity (see paragraphs 10, 12 above) sialorrhœa (12), dysphagia suddenly disappearing at a late stage of the disease (17, 26), bradyteleokinesis (19), volume of thyroid (22), general attitude of body (26), spasmodic weeping (32), especially the dysarthria (15, 23), the symptoms are in essence mobile and differ according to their period, so that we already get the idea (unless we are content with a fragment of the clinical picture artificially separated) not of a static disturbance (like an organic hemiplegia of vascular origin which has reached the residual stage of von Monakow), but a dynamic affection of a peculiar kind.

Further, a glance at the urinalyses, conducted sometimes at intervals of only a few days, or at the blood examinations (of less demonstrative value), will reveal the same variability (though the alimentary regime was identical). We see, for instance, the total nitrogen pass from 7.89 to 12.80, Maillard's coefficient from 5.1 per cent. to 3.7 per cent., or the ratio of NaCl to urea pass from 100 per cent. to 81.5 per cent., whereas the normal figure is 42 per cent. The internal milieu, one of the essential components of the vegetative system in the sense of F. Kraus, characterised here in a rather crude fashion, we admit (it is impossible, according to Zondek, to have at present a complete intratissular representation of it) varies notably, even remarkably, in the course of time. Here is an evident dysregulation which laboratory methods, simple enough, are able to demonstrate. Thus the question is at once reached: What is this dysregulation, and does it bear any relation to the dysregulation immediately suggested to the mind by the variability of the symptoms?

RELATION OF SYMPTOMS TO LESIONS.

A preliminary remark must first be made. Some years before the War there were still writers who classed with the neuroses syndromes accompanying nervous lesions as obvious as those which concern us here. They relied both on precise observation—the occurrence of phenomena dubbed hysterical in such patients—and on a defective method which concealed simple ignorance by the use of a word. Real progress was attained by the method which succeeded it, at least to begin with. Legitimately proud of the acquisitions of anatomy (secondary degenerations) and of clinical medicine (precise semeiology of affections of pyramidal and cerebellar paths), neurologists have termed 'extrapyramidal' (a vague expression) everything that could not be classed in the other categories. Justifiably enough: but the method appears to have been imperfect when the neurologist has sought to assign to each symptom or

group of symptoms a strict and precise anatomical localisation; examples might be furnished from the literature of any country in the world. Such procedures have led to the development of the sophism denounced by von Monakow, which consists in identifying the localisation of lesions and of functions. From this viewpoint Wilson has submitted current interpretations, attributing a host of heterogeneous symptoms to the corpus striatum, to a most searching criticism in his Croonian Lectures of 1925, which, in our opinion, form a contribution destined to constitute a landmark in the neurological history of a type of disease which he was the first to study (1912) in a truly fundamental manner.

In point of fact it is only too evident to anyone who has in mind (1) the integration of motor function from the foetus to the adult, and (2) the emigration of function towards the superior surfaces of projection and association (Steiner and v. Monakow), that it is impossible to localise in the corpus striatum the automatism of movements (itself merely an abstraction) and akathisia! We wish now to go further and ask whether, apart from the mechanisms playing a genuine rôle in the pathogenesis of affections here considered (cortical, striate, rubral, cerebellar, mesencephalic components, and others), admirably studied by physiologists of the schools of Sherrington and Magnus, and by anatomo-clinicians, there is not room to pose the question of a more general factor, from the standpoint of biology as we shall define it.

THE BIOLOGICAL STANDPOINT.

We mean thereby not the study of such and such a function artificially isolated—which is the work of experimental physiology—but the study of the ensembles of phenomena having for their purpose not merely the conservation of the individual considered as a whole but also the realisation best adapted for all his potentialities. From this point of view the propulsive and at the same time regulatory force resides in the *vegetative system*. By that term we understand, after F. Kraus, not only the vegetative nervous system in the strict sense (sympathetic and parasympathetic), which plays a certain regulatory part, but also the electrolytes, among which calcium and potassium are the best known, the hormones, and the colloidal balance, local in the tissues. Probably many other components exist as well. From this standpoint Zwaardemaker has opened up wide perspectives through his admirable researches on the relations between the various radiations discovered by the physicists and the function of the vegetative nervous system. This is the conception of Kraus and Zondek, the only one at present capable of taking into account innumerable phenomena that cannot be interpreted by the 'classic' doctrine of Eppinger and Hess.

We owe to W. R. Hess of Zurich a very important contribution to the study of sleep conceived of as a biological process of defence of the organovegetative system (Hess in fact adopts the classical doctrine in this matter), guaranteeing the animal system against exhaustion. Recently the conception has been

extended by Hess, Foerster, Altenburger, Kroll and others to the function of the receptors, which are taken to be sheathed in a vegetative apparatus destined for the regulation of function.

If it really is so, if modifications of tonus and of static function during sleep are in correspondence with the vegetative system, why should it not be the same during waking life, so far as concerns the normal regulation of function of skeletal muscles and their dysregulation in the course of certain affections? We think it is precisely so-called extrapyramidal syndromes (at least in some of their aspects) that are of a kind to confirm this way of looking at the matter.

Clinicians have always been struck by the frequency therein (one might say constancy if they were properly looked for) of undeniable vegetative disorders. In our case of Wilson's disease in the adult we note salivary trouble from beginning to end, as well as of lachrymal and sudatory secretions (16); disorder of thermal function (5); of cutaneous pigmentation (10, 15); of micturition and defæcation, throughout; vasomotor disturbances (27); transient respiratory affection (21); transient thyroidal disorder (23); trophic change (25); and finally the 'vegetative death' of L. R. Müller (32).

Again, in this category of patients symptoms reminiscent of hysteria have all along been remarked. Is it not a curious thing in our case (see 8) that the muscular rigidity reached the mid-thigh, recalling the stocking- or garter-anæsthesia of the classical hysteric, which has not always been the result of suggestion though thought to be so? Above all, in this case observed during its evolution of seven years, what has impressed most has been the enormous variability of the symptoms, filling the entourage with astonishment and leading them to doubt my prognosis. This was particularly noticeable in regard to speech, which was often normal at the commencement of an interview and became dysarthric only after some minutes (15). Similarly, the dysphagia which had lasted for years (with some variations, it is true) disappeared completely for a fortnight (17, 26); likewise, the spasmodic crying vanished towards the end (32). The same changeableness affected muscular rigidity (10) and the secretions. The intensity of the dysuria and the dyschesia was also subject to variations, though they were the most persistent symptoms observed. Finally, the patient once presented complete disappearance of all his symptoms for 24 hours (6).

From all these facts of observation a profound difference may be noted from what occurs in the course of 'morphological disorders' (v. Monakow and Mourgue) through lesions in continuity of nerve substance at a residual stage. If some youthful subjects of traumatic hemiplegia sometimes recover part of their movements, so far as I know a return to normal for 24 hours has never been observed. Facts of this kind have led authors to speak of neurosis, and of hysteria in particular.

The following facts, to which we attach some importance, must also be added; their theoretical significance will be discussed later on. The patient

presented the bradyteleokinesis described by Schilder, for the first time, we believe, apropos epidemic encephalitis. Now by the aid of strong instinctive stimulations, in an imperious tone, the symptoms could be made to disappear rapidly (19). It was the same with dysphagia (25). We shall see that in these instances there is activation of the vegetative system, it having been shown that every psychical action of one person on another can be effected only by the intermediary of the instinctive or vegetative sphere.

FATIGABILITY.

We reach now what we consider the essential feature of our case: the rapid fatigability. It was general, and involved the dynamic as well as the static function of muscle, contrary to what Trousseau had formerly observed in the case of Parkinsonism (Dyleff, 1909). To be sure of this one has only to examine the electromyographic tracings of flexor communis digitorum (right and left) during the action consisting of compression of a rubber bulb for about one second, and those of the sural triceps (right and left) when the patient is on his toes (figs. 3—10). The first series (figs. 3—6) was taken after a rest of half an hour, in the recumbent position, the second (figs. 7—10) about two minutes later. The first tracings are normal, except for a slight tendency on the left side to fusion of excitations. Throughout it is seen that the left side (especially the left leg) is constantly more affected than the right. The second series show a set of biphasic oscillations, with a frequency of 24/27, characteristic of commencing muscle fatigue. Such is the interpretation given us by the late Prof. Wertheim-Salomonson, who had an opportunity of seeing the tracings taken by M. Bull in the Institut Marey using a string galvanometer of his own construction.

This extreme fatigability also involves another apparatus of the animal life, viz. the larynx. The methods of experimental phonetics, with the help of M. l'abbé Rousselot, of the Collège de France, have furnished exact information on the nature of the dysarthric disorders of our patient. The registering of laryngeal vibrations is made on a rapidly rotating cylinder with the help of the laryngographic capsule of l'abbé Rousselot. As he has explained to us, in the tracings (figs. 11 and 12), with two successive pronunciations of the same syllable the patient makes a great effort, so much so that the first is violent and acute, the second, on the contrary, is soft and trailing (to po, fig. 11). The patient's power of effort is largely exhausted on the first syllable. The fact is so definite that in this group of two syllables, forming for the French, in a way, one word, the accent is never on the final but always on the initial syllable. Further, when the repeated syllable commences with an occlusive, this consonant fails to lead to occlusion in the middle of the word, between the vowels, showing that the patient is almost incapable of making a sufficient effort to obtain this by complete closure of his mechanisms (té pé, fig. 12). To sum up in two words: extreme fatigability.

ELECTROMYOGRAPHIC TRACINGS TAKEN DURING REST.

FIG. 3. Tracing of right flexor longus digitorum. Sustained contraction. Feb. 11, 1921

FIG. 4. Same muscle, left side.

FIG. 5. Sustained contraction of right sural triceps (the patient being erect on his toes)

FIG. 6. Same muscle, left side.

ELECTROMYOGRAPHIC TRACINGS TAKEN TWO MINUTES AFTER THE PRECEDING.

FIGS. 7-10. Corresponding muscles to those of first series. Time intervals (vertical lines) 1/100 sec.

BIOLOGICAL MEANING OF THE SYMPTOMS.

What, now, is the biological meaning of the facts of observation just described? For a long time it escaped us, which explains why we only decided to publish the clinical record and the protocol of part of our experimental researches several years after the death of the patient.

From what has been said, numerous facts of observation plead in favour of involvement of the organo-vegetative system: in 1919, in a paper on 'The psychomotor function of inhibition studied in a case of Huntington's chorea,' we established experimentally the primary involvement of the central sub-cortical representation of the system, a point to which F. H. Levy indicated assent later (*Die Lehre vom Tonus und Bewegung*, 1923).

Up till the present, however, physiological findings to which the neurologist must submit himself were calculated rather to mislead than to inspire. It is

FIG. 11. Laryngeal vibrations during the pronunciation of 'to-po.' Time marked by tuning fork of 200 double vibrations a second. June, 1921.

FIG. 12. Same as in fig. 11. Pronunciation of 'té-pé.' June, 1921.

not necessary for our purpose to enter into the complex question of the vegetative innervation of skeletal muscles. Although it has been anatomically established for certain muscles (Boeke), the views advanced by different authors (Bottazi, de Boer, Hunter, Langelaan and others) on the direct sympathetic regulation of muscular tonus have encountered too many experimental objections to be regarded as proved. Langley in particular showed the impossibility of accepting the plausible theory of Pekelharing according to which muscle tonus is accompanied not by a breaking up of carbohydrates but of proteins with formation of creatin.

In recent years the problem, obscured by the tenacity with which the above-mentioned authors have regarded tonus and sympathetic as equivalent terms, has been entirely reshaped by the researches of the Russian physiologist Orbeli and by those of his pupils, who have shown that sympathetic stimulation

is capable of producing delay in the appearance of fatigue or a transient restitution of the capacity for work of a fatigued muscle. The tension of muscle during isometric tetanus can be augmented by sympathetic excitation. Fulton (*Muscular Contraction*, 1926) has recognised the solidity of Orbeli's work. His own tracings and those of Nakanishi show the reinforcement of tetanic contractions when, in addition to somatic nerves, sympathetic fibres are stimulated. These facts have been confirmed by the following negative data from Orbeli's laboratory. After unilateral extirpation of a sympathetic chain in the dog the reflexes of the limbs are profoundly altered. In eliciting rhythmically the patellar reflex, the limb deprived of its principal sympathetic connexion fatigues quicker and the reflex twitches are slower; similarly the reflex reactions to thermal and electrical stimuli—normally of the same threshold right and left—develop a threshold altogether asymmetrical after unilateral sympathetic extirpation.

Independently of the Russian physiologist, Achelis of Leipzig has been able to determine the influence of the sympathetic on the cerebrospinal nervous system. Starting with the important discovery of Lapicque, that the excitability of a peripheral nerve increases after separation from the spinal cord or ablation of the optic lobes (in the frog), Achelis has confirmed it and found in addition that interruption of conducting paths anywhere between eye and ventral spinal roots is followed by augmentation of peripheral nerve excitability. This signifies that in the normal frog (which Achelis studied) the excitability of peripheral nerves is inhibited by excitations of optic origin. Conversely, he proved that section of rami communicantes entails diminution of excitability of sciatic nerves. Hence one may conclude for increase of excitability of the peripheral motor neurone of sympathetic origin—and this, as we have seen, is entirely corroborated by the experiments of Orbeli.

All these researches have been repeated in animals bled to death; vasomotor effects can therefore definitely be excluded. Quite recently (1931) the views expressed by Orbeli have been confirmed by Altenburger and Weisz.

As can be seen, this conception of the rôle of the sympathetic strikingly confirms conceptions previously expressed by Hess, who, in his magistral study of the problem of sleep, originated the idea that the central nervous system of the animal life may be regarded as the effector organ of the organo-vegetative system. This theory is in complete accord with the primary rôle of instinct in nervous pathology as v. Monakow and I have explained.

To return to the problem of skeletal musculature, we see how much wider is the conception than that, calculated on our ideas of the nerves of the animal life, of tonic sympathetic nerves. Thanks to the admirable work of Sherrington and his pupils, during the last ten years, there is no longer any doubt that tonus (a term sanctioned by usage but defective) should be identified with the stretch-reflex. In Fulton's words: 'Stretch, therefore, appears to be the adequate stimulus for the maintenance of the tonic condition; in the stretch reflex

we have tonus in its making' (p. 426). This is also the attitude of Rademaker, who in his fine book *Das Stehen* distinguishes several varieties of stretch-reflexes in accordance with the anatomical level involved. Tonus is a proprioceptive reflex, and the idea of a tonic sympathetic activity, conceived of in anti-physiological fashion as passing from a sympathetic 'centre' to muscle, whereas every nervous activity constitutes a closed cycle (Morat), must be discarded. This does not mean—let it be well understood—that there can be no indirect connexion between tonus and the organo-vegetative system: one has only to recall the modifications of tonus during sleep. Besides, there is not a single biological phenomenon, inclusive of the highest cerebral functions of man, which is not in connexion with the system: it is in this general sense that tonic function, like phasic function, depends on the vegetative system. As a matter of fact it is to the theory of Kraus that adherence should be given for a clear view into the extraordinary complexity of the relations of the organic and the animal life.

ORGANO-VEGETATIVE SYSTEM.

If now, returning to the facts narrated above, we seek to interpret them, it is easy to perceive that they receive a new light from recent physiological advances. Two series of facts can be recognised: (1) a series of organo-vegetative phenomena (secretory disorders, metabolic and sphincteric disturbances, etc.): (2) a series of motor phenomena remarkable for their variability and specially distinguished by extreme fatigability. It is here convenient, before going further, to say a word on the limits of applicability of experimental physiology to clinical medicine.

(1) First of all there is the question of the physiological level involved. The lower this level is, the more general is the value of physiological data: it is the case here, where the function is old from the viewpoint of phylogeny and ontogeny. (2) Physiological method requires the artificial isolation of function (decerebrate, mesencephalic, spinal, neuromuscular preparations, etc.). Pathology, which in certain circumstances can produce dissociations of which physiology is incapable, usually deals with gross and diffuse lesions (as in Wilson's disease) involving several functions at once. Besides, one must take into consideration the action of *diaschisis* at a distance (v. Monakow), as well as the processes of compensation and of effort for restitution of function, as we have ourselves worked out with v. Monakow. In our opinion, and it is true for both neurology and psychiatry, every syndrome is an aggregate of symptoms of which only some possess, in the present state of knowledge, a biological significance in the sense defined above. Thus, for instance, in our patient the exaggerated salivation, dysphagia, sphincter impairment cannot seemingly be ranged in the imbalance of the regulatory function of the vegetative system in its connexions with the animal system. They consist probably of derangements related to diffuse lesions of the periventricular grey matter. By contrast, the excessive fatigability and its variations seem properly to be a

phenomenon of the same order as those discovered by Orbeli. The fatigability recalls Addisonian adynamy; in point of fact our patient showed pigmentation of the skin (though not of the mucosæ, while blood pressure was normal) as Söderbergh has also seen in a case of the kind.

It would be more than hazardous to incriminate here the sympathetic in the strict sense as the physiologists might do, in the first place because we have no incontestable criterion in human pathology of sympathetic deficiency, and above all because there is here an abstraction without reality. All that can be said is that it is highly probable that the conditions of existence of fatigability should be sought in the severe perturbations of the vegetative system (in the sense of Kraus) in our patient. As can be ascertained above, the classical pharmacodynamic tests, false in theory and practice (Söderbergh) furnish none of the information which one expected of them, not so long ago. Nor should it be forgotten that adrenalin and other drugs act particularly on the neuromuscular junction, the 'periterminal network' of Boeke (Langley). In addition to the tremors with adrenalin it is interesting to note the nystagmus with atropin and scopolamine, which seems to indicate a susceptibility of the labyrinthine vegetative apparatus (Spiegel). On this subject we draw attention to the great variations in the size of the thyroid (23), variations which we have also observed in certain cases of disseminated sclerosis. Possibly these variations constitute a reactional phenomenon of compensation, if one allows (as seems well established) that one of the essential functions of the thyroid is sensibilisation of the vegetative system, especially of the sympathetic in the strict sense (Asher, 1931).

We must now add that if the vegetative apparatus can condition fatigability, inversely that apparatus is not independent of the animal system in its behaviour; this shows once more the extreme complexity of the phenomena we are dealing with and the relativity of our divisions, which possess mainly a heuristic and provisional value. Here is an example. Up to recent years fatigue during static muscular exertion was considered to depend on the formation of lactic acid. This view can no longer be maintained since the studies of Dusser de Barenne and Burger, Zondek and Matakas, and others; according to the first two of these, fatigue cannot be explained chemically (formation of lactic acid) nor mechanically (arrest or slowing of blood circulation); it can only be accounted for by the summation of *afferent excitations* (pressures and tensions to which the sensory neural terminations of skin and muscles are subjected). This hypothesis explains why fatigue does not appear in states of catatonia, catalepsy, or hypnosis.

Much earlier (1904) Féré had already proved by ergographic methods that all afferent stimuli (cutaneous, visual, auditory, etc.) are capable of producing fatigue, but neither he nor any subsequent author, so far as I know, has sought an interpretation of the phenomenon. Now it is very curious to note the state of affairs in our patient. At the period when the tracings were

taken, reproduced in figs. 13—16, we were surprised by a seemingly paradoxical feature. We took the graphs with the mercury column dynamograph of Charles Henri, right and left hand alternately, first in the erect and then in the recumbent position, the patient lying on a couch stuffed with hair. In both

FIG. 13. Dynamogram (dynamograph of Ch. Henri) of the flexors of the right hand : standing position, slight anteroflexion of trunk. July 25, 1920.

FIG. 14. Same as in fig. 13. Left hand. July 25, 1920.

FIG. 15. Same as before. Right hand : position, lying down. July 25, 1920.

FIG. 16. Same as before. Left hand : position, lying down. July 25, 1920.

positions the patient employed not merely the flexors of fore- and upper arm, but also the muscles of the trunk and lower extremities. It may be recalled that the dynamograph works by means of manual compression of a rubber bulb filled with mercury communicating with a vertical tube similarly filled : each test was separated from the next by a repose of 25 minutes in a comfortable

chair. Examination of the tracings shows that in the erect position the output of work was superior to but less regular than that in the horizontal position. On the other hand, the patient affirmed categorically that he experienced less fatigue after tests in the latter position. This is the exact contrary to what I have been able to observe on myself and on normal subjects.

Such a result, it would appear, can be interpreted only in the sense indicated by Dusser de Barenne and Burger. In the lying-down position exteroceptive stimuli (plantar surface in particular) and proprioceptive stimuli (postural tonus in relation to antigravity function) are totally suppressed; the nervous system of our patient was in such a state that he could only receive a limited number of afferent excitations without fatigue (a defence reaction) developing.

The question now arises: what is the terminus of these afferent stimulations? Let it be said at once that the hypothesis of the organo-vegetative nervous system appears to be the most probable.

One of the most important principles of vegetative physiopathology, evidenced by Danielopolu, is to the effect that afferent impulses coming via centripetal visceral paths (as in angina pectoris), or via general sensory routes (as in the gastric crises of tabes) have a certain influence on the vegetative centres with which they enter into direct or indirect connexion. So far as concerns somatic muscles, not only are other afferent impulses than those from muscles (optic and auditory mechanisms) capable of causing fatigue (Féré), but, above all, proprioceptive and exteroceptive impulses (skin, articular and juxta-articular tissues) are susceptible of action on the central representations of the organo-vegetative system and of there producing modifications (still of unknown nature) provocative of fatigue. What is repose if it is not the more or less complete cessation of proprioceptive stimulations?

What shows well that the essential part is played, not by products of muscle metabolism (which, for that matter, may excite afferent intramuscular terminals) but by the central condition, is the existence of fatigue persisting in the absence of all muscular labour. We shall make allusion to but a few of a whole series of facts. (1) Popular language has ever confirmed the rôle of the organo-vegetative system by such expressions as 'excitement has taken away the use of my arms and legs' (Cannon would see there the consequence of a powerful suprarenal discharge); or 'emotion has left me speechless' (the *vox faucibus haesit* of the Latin poet). Some years ago we had under observation the case of a woman who after repeated emotional shocks developed an organo-vegetative dystonic syndrome with two predominant symptoms, viz. rapid fatigue, amounting in the end to unintelligibility, of the vocal cords when a given consonant was repeated, and the development of a husky voice about five in the evening (at the time of normal organo-vegetative change in the nycthemeral cycle); also, about the same hour, fatigue of the arms with the slightest emotion, preventing her from holding a newspaper at the level of her face.

In our patient the fatigability of the phonetic muscular apparatus was altogether independent of that of the skeletal musculature. In amyostatic syndromes, therefore, fatigue cannot be ascribed uniquely to muscular work continually produced to maintain faulty static processes, as suggested by Froment in studies of much interest.

(2) We may cite here also the syndrome of muscular fatigue on an organo-vegetative basis seen in the Beard type of neurasthenia (the term is unsuitable for any other syndrome). We have had the chance of following for eight years continuously a case of this kind, connected probably with a 'plexitis' (hyperfunction of the choroid plexuses of the fourth ventricle), consecutive to trigeminal excitation of nasal origin. The case is too complex to be related here, but we may say that after minute study of each function by authoritative specialists we come by exclusion to the hypothesis indicated above, favoured also by v. Monakow. In this case, which presented a severe vegetative dystonia, it was curious to note the recurrence of fatigue coincident both with moderate muscular exertion and with emotion. In view of the dystonia all pharmacological therapeutics (purely theoretical at present) proved not only inefficacious but actually harmful, whereas a complete cure resulted from absolute rest and psychotherapy. It must not be forgotten that the phenomena with which we are here concerned have always a psychical aspect revealing itself clearly in the patient's dreams.

It may also be mentioned (we will return to the point) that the patient to whom we have just referred, only after severe fatigue and at a given moment, exhibited the *Randreflex* of v. Monakow, a form of plantar reflex common in mild degrees of pyramidal involvement. We do not think (we shall see later why) there was here any interruption of pyramidal fibres.

(3) Finally, it is known that one of the commonest symptoms of disseminated sclerosis (found in 90 per cent. by Sachs and Friedmann, 1922) is extreme fatigability coupled with muscle weakness and with others that need not be mentioned. It is also one of the most constant symptoms of the atypical cases of the affection, frequent now in the literature, and denominated diffuse encephalomyelitis. We have had an opportunity of observing a case with a peculiarity of interest in connexion with the present problem. It is that of a man of 35, wounded 15½ years ago by a bullet through the dorsal external border of the *left* foot, with exit towards the middle of the anterior part of the sole. Continual suppuration led to several curettings of bone. At the base of the second toe is an area of about the size of a two-franc piece in which originate excessively painful sensations of protopathic type to be inhibited only by firm pressure. For a year the *right* leg has been seized with violent tonico-clonic twitches whenever pressure is put on the anterior plantar surface of that limb. A sympathectomy was performed on the femoral artery (about 12 cm.) on the right, and the tonico-clonic movements, which interfered severely with walking, improved to the degree of rendering the latter

possible, although slight scratching of the sole still evokes a flexor contraction of the limb with clonico-tonic convulsions.

Simultaneously in this case unmistakable signs of disseminated sclerosis have made their appearance (cerebellar and labyrinthine signs, absent abdominal reflexes, nystagmus, etc.), together with considerable fatigability of the legs, which did not improve until the patient followed my advice and worked seated. One may ask whether the continual protopathic afferent impulses from the plantar surface of the left foot may not have been reflected, at the corresponding spinal level, (anterior and lateral horns) over to the contralateral leg. It is interesting to note that the sympathectomy appears to have acted as in the stump epilepsy of amputated limbs by suppression of a part of the afferent path.

And now, what is the bearing of this instance on our case of hepatolenticular syndrome? As for connexions of the vegetative and the animal systems, it seems to us that, in disseminated sclerosis equally, muscle fatigability is a function of the former, if it is true that periventricular grey matter is practically always involved. We do not consider, naturally, that the lesion, a negative phenomenon, can explain the positive symptoms of fatigue; but the lesion is an index of regulatory defect which has its sphere of action elsewhere and which is, further, still unknown so far as its exact nature at this level is concerned.

DYSREGULATION OF THE NORMAL RELATIONS BETWEEN THE ORGANO-VEGETATIVE SYSTEM AND THE ANIMAL SYSTEM.

What is meant, in our case, by defect of regulation? From numerous contemporary researches in the domain of experimental physiology (Sherrington and his school) and of clinical physiopathology (Head, Wilson, Walshe, v. Monakow, Mourgue, etc.) the essential problem of neurology is conceived to be one relating to the extremely complex laws of the circulation of neural influx. Even at the spinal level, most simplified by physiological technique, the organisation of reflexes in time corresponds to a purely functional scheme; as Sherrington has recently said: 'The simplest spinal reflex thinks, so to say, in movements, not in muscles' (1931).

From the standpoint of physiopathology, the studies of Wilson on chorea, as well as the experimental work of Minkowski, have shown clearly that certain syndromes called extrapyramidal can result from lesions at very different neural levels; the symptoms themselves result from disorder of co-ordination between afferent and efferent impulses. This disorder shows itself in numerous modalities (false summations, reduplications, anticipations, viscosity, etc.) as we have shown along with v. Monakow.

Another characteristic instance is that of disseminated sclerosis. Is it not strange, from the standpoint of the old anatomo-clinical method, to note that this syndrome, whose lesions are even by definition diffuse, betrays itself by an ensemble of symptoms sufficiently constant to allow of diagnosis?

The reason in our opinion is that the nature of the syndrome, as with those known as extrapyramidal, is different from disorders by interruption of continuity or congenital lack of neural tissue ('morphological disorders' of v. Monakow and Mourgue). I hasten to add that the relationship indicated above was established for the first time (from a different point of view) by Wilson.

That author, in point of fact, sees the common ground of the two conditions to consist of the effect of toxins of undetermined nature. This is extremely probable; but we think we can go further in the same direction. It is admitted to-day that the site of application of drugs and toxins alike is primarily the vegetative nervous system (Orr and Sturrock); only, for reasons still unknown, it is such and such a part of the vast system that is affected. In respect of the two groups of diseases mentioned above, pathological anatomy informs us that periventricular and subthalamic formations are involved: in these cases there always appears to be a chronic derangement of the regulation of neural influx. This was particularly noticeable in the case of our patient.

What lends support to this view is for example the appearance, on left plantar stimulation, of a contralateral clonus of the toe, and then of the homolateral foot (12). Ionic modifications of the internal milieu followed by modifications of nervous influx may here be recalled; we noted above (19) how slight acceleration of respiration sufficed to provoke sometimes a severe tremor of the right toes and then a spontaneous fan-like extension, sometimes extension of the last four toes on the right, left great toe, and trembling of the former. We know from the conception of v. Monakow that the extensor plantar response corresponds to a fixed change in the ordinary course of neural influx: nothing however here authorises us to associate it with interruption of pyramidal fibres, of which there is no evidence by classical tests. To speak in these cases of a latent pyramidal lesion is a *petitio principii* due to crude ideas of nervous function. Babinski's sign is found during the epileptic attack and in sleep.

On this matter we wish to direct attention not merely to the defect of regulation in the sense that the neural influx takes wrong routes but also that it persists sometimes in normal paths longer than is habitual with normal persons. After urination it is common to experience a brief shiver in skeletal muscles analogous to what obtains in fevers or accompanying a sudden chill (in both cases, organo-vegetative phenomena): it is just as though proprioceptivity emanating from the tonic contraction of the vesical sphincter irradiates through skeletal muscles. In our patient, at an advanced stage, micturition, especially at night, was accompanied by attacks of generalised trembling (26).

Whatever be the opinion on the existence of vegetative fibres of 'tonic function,' we can rely on the active interrelation of the vegetative and animal systems. It is unnecessary to appeal to any special innervation. Renner

(in Müller's treatise on the organo-vegetative system) says a cortical bladder centre is more than doubtful; whereas the researches of Karplus and Kreidl show the possibility of influencing the vesical sphincter from the regio sub-thalamica, a region which forms, so to speak, a reservoir of nervous energy. There is thus nothing remarkable, in a case of dysregulation, in the accompaniment of vesical proprioceptivity by violent irradiations to the skeletal muscles. The neighbouring sphere, the genital, present a similar phenomenon; modifications of muscle tonus in skeletal muscles accompany the orgasm. Unfortunately in our patient libido sexualis was completely abolished, so that we can add no observations in this matter.

Two other facts of observation should in our view be interpreted as indicating derangement in the circulation of neural influx. These are the facial paresis of supranuclear type (11), which, having undergone remission, can only be assigned to a phenomenon of diaschisis; and the hemiplegic attitude noted at one time (19). It should not be forgotten that the patient never exhibited any of the signs regarded to-day as proof of anatomical interruption at any point in the pyramidal tract. Just as irradiation phenomena are a sign of

FIG. 17. Myograms of the extensor communis of toes. Faradic excitation, 14 interruptions per second. V = Right. VI and VII = Left. Time marked in fifths of a second.

disintegration resembling fragments seen in the new-born, so the hemiplegic attitude seems to correspond to predominance of the biceps, which according to Minkowski is a foetal characteristic attitude. We have seen the same thing in a typical Parkinsonian case in a woman of 64.

Finally we may ask whether in one respect at least the hypertonus of the left side, especially in the leg, may be, if not caused, at least reinforced by the vegetative system. We underline the reservation intentionally, *if not caused, at least reinforced*, because as we have seen the proprioceptive origin of tonus can no longer be demonstrated. None the less proprioceptivity does not allow us to interpret the arrest of muscle tonus about five centimetres above the knee in the left leg. We have had the good luck to observe, in the case of Parkinsonism alluded to above, the same phenomenon on the left side but accompanied by trophœdema and paræsthesiæ (in intimate relation to vasomotor disturbance, according to Wilson), the whole extending to some five or six centimetres above the knee. The trophœdema leaves no doubt of their organo-vegetative origin. It was absent in the case forming our study, but the hypertonia thus localised was subject to variation from time to time. We established its genuineness by relying on the work of Wertheim-Salomonsen,

FIG. 18. Tapping test. Time marked in fifths of a second. From below up:
1. Normal subject: right middle finger. 2. Patient: right middle finger.
3. Normal subject: left middle finger. 4. Patient: left middle finger.

according to which faradic tetanus is obtained in hypertonic muscles with a much weaker current than in normal muscles. His tracings from a case of disseminated sclerosis are quite demonstrative; no less are ours (fig. 17), in which the lower tracing is that of the right extensor communis of toes, the two upper representing the faradic tetanus of the same muscle of the left leg, with the same interruption of 14 per second. For normal muscles the average figure is 20, according to Wertheim-Salomonsen. In the upper limb we have given another illustration of hypertonus, calculated to show the influence of tonic on phasic activity (which follow each other as the shadow does the body)

FIG. 19. Knee-jerk : right leg. Time marked in fifths of a second. July 7, 1920.

FIG. 20. Knee jerk : right leg. Same time. April 18, 1921.

by the help of the tapping test. This consists in making rhythmic percussion on a rubber ball connected with a Marey's capsule. The slowness and irregularity of the movement compared with the right side, and with that of a normal person, can be seen in fig. 18. But it cannot be too often repeated that these results are valid *only for a given moment in time*. The graph of the normal knee-jerk reveals the existence of two components, one tonic and one clonic (Piéron, Wertheim-Salomonsen, and others). In accordance with the predominance of one or other we speak of hypertonus or no hypertonus. A glance at the figures will show that the same right side at one time exhibits predominance of the tonic component (fig. 19), at another of the clonic (fig. 20),

conformably to the moment of time ; on the left, incontestably hypertonic for the greater part of the time, a transient predominance of the clonic element is seen (fig. 21), when relative hypertonus has passed to the right.

Thus it may be questioned whether in extrapyramidal affections tonic phenomena are not complicated by secondary effects of organo-vegetative origin, deforming them more or less, and rendering them the least suitable affection for examination of tonus in a 'pure state.' At any rate, a hypertonia to the mid-level of the thigh is an altogether peculiar phenomenon. It should be remembered that vegetative phenomena are a function not merely of regulation of the vegetative nervous system but also of the local cellular condition. With the schematism inherent in our habits of mind we speak in current parlance of skeletal muscles, yet we know from the work of Schiefferdecker and Prenant that, histologically considered, 'the diversity of morphological characters, and their variation when one animal species is compared with another, suggest that each muscle, perhaps each muscle fibre, has its own

FIG. 21. Knee-jerk : left leg. Same time. July 7, 1920.

specific constitution, its own functional structure' (Prenant). Given this polymorphism, which my chief, the anatomist Vialleton, equally admitted, it is possible that the local electrolytic constitution, to which Zondek attaches so much importance as a component of the vegetative system, may, in the course of disorders like hepato-lenticular syndromes, profoundly affecting metabolism, differ at different spots in the same muscle. In this way would be explained both the inconstancy and variability of pharmacodynamic action, and the apparent paradox of irregular topographical distribution of the hypertonicity.

MIMIC AND EMOTIONAL SYMPTOMS.

We have not yet spoken of another group of symptoms in our case which may also be regarded as an aspect of maladaptation of the normal relations between the vegetative and the animal spheres. We allude, on the one hand, to the disappearance of facial mimicry (fixity of expression) and, on the other, to spasmodic weeping. The problem has been handled in a striking way from

the anatomo-clinical side by Wilson in his *Modern Problems of Neurology*. He relies on researches of Spencer and Graham Brown in attaching great significance to the facio-respiratory synkinesis during laughing and crying, and also to the existence of cortico-bulbar paths passing by the mesial part of the sub-thalamic zone bordering on the walls of the third ventricle and the tegmentum. In these conditions spasmodic laughing and crying are taken to be a phenomenon of escape of control, or of isolation in the sense used by Munk (Wilson does not employ the latter expression).

In support of these views, we may point out that (1) in syndromes designated extrapyramidal the lesions, as a matter of fact, predominate in the regions

FIG. 22. Pneumograms. Instinctive reactions. July 17, 1920. Time: fifths of a second. Speed of cylinder: one revolution per minute.

Down curves=inspiration. Up curves=expiration.

1. Violent and unexpected auditory stimulus.
2. Another, less loud.
3. Slight prick of left shoulder.
4. Spray of ethyl chloride, posterior aspect, left arm.
5. Spontaneous transient apnoea.
6. 'I am sure you will be cured.'
7. 'Your disease is very serious.'
8. 'You remember your nephew killed in the war?'
9. 'Think of your nephew.'
10. 'Think nothing more of it.'

where the above-mentioned paths run; and (2) it is actually the case, in our patient, that to mimic facial inertia corresponds a diminution in the 'voluntary' power of respiratory acceleration.

All this is exact, we believe, but yet constitutes, we consider, only the *mechanical* side of the question, so to say; it does not give us the *biological* significance. As with the problem of sleep, knowledge of the local changes found does not provide the key to its meaning, as Hess has well recognised.

Some dozen years ago (1919) I was able to show experimentally, in a case of Huntington's chorea, using as tests plethysmography of the hand and graphic inscription of respiratory movements (a most delicate test, as Ponzo has shown), that such a case did not react to stimuli capable of evoking in the

normal subject active respiratory derangements emotional in nature. Yet the same patient exhibited attacks of violent rage of an automatic kind, since they supervened in the absence of any external stimulus.

Now the case is practically the same with our patient here. If one looks at fig. 22 and its legend, it will be seen he reacts only in a feeble manner (as compared with the normal) to sensitivo-sensorial excitations: this is true also of psychical stimuli, intentionally chosen from among those capable, as we know, of provoking strong reactions in the sphere of instinct. The attack of spasmodic crying at the end of the graph (to the right and above) need cause no confusion, in the first place because of its late development and in the second because a similar excitation (see 8) was not followed by any effect. Besides, the patient himself said that the attack of weeping had arisen in an unexpected way, as he had not been able to obey the order given. Similar experiments were repeated with the psycho-galvanic test and yielded the same results.

At the commencement of our observation the patient made it clear that from a subjective viewpoint (which must not be ignored) spasmodic weeping corresponded to something quite different from normal weeping. We may recall his own words: 'when I weep for sorrow, I sob; when I weep as I have just been doing, it is not the same thing. When I weep for sorrow, I feel it comes from the heart: when I weep like this, it is in spite of myself: I feel it comes from the stomach. When I am sympathised with, all at once I am compelled to cry; when I experience joy, I also have the inclination to cry. When I weep, I feel as I were being gripped (indicating the epigastrium): it is very hard to explain what I feel. It seems as if my stomach were shrivelling, and that ends with pains.'

According to this statement, it would appear that the patient shows at a given moment both forms of emotional expression, the normal and the spasmodic. According to his wife's information this is only true of the earlier years of the disease, and even then he seemed usually indifferent to happenings which would normally have aroused his emotions. We have been able to photograph the patient at a time when he said he felt a vivid emotion of annoyance (after an argument with his wife) supervening just when we were arranging to photograph the hemiplegic attitude of the left arm. The expression of his physiognomy at these successive moments is exactly the same, the more so as such patients have no difficulty in preserving complete immobility (fourth year of the affection).

To another fact we attach great importance, one often mentioned by the patient (see 16 in particular): at the moment of a spasmodic crying attack he is conscious of a particularly painful feeling of shrivelling in the epigastrium, which he has difficulty in describing exactly. We then wondered whether it was not a contraction of the gastric wall of vagal origin. We found this to be the case with the aid of the radiosopic screen (with the help of M. Contre-

moulins, radiologist to the Necker hospital in Paris). After ingestion of a bismuth meal it was easy to provoke the spasmodic weeping and to observe slow but definite contractions of the stomach. Everything points to vagal discharge at the moment of the weeping attack. This merely appears to be an exaggeration of a normal phenomenon ; as was emphasised by van Helmont even in the eighteenth century, the stomach reacts most delicately to all emotions (cf. also Pavlov), and after depressive emotions the organ is 'fermé,' as a popular French expression has it. In our case this protopathic sensation had the strange, indefinable tonality characteristic of organo-vegetative phenomena of isolation (Munk).

How may the biological significance of spasmodic weeping be made to fit in, in our case ? To do this it is necessary to pose first the more general question of the significance of what are called in classical psychology the 'physiological concomitants of emotion.' It cannot be here treated in extenso ; we shall content ourselves by stating that we adhere to the view sustained by v. Wyss, a pupil of Hess, which declares that visceral reactions taken as a whole should be considered 'means of expression' (Ausdrucksmittel). This conception lends support to the views of Wilson on the respiratory synkinesis already alluded to.

What are these 'means of expression' ? Von Wyss, after Sherrington ('emotion moves us, hence the word') and Klages take them as the mode in which the organism expresses by its attitude the instinct of interest in its connexion with the object (tendency to 'klisis' or 'ekklisis'). We add that in the circumstances the instinct utilises the skeletal muscles, a particularly important point. As a matter of fact we have here, at a somewhat low level, a manifestation of that connexion of the vegetative with the animal life which seems to us profoundly disarranged at that level in extrapyramidal syndromes. Our graphs provide the evidence for a hiatus between sensorial perception and effector organs ; on the other hand, in spasmodic weeping, the latter come into play with the participation of exteroceptivity. Naturally the moment of time must never be omitted ; at a certain stage of evolution normal mechanisms may still come into action at one time or another. It is not then paradoxical to admit that the 'fixed expression' is fundamentally a disorder of the same nature as fatigue, if we interpret the latter as has here been done. Thus the biological point of view, which since 1912 we have contrasted in superiority with the synthetic (after analysis) point of view, allows a unification of symptoms and a more profound comprehension of pathological processes.

METABOLIC DISORDERS.

Can we now go further and combine in the same formula even the metabolic disturbances making hepato-lenticular syndromes and the majority of extrapyramidal troubles following epidemic encephalitis affections of a fatal kind in a restricted time ? We have already alluded to the 'vegetative death' to

which these patients succumb. Like general paralytics before malaria Therapy, like some juvenile catatonics, such patients reach a stage of extreme cachexia ; to them applies perfectly the expression formerly introduced by Edinger (though in another sense) of 'disease by exhaustion' (Aufbrauchkrankheit). Verworn has argued that cellular life depends on the formula $\frac{A}{D}$ where A=assimilation, D=disassimilation, and which he calls *biotonus* ; on condition that reserves are made, in agreement with Kraus, it might be replaced by $\frac{P}{S}$, where P=parasympathetic, S=sympathetic, the first system furnishing the necessary energy for the second, which expends it essentially by the intermediary of the phasic function of skeletal muscles.

It certainly seems that extrapyramidal syndromes terminating by rapid cachexia are signalled by the excessive predominance of the factor S, the sympathetic. Only, instead of the principal expenditure of energy involving phasic function, in its normal connexions with the external world, it would appear that without furnishing work the cell exhausts its reserves on the spot, so to say. Here is a process analogous to cellular autolysis, of which we know practically nothing.

But, as we have just said, the process seems to conduct itself, also as previously indicated, in the sense of a rupture of normal relations between vegetative and animal life. The vegetative system no longer holds at the disposition of skeletal muscles the amount of energy for their needs (hence fatigue), and as tonic proprioceptive function is already disordered a highly complex picture results whose variability is chiefly in relation with that of the vegetative system and which, in our opinion, forms the picture of the affections known as extrapyramidal.

CONCLUSIONS.

We should like to repeat again what was stressed at the outset, viz. that we have no intention of dealing here with disorders of tonus properly so called, but with the biological significance of extrapyramidal affections considered as a whole. It is convenient now to summarise what has been remarked in the preceding pages on this subject.

In our *Introduction biologique* (with v. Monakow) we distinguished rather schematically two main varieties of pathological disorder : (1) *morphological disorder* by interruption of continuity or congenital absence of neural tissue ; and (2) *secretory disorder*, which is the manifestation of derangement in the instinctive sphere. In the latter we distinguished diverse modalities, characterised by the examples of hysteria on the one hand and schizophrenia on the other, but we took the precaution of remarking that there are certainly others still (l.c., p. 313). If one admits (as we did with v. Monakow) that the whole life of the nervous system, under normal and pathological conditions, is dominated by the difference and interaction between two spheres (vegetative life and animal life, or, as we called them, sphere of instinct and sphere of orientation

and causality), one can perfectly understand the multiplicity of relations which may exist in man by reason of the degree of complexity which both spheres may attain. Thus there is no morphological disorder which may not be influenced in its behaviour by the vegetative or instinctive sphere. We may go further and affirm that every morphological affection has for correlate a disturbance of behaviour called *psychical*, which requires to be studied by appropriate methods (psychoanalysis in particular). We need not enlarge on this point, but we have indicated above (2, 30) the abnormal nature of the dream life of our patient.

We do not wish to insist on this, but rather on the fact that in the large group of secretory disorders the level involved must be specified. (1) From this standpoint we may put on one side *pyramidal* affections in their residual phase as constituting a class of morphological disturbances involving in almost pure fashion (in their circumscribed forms) the animal life at a high level, e.g. movements of dexterity, and leaving, almost intact, locomotion as a crude phenomenon. (2) Affections schematically designated *extrapyramidal* imply, as we have tried to show, rupture of normal equilibrium existing at different levels between the animal and vegetative spheres, the former considered principally but not solely at the postural level, since neural corticomotor regulation is also greatly disordered, as Wilson has shown. (3) *Psychoneurotic* motor affections constitute expressions of instinctive origin, organo-vegetative life being taken as the representative of instinct, either exclusive ('*hormétères*' or primary instincts), or partial, in connexion with the sphere of orientation and causality ('*noohormétères*' or elaborated instincts). The reader is referred to our book (with v. Monakow) for details of the conception; but we may add now that the animal life is involved at a much higher level than in the course of extrapyramidal syndromes, and that is, the ensemble of the cortex. At this level motor disorders have in man a symbolic significance. The experimental work of Hess and of Pavlov, though undertaken for different ends, harmonises in proving the process to involve the regulation of nervous influx. We may merely add that these processes can be effected by either the psychical or the physiological route—to employ the usual terms, absolutely vicious though they are; we showed in the work already quoted that in both instances an action is effected on the vegetative system, a true 'common path' (Sherrington). (4) Finally, *psychotic* disorder appears to differ from the preceding only by the extent and modality of the rupture of equilibrium at a very high level, that of the '*noohormétères*.' Psychomotor phenomena there present themselves not as disorders of movement but as phenomena of expression (*Ausdruckbewegungen*), symbolic of the primary derangement of the instinctive sphere.

We may add that these distinctions are purely schematic and rather abstract, seeing that all the phenomena of disintegration are subject to the law of disintegration '*en briques*.' The following examples illustrate the

point. (1) Extrapyrarnidal disorders, if they supervene in persons who have in the past (sometimes in infancy) undergone a severe traumatism in the instinctive sphere, are complicated by unmistakable psychoneurotic disorders. Thus in the cases of oculogyric crises we have seen in postencephalitics we have nearly always been able to find evidence of old traumatisms involving the sexual instinct : occasionally the symbolic character of the act of looking up is conscious on the patient's part, without any interference of suggestion. Jelliffe has written an excellent study on this, apropos attacks of tachypnœa. One may question whether any case of extrapyramidal disorder is unassociated with psychoneurotic symptoms. Every interruption of continuity between the sphere of exteroceptivity elaborated by causality and the instinctive sphere has always, more or less, for consequence a regression to the narcissistic stage of Freud, whence the door opens for psychoneurosis. One may here see the richness of the aspect from which we have sought to interpret extrapyramidal affections. (2) Motor disorder of extrapyramidal type is so little rare in the course of psychoses that special studies have been devoted to it (Schilder, Steck, and others). We do not range in this category schizophrenic catatonia, which is different in nature from the toxic phenomena superficially resembling it (v. Monakow and Mourgue, Claude and Baruk). Toulouse, who has had wide experience in examining psychoses at their apparent beginning, has found among the prodromes one presenting itself with singular constancy, viz. fatigability. Much taken up with the early unrolling of psychotic disorders, he has concluded—prematurely, as we think—that one of the tasks of mental prophylaxis is to discover objective tests revealing this tendency to fatigue. Several of his collaborators have undertaken researches in this connexion, mainly of a chemical kind ; in spite of their value so far as analysis of accompanying phenomena is concerned, we think the question wrongly conceived. As we have shown, fatigue appears to be an index of dysregulation supervening in the relations of the vegetative and the animal life, its starting place being in the vegetative system.

We should not forget that only on the occasion of interaction of the two spheres is fatigue felt ; it is always located in the interior of the animal sphere though having its real origin elsewhere. There is in reality no fatigue, in the strict sense, of vegetative visceral functions. It appears to be the economic reaction of defence calculated to protect the living organism against exhaustion and to prevent it from expending energy in favour of animal functions to the detriment of the conservation of life. In this sense it is a manifestation of the instinct of preservation at a low level. Hence it does not astonish that fatigue should occur at the onset of psychoses, since these have their origin in the world of instincts in close connexion with the vegetative life. It is only a sign, like fever.

We cannot at present determine many points which are still obscure. One of the most difficult, on which we have but a fitful light, is the existence

of a *chronogenic localisation* in the vegetative nervous system, like what obtains in the cerebrospinal nervous system (Semon and v. Monakow). Nevertheless researches such as those of Claude and Baruk, to which we draw attention, tend to produce a reaction against the simplistic views still reigning in the minds of some neurologists. The same movement is showing itself in different countries. We think this provides verification of the necessity of posing problems in biological terms, as we have defined the term, and that we have not been in error in urging for the last twenty years the insufficiency of the analytic point of view in biology.

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