CLINICAL NOTES.

Chronic bronchitis as a distinct entity is especially prevalent in Manchester and Salford. Many cases date from an attack of acute bronchitis contracted on active service in France. Attacks of a spasmodic or asthmatic type are very frequent. The expectoration varies greatly in different cases, but is usually abundant and mucopurulent.

The physical signs include marked diminution of expansion and respiratory capacity, hyper-resonant percussion note, and widespread mixed râles and rhonchi. There is marked deterioration in health and capacity for employment, and as a rule there is evidence of cardiac muscle weakness.

In the presence of such changes in the physical state of the chest, and probably of permanent changes in the anatomical structure of the lungs, the influence of vaccine treatment must necessarily be limited, but several salient facts emerge from observation of a series of cases treated in this manner:

1. In most cases there is distinct improvement in the patient's general condition, in colour, vigour, and capacity for activity.

2. The sputum, which may at first increase in amount, in practically every case diminishes in quantity and loses its mucopurulent character, becoming white and less profuse.

3. The cough becomes less persistent and the attacks or paroxysms much fewer and less severe, particularly those occurring in the night and early morning.

4. A striking feature has been relief from asthmatic attacks; from the clinical point of view this is the most conspicuous effect produced by the treatment.

The clinical observers have not known the type of vaccine employed in any given case, and the results must speak for themselves.

Summary.

1. It is not possible, short of gross destruction, to detoxicate completely a suspension of pathogenic bacteria.

2. The residual toxic substance is not affected by a temperature of 120° C., it is not destroyed by weak solutions of oxidizing agents, but it is precipitated by mineral acids.

3. It is possible to remove from a suspension of organisms all the thermolabile toxins and endotoxins. Thomson's method, Dean's method, or that of the author are equally efficient.

4. It is probable that the residual toxic body is an integral part of the bacterial protoplasm.

5. Residual vaccines can be sterilized in the autoclave, so sterilization is simple and certain.

6. Residual vaccines are highly efficient therapeutic agents.

7. They retain their maximum efficiency indefinitely.

8. Most cases of uncomplicated chronic bronchitis respond to treatment by residual vaccines.

The author cannot conclude without acknowledging his indebtedness to Professor Dean for much valuable advice and constructive criticism, and to the physicians who contributed the clinical notes for their kindness in undertaking the large amount of clinical work which this investigation required.

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ENCEPHALITIS LETHARGICA.

BY

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[AFTER a brief reference to the history of the disease, and the use of the term "encephalitis lethargica," Dr. Haynes quoted a classification of the symptoms given by Dr. F. M. R. Walshe in *Brain*, November, 1920. The primary division was into general symptoms and nervous symptoms. General symptoms were such signs of toxic infection as fever, eruptions, malaise, pain, headache, and gastrointestinal disturbance. The nervous symptoms were general or focal, and in each case were classified as

positive or negative, the terms being employed in the sense in which Hughlings Jackson originally used them.]

Positive symptoms are expressions of exalted function, either from irritation or loss of higher control, and negative symptoms express depression or loss of function. The general positive symptoms in lethargic encephalitis are delirium, restlessness, hallucinations, and so on; the general negative symptoms lethargy and coma. The focal positive symptoms are convulsions, involuntary movements and muscular contractions, ataxy, rigidity, and pain; the focal negative symptoms are paralyses.

Recognition of these two classes of symptoms—positive and negative—is very helpful, enabling us to understand that a lesion of a single area might give rise to convulsions as well as to paralysis, and that whether a clonic twitching of a muscle or weakness occurred depended not on the site, but upon the nature of the lesion.

The disease occurs at all ages, and affects both sexes equally. Three stages can be distinguished—the prodromal stage, the acute stage, and the stage of regression. The incubation period has not yet been determined. The chief prodromal symptoms, which last usually from one to seven days, but may be prolonged for three weeks, are headache, giddiness, lethargy, blurred or misty vision, and diplopia; vomiting is not common; muscular weakness frequently occurs.

The acute stage is characterized by fever (101° to 102° F.), lasting from two to five days or longer, the pulse and respiration being as a rule unaffected. The patient lies in bed semi-conscious and immobile, or with much muscular asthenia; the face is expressionless and mask-like; the limbs in many cases are rigid, and in some they remain in any position in which they are placed, as in the condition known as *flexibilitas cerea*. Usually patients can be roused from their stupor to take food or to answer questions; this they do intelligently, but in a voice often nasal and monotonous, the sentences being uttered very slowly. There may be emotional irritability, and nocturnal delirium frequently occurs. In this stage muscular twitchings and tremors may occur. There is no characteristic skin eruption, though petechiae, papules, or erythema have been observed; one case was notified as scarlet fever and another as measles. *Tache cérébrale* is readily elicited in most cases. Other symptoms are dysphagia, nausea, and constipation; the tongue is dry and coated. Retention or incontinence of urine is of frequent occurrence; the urine is concentrated, loaded with urates, and transient albuminuria is found during the febrile stage.

Paralysis of the cranial nerves is a characteristic feature the third and seventh being most commonly affected. The fundus oculi is normal. Ptosis is the usual form of third-nerve paralysis; it may be unilateral or bilateral, and slight or complete. The ciliary muscle is often involved early and paralysed longer than other ocular muscles; the pupils may be unequal; divergent or convergent squint is seen; diplopia is common. Whereas ptosis and strabismus are only transient, involvement of the movements of the eyeball may last several weeks, as may disturbance of accommodation. Facial paralysis has often been observed; it is, as a rule, bilateral, but more marked on one side than the other; the tongue and pharynx are sometimes affected and deafness has been noted.

Netter's statistics place the frequency of lethargy and ocular palsies as high as 75 per cent. of all cases, but, though with fever this is the characteristic syndrome, a large number of cases do not conform to this type; some begin with excitement and muscular twitchings or spasms, or with severe pains in the limbs; others have quiet delirium with delusions; others, again, go about with persistent headache, apathy, and lack of facial expression. In fact, as Farquhar Buzzard has pointed out, an inflammation of the encephalon can produce as many symptoms as there are functions of the brain.

Of the lethargy, which is an interesting feature of the disease, three explanations have been suggested: (1) That it is due to internal hydrocephalus, the result of occlusion or partial occlusion of the aqueduct of Sylvius by inflammatory processes in the region of the corpora quadrigemina. It is noted that sluggishness or total abolition of the pupillary reflexes frequently occurs with the lethargy, and that this combination is characteristic of tumours of the posterior end of the third ventricle. (2) That it is due to interference with the afferent paths of stimuli from the

* Abstracted from a paper read before the Cambridge Medical Society.

environment, whereby stupor results. It is argued that an inflammatory lesion in the crura cerebri and optic thalami might, in addition to blocking afferent stimuli, involve the nucleus of the third nerve and give rise to the frequently observed ocular phenomena. Optic neuritis is generally absent, indicating that the lethargy is not part of a general cerebral condition, such as would be caused by hypertension, as in tumour or abscess. (3) That it is due to pressure on and inflammation of the pituitary gland. Sluggishness, with a tendency to somnolence, is a sign of hypopituitarism.

The differential diagnosis of the characteristic syndrome, with "negative" nervous signs, is to be made from the following conditions: Cerebro-spinal meningitis, in which there is commonly retraction of the head and a turbid spinal fluid containing the meningococcus; tuberculous meningitis, a somnolent form of which may occur in infancy, characterized by a dissociation of pulse and temperature and irregularity of the pulse, choked disc and choroid tubercles, with lymphocytes, albumin, and frequently tubercle bacilli in the spinal fluid; influenzal encephalitis, usually accompanied by bronchial or pulmonary signs. Cerebral syphilis is generally unaccompanied by fever; optic neuritis is frequently present, and the complement deviation test is in most cases positive. Sleeping sickness is distinguished by the presence of the trypanosome in the blood, cerebro-spinal fluid, and enlarged glands. Cerebral forms of poliomyelitis are rare; they commonly occur in the summer months; the paralyses are more generalized and are maximal when declared, whereas in lethargic encephalitis the paralyses are often slight at first but progressive. Cerebral softening, following embolism or thrombosis, or cerebral haemorrhage may simulate encephalitis, in which large areas of softening and gross haemorrhages have been found. Naked-eye *post-mortem* changes are not sufficient to distinguish between ordinary cerebral haemorrhage and a haemorrhagic encephalitis.

The diagnosis of cases presenting "positive" nervous signs, the excito-motor syndrome, is more difficult, especially when a history of an acute attack is lacking. Such cases are those showing involuntary movements and muscular contractions; they have been classified by Marie and Levy, who describe forms resembling chorea and paralysis agitans, and forms with rhythmical and myoclonic movements of the face, trunk, and limb muscles.

These excito-motor signs may not develop until weeks or even months after apparently complete recovery from the acute illness or after an unrecognized mild attack.

If no history of an initial acute illness be obtained the following minor symptoms may confirm the occurrence of a mild attack: onset of an illness with occipital headache and painful rigidity of the neck, accompanied by slight fever and nocturnal delirium; disturbances referable to the muscles of mastication, such as difficulty in opening the mouth fully, tremor of the jaw, chattering of the teeth, neuralgic pains in the distribution of the fifth nerve; attacks of facial spasm; excessive salivation; slowness and difficulty in articulation; a sense of constriction of the throat with difficulty in breathing or swallowing; frequent attacks of yawning or of hicough; slight painful swelling of joints, and finally, neuralgic pains of root distribution and painful muscular cramps. One or more of these symptoms associated with slight signs of general infection indicate the occurrence of the initial infection.

The diagnosis of lethargic encephalitis can never depend upon the presence or absence of any symptom or group of symptoms. It must be determined by a consideration of the onset and course of the disease, and by the elimination of other pathological conditions which may produce similar symptoms and physical signs.

The course of the disease is very variable. Some cases are rapidly fatal, death being apparently due to paralysis of the respiratory nervous centres. The stupor may clear away in a few days or persist for several weeks, even as many as eight, and recovery may then ensue; pneumonia, wasting and bedsores have been noted as fatal complications.

The Cerebro-spinal Fluid.

The cerebro-spinal fluid is normal in appearance; in some cases, but not in all, it is under pressure; during the first few days lymphocytosis may occur, but this is not one of

the fundamental characters of the disease, as it is of tuberculous or syphilitic meningitis, and is only of short duration; an excess of glucose is frequent but not constant, and is attributable to a certain degree of hyperglycaemia due to a lesion of the floor of the fourth ventricle.

The Blood.

The blood count is normal. Some Italian bacteriologists have isolated from broth cultures of the blood a small Gram-positive diplococcus, which was agglutinated in a dilution of 1 in 100 by the serum of the patient from whom it was isolated, and by that of other patients and of convalescents from the disease. It was not agglutinated by normal blood or by the blood of typhoid patients. Guinea-pigs inoculated with blood containing the diplococcus died on the fifth or seventh day after presenting subnormal temperature, paresis of the limbs, intense somnolence and often muscular jerking of the limbs. The brain showed punctiform haemorrhages, especially in the grey substance.

In the Government report referred to previously, James McIntosh states that, as a rule, no macroscopic changes sufficient to account for death are found *post mortem*. A common appearance is dilatation of the vessels, which in many instances is likely to be mistaken for haemorrhage. Histologically the changes consist of cellular infiltration of the perivascular lymphatic sheaths and of certain areas of the grey matter. The lesions are most extensive in the basal nuclei of the brain, in the upper part of the pons, particularly in the grey matter of the floor of the fourth ventricle, much less prominent in the medulla; in the cord lesions are very slight or absent.

At the annual meeting of the British Medical Association held in Cambridge last year Dr. Greenfield showed a series of lantern slides illustrating the morbid anatomy of this disease. The changes found in most early fatal cases were very diffuse, and could usually be traced from the medulla to the cortex. The most constant appearances were capillary dilatation and infiltration of the brain substance with small cells of the lymphocyte type, which were often grouped round the nerve cells as though attacking them. A comparatively common feature of the disease was infarction of the brain due to thrombosis of smaller or larger arteries.

In cases of longer standing calcareous and thrombotic changes in the vessel walls were sometimes found.

Other observers draw attention to the occurrence of gross haemorrhages chiefly in the mesencephalon.

Loewe and Strauss find that the Berkefeld filtrates of brain material, nasopharyngeal swabs, and nasal washings from cases of epidemic encephalitis produce the typical lesions of the disease in rabbits and monkeys. Spinal fluid and blood are also capable of producing the disease in this way; many of the infected animals die with the typical clinical picture of lethargic encephalitis. These observers have succeeded in cultivating a minute filtrable organism, seen as clumps of minute globular bodies with Brownian movement, young cultures of which are Gram-positive. It is obtained from the brain, nasopharyngeal mucosa, cerebro-spinal fluid, and blood of cases of the disease in man and from inoculated animals dead of the disease. The organisms thus recovered from rabbits are virulent for other rabbits.

The prognosis is not good; death occurs in from 40 to 50 per cent. of cases notified, but as probably many mild or abortive cases are not recognized and not notified the true mortality is almost certainly less.

In severe cases which recover from the acute stage, sequelae, such as impairment of the higher faculties, loss of memory, defects of speech, mental lethargy, and a general loss of intellectual tone, are common. Other sequelae are the persistence of cranial nerve palsies, paresis, and even paralysis of a limb or of limbs, athetosis, myoclonus—that is, sudden shock-like spasms of limbs, sometimes also of diaphragm and larynx. In one of my cases this myoclonus is well marked fifteen months after the onset of the disease. Symptomatic paralysis agitans may be observed. Recovery from the disease is, as a rule, gradual and tedious, chiefly on account of the great prostration and muscular weakness that are so common.

Treatment.

No specific treatment is known. Hexamine, as being the most active disinfectant of the cerebro-spinal fluid, has

been largely used; it has been given by the mouth, by the rectum, and intravenously.

Lumbar puncture, repeated at intervals, has been used with some success. The intravenous injection of salvarsan has been tried in some cases and good results reported.

The French have treated many cases by fixation abscess; 1 or 2 c.cm. of oil of turpentine is injected subcutaneously into the middle part of the outer surface of the thigh. If no reaction occurs at the end of a few days, the injection is repeated. The resulting abscess is incised on the fifth or sixth day, or it may be aspirated. The pus is sterile. That this method is efficacious in the collection of toxic substances into one part of the body is shown by the following experiments. Toxic doses of arsenic in the form of sodium cacodylate were given to animals, and at the same time an experimental abscess was produced. The animals recovered from the arsenical poisoning, and a large proportion of the arsenic administered was recovered in the pus. A disadvantage of this form of treatment is that sometimes severe pain is caused. It has been used in cases of cerebro-spinal meningitis and of influenza and pneumonia. Other remedies which have been tried in lethargic encephalitis are strychnine, horse serum, and the serum of convalescents.

During convalescence the patient should be kept at rest and free from worry; sedatives and hypnotics, such as ammonium bromide and chloralamide, being prescribed, if required, in order to limit the liability of permanent cerebral lesions occurring.

Of the thirteen cases I have seen, ten were under treatment in Addenbrooke's Hospital. Most of them were of severe type, and seven died.

The following is an example of a case of average severity:

A woman, aged 24, had been in poor health for some months; in October, 1920, her tonsils were removed, and she subsequently resumed her work. About the middle of December she became sleepy and apathetic, and was troubled by vomiting in the morning. The vision became hazy, and she had difficulty in focussing. On December 21st, she complained of frontal headache and sleepiness; she was lethargic, lying with her eyes closed, but easily roused, answering questions briskly and intelligently, and then relapsing into slumber. The temperature was 103°, the tongue thickly coated, and the reflexes very sluggish; otherwise no abnormal physical signs were observed. She was admitted to Addenbrooke's Hospital on December 22nd, and for about a fortnight remained in a drowsy condition with constant headache, and mental condition slightly confused. She had partial double ptosis, misty vision, occasional diplopia, stiffness of the masseters with inability fully to open the mouth, and paresis of the facial muscles. A recurrence of vomiting and increase of headache came on three weeks after admission, but this passed off in a few days, and the condition slowly improved, so that she was discharged after five weeks in hospital. During this time she lost nearly two stone in weight. She is now making progress, but very slowly. There is still much muscular weakness, and considerable mental depression. She is gaining 1 or 2 lb. a week in weight.

The following is an example of a very severe type of case:

A woman, aged 21, consulted a doctor on December 8th, 1920, for misty and double vision. She was sent home to bed, but grew weaker and became comatose. When first seen on December 11th she was very drowsy but could be roused to answer questions, which she did in a sleepy voice, slowly, immediately relapsing into stupor. There was some fever, a crop of red papules on the chest only, double ptosis and right external strabismus, twitching of the right ala nasi, coarse tremors, and rigidity of limbs with *flexibilitas cerea*.

On admission to Addenbrooke's Hospital on December 11th the coma increased, and the temperature rose; it reached 105.6° in the early morning of December 16th, when the patient died.

The result of the examination of the cerebro-spinal fluid was negative; there were no pathogenic signs; there was a little excess of sugar.

In the following case myoclonus was a prominent symptom.

A woman, aged 30, attended as an out-patient on June 9th, 1920, complaining of aching in the left arm and leg, with "jumping sensations." Her illness had commenced at Christmas, 1919, with sleepiness and loss of speech lasting a fortnight. In February there was aching in the back of the neck, and later in the left side, arm, and neck. Involuntary movements of the left arm and leg now commenced and have continued ever since.

On examination the general condition was found to be good. There was tenderness about the left deltoid, the muscles of the left shoulder girdle generally were slightly wasted, and the circumference of the left calf was 1½ in. less than the right.

There was no paralysis, no ocular palsies, no sensory changes, and the reflexes were present. There were jerky involuntary movements of the affected arm and leg, occurring about every two minutes. The condition suggested hemichorea.

After treatment with arsenic and bromides with but little improvement, she was admitted. Dr. Prideaux reported as follows: "I do not think there can be any doubt that this is a genuine case of myoclonus associated with encephalitis lethargica. She is certainly not a functional case, though, as in other cases of myoclonus, the spasms are increased during emotional excitement and in fatigue. The prognosis is fairly good—that is, eventually it should clear up; cases hitherto reported have cleared up in from six months to three years."

When seen on April 2nd, 1921, fifteen months after the onset of the disease, she complained of great weakness, unsteadiness of the legs, constant twitchings of the left arm and leg, and sleeplessness. Her general condition was very poor; she was pale, weak, and thin; there was some instability on walking, and especially on turning; she was apathetic and dejected, and her face expressionless; there were regular rhythmic movements of the left arm caused by clonic spasms of the muscles of the left subscapularis, and also similar movements in the left leg synchronous with the arm, caused by spasm of the hamstrings. These movements ceased at times, and were not present during sleep.

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OCULAR SYMPTOMS IN THE SLIGHTER CASES OF ENCEPHALITIS LETHARGICA.

BY

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EXETER.

THERE is a special fascination in the study of borderland cases of any disease. Moreover, to obtain a complete picture of any subject it is necessary to study its fringes. The following cases are cited as bearing upon the ocular symptoms in slight cases of lethargic encephalitis; doubtless there are other groups in which symptoms other than ocular predominate, but they would not come to an oculist.

CASE I.—*Diplopia: Paresis of Accommodation: Retrobulbar Neuritis: Drowsiness.*

C. H., aged 32, was first seen on February 11th, 1921. His illness had started three weeks earlier with diplopia for two days, and drowsiness for a week. At the beginning there was pain in the frontal region and at the root of the nose, and "weakness of the eyes," "darkness, as if a blind were drawn down." On February 11th, vision with correction was: R. 6/6, L. 6/12; loss of accommodation was: R. +75, L. +1. There was no diplopia present. The discs were white and filled in, the edges very well defined, the branches emerging after division suddenly out of the white disc; the main vessels were not visible. This condition was more marked in the right eye.

Fields (white object) 5/300:

			Up.	In.	Down.	Out.
Right eye ...	...	...	25°	20°	20°	35°
Left eye ...	...	...	20°	25°	22°	50°

The blind spots were not charted.

The condition on May 2nd (communicated) was:—With correction: R., 5/5; L., 5/10. Near vision with same correction: R., J.1; L., J.1, imperfectly; there was no diplopia, the fundi was unchanged, the general condition was much better, and work was about to be started.

CASE II.—*Diplopia: Paresis of Accommodation: Sleepiness: Weakness of Limbs: Retrobulbar Neuritis.*

Mrs. B., aged 53. Her history was as follows: On February 27th, 1921, diplopia and sleepiness began. On March 2nd, on waking, she found that she could not walk without help because of weakness of the legs. On March 11th the condition was that she had near glasses +3.5; distance glasses +2. Her vision was R. +2 = 6/12; L. +2 = 6/9 partly. The loss of accommodation was +2.5 in each (not excessive for her age, but apparently +1 more than before the attack). The irides and fundi were normal. In regard to the fields, the right eye was contracted to from 20 to 30 deg., and the blind spot enlarged (object 5/300 white). The left eye was contracted to from 15 to 20 deg.—that is, inside the blind spot (object 5/300 white). Diplopia was crossed, and was greatest in the right half of the field; that is to say, there was paresis of the left internal rectus. The limbs were weak, but the left arm and leg were weaker than the right arm and leg. The knee-jerks were equal and exaggerated. Her memory was bad. The subsequent history (communicated) was as follows: On March 29th diplopia disappeared; on April 12th vision became normal; on April 18th she was well in every respect, except for her memory, which remained very bad.